# Study in support of the evaluation and impact assessment of the EU general pharmaceuticals legislation

Impact Assessment Report

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## LEGAL NOTICE



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## GLOSSARY

| *Term or acronym* | *Meaning or definition* |
|---|---|
| AMR | Antimicrobial resistance |
| API | Active Pharmaceutical Ingredient |
| ATMP | Advanced therapy medicinal product |
| BTC | Blood, tissue and cell |
| CAT | Committee for Advanced Therapies |
| CHMP | Committee for Medicinal Products for Human Use |
| CP | Centralised authorisation procedure |
| CPMP | Committee on Proprietary Medicinal Products |
| DCP | Decentralised authorisation procedure |
| EC | European Commission |
| EEA | European Economic Area |
| EHDS | European Health Data Space |
| EMA | European Medicines Agency |
| EMEA | European Agency for the Evaluation of Medicinal Products |
| EMVS | EU medicines verification system |
| ERA | Environmental Risk Assessment |
| GDP | Good Distribution Practices |
| GMP | Good Manufacturing Practices |
| GMO | Genetically modified organism |
| HMA | Heads of Medicines Agencies |
| HTA | Health Technology Assessment |
| MA | Marketing authorisation |
| MAH | Marketing authorisation holder |
| MP | Medicinal products |
| MRP | Mutual recognition procedure |
| MS | Member State |
| NCA | National Competent Authority |
| REFIT | Regulatory fitness and performance programme |
| RDP | Regulatory data and market protection |

| | |
|---|---|
| ROI | Return on investment |
| RWE | Real world evidence |
| SDG | Sustainable Development Goal |
| SmPCs | Summary of product characteristics |
| SPC | Supplementary Protection Certificate |
| UMNs | Unmet medical needs |

## ABSTRACT

A new revision of the general pharmaceutical legislation (covered by Directive 2001/83/EC and Regulation (EC) No 726/2004) is planned, for which an impact assessment was conducted by Technopolis Group. The general objectives of the revision are to 'guarantee a high level of public health by ensuring the quality, safety and efficacy of medicines for EU patients' and harmonise the internal market. Specifically, the revision is looking to promote innovation (especially for unmet medical needs) and affordability of medicines, ensure access to medicines and security of supply, reduce the environmental footprint of medicines, reduce regulatory burden and provide a flexible regulatory framework.

Three policy options (A, B and C) with varying degrees of changes were compared to the business-as-usual scenario (no policy changes). Overall, Option C comprising a modulated system of incentives combined with obligations emerged as the strongest option. Option C addresses the specific objectives of the revision most effectively, and has the most positive overall impact. It also performs well in terms of coherence, proportionality, feasibility and EU-added value of the policy measures.

## EXECUTIVE SUMMARY

The EU general pharmaceutical legislation was established in 1965 with the dual objective of safeguarding public health and harmonising the internal market for medicines. It has developed considerably since then, but these overarching objectives have guided all revisions. The general pharmaceutical legislation governs the granting of marketing authorisations for medicines for human use by defining conditions and procedures to enter and remain on the market. A fundamental principle is that a marketing authorisation is granted only to medicines with a positive benefit-risk balance after assessment of their quality, safety and efficacy.

The most recent comprehensive revision of the EU general pharmaceutical legislation took place in 2004. In the almost 20 years since this revision, the pharmaceutical sector has changed and has become more globalised, both in terms of development and manufacture. Science and technology have evolved at a rapid pace. Even so, unmet medical needs (UMNs) persist in terms of diseases or conditions for which treatments are not available or are suboptimal. Moreover, some patients do not benefit from innovation in treatments because these medicines may be unaffordable or not launched (placed on the market) in the Member State concerned. There is also a greater awareness of the environmental impact of medicines. More recently, the COVID-19 pandemic has stress tested the framework in terms of how to deliver authorisation of vaccines in very short timeframes and maintain business continuity.

To support a further revision of the general pharmaceutical legislation, an impact assessment study was carried out by Technopolis Group. This impact assessment covered Directive 2001/83/EC[1] and Regulation (EC) No 726/2004[2] ("general pharmaceutical legislation") and analysed policy options designed to address shortcomings highlighted in the parallel evaluation of the general pharmaceutical legislation (also conducted by Technopolis). The revision is part of the implementation of the Pharmaceutical strategy for Europe[3].

### Problems to be addressed in the revision

The evaluation of the general pharmaceutical legislation showed that the legislation delivered on all objectives of the 2004 revision. The objective to ensure quality, safety and efficacy of medicines was achieved to the largest extent, while that to ensure patient access to medicines in all Member States was achieved only to a limited extent. The legislation performed to a moderate extent in terms of ensuring a competitive internal market and competitiveness and attractiveness of the EU pharmaceutical sector globally. Nonetheless, some problems persist as described below.

(1) Medical needs of patients are not sufficiently met with no or few treatment options for some diseases e.g. Alzheimer's disease and disease-resistant infections

(2) Unequal access to medicines across the EU because of pricing and reimbursement policies or strategic decisions by companies whether to launch a product in a given Member State

(3) Affordability of medicines is a challenge for health systems. Innovative medicines are often costly and medicine prices also vary significantly between Member States.

(4) Shortages of medicines are putting health systems and patients at risk[4]. There has been a strong increase in the number of shortages notified in the EU from a few in 2008 to nearly 14 000 in 2019[5]. Root causes include more complex and diversified global supply chains, quality and manufacturing challenges, commercial decisions and unexpected increase in demand.

(5) A regulatory system that does not sufficiently cater for innovation and can involve high administrative burden. Rapid scientific and technological developments have resulted in new challenges for the system, which has become more complex over time, e.g. the expansion of the number of EMA scientific committees and their interactions[6]. The system needs to be

[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p.67.
[2] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency, OJ L136, 30.4.2004, p.1.
[3] COM(2020) 761 final.
[4] European Commission, Directorate-General for Health and Food Safety, Jongh, T., Becker, D., Boulestreau, M., et al., Future-proofing pharmaceutical legislation: study on medicine shortages: final report (revised), 2021, https://data.europa.eu/doi/10.2875/211485.
[5] Analytical report, indicator SM-1, Annex 10. Data only collected for period 2008-2020, during which many Member States put in place new systems or requirements for notification of shortages.
[6] COM(2021) 497 final.

agile to be able to accommodate innovation in both medicines and allied technologies e.g. manufacturing and digital technologies. There is also a need for rationalisation and simplification to reduce unnecessary administrative and compliance costs, duplication and support innovation e.g. in SMEs or new technologies.

(6) Residues of medicines in the environment coming through manufacturing, use by patients and disposal present a risk to the environment and human health. This is an area where the legislation was found to be less effective by stakeholders in the evaluation. The current requirement for an environmental risk assessment (ERA) accompanying the application for marketing authorisation has been found to include some weaknesses as regards compliance and the content and scope of the ERA.

## Objectives of the revision

The general objectives of the revision are to 'guarantee a high level of public health by ensuring the quality, safety and efficacy of medicines for EU patients' and harmonise the internal market.

In response to the problems identified, this revision's specific objectives are to:

(1) Promote innovation, in particular for unmet medical needs to enable major biomedical research advances, ensure a pipeline of innovative new medicines for use across the EU and strengthen the competitiveness of the research-based EU pharmaceutical sectors.

(2) Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation. The aim is to enable competition and to promote affordability of medicines for healthcare systems across the EU, but not at the expense of innovation. The underlying ambition is to create a balance where, on the one hand, innovation is rewarded, and on the other hand, faster market entry of generic and biosimilar medicines is facilitated, as a means to improve competition across the EU and drive down costs for medicines

(3) Ensure access to innovative and established medicines for patients, with special attention to enhancing security of the supply across the EU e.g. by preventing and addressing shortages of medicines.

(4) Reduce the environmental footprint of the pharmaceutical product lifecycle

(5) Reduce the regulatory burden and provide a flexible regulatory framework to future-proof innovation, and thereby increase the attractiveness of the EU regulatory system

## The available policy options

Three policy options (A, B and C) which include different policy measures and combinations thereof were compared to a baseline – the business-as-usual scenario where no policy changes are made to the current system. A multi-criteria impact analysis was conducted for each policy measure, based on data, literature review and stakeholder feedback, to allow alternative groupings (other than the three policy options) if needed.

The three policy options represent alternative ways of reaching the general and specific objectives. Option A is closest to the current system and addresses the identified problems through incentives coupled with a stronger enforcement of existing obligations and information requirements. In contrast, Option B incorporates more obligations with stronger monitoring mechanisms and interventions at different milestones in the lifecycle of a medicine to foster patient access, affordability and security of supply. Option C is somewhere between Options A and B with a 'quid pro quo approach' consisting of a modulated system of incentives combined with obligations.

A key feature of the current system is incentives for innovation in terms of data (8 years) and market (2 years) protection to give time to developers to recoup their investment by delaying the entry of generic or biosimilar medicines. Option A maintains the current system of regulatory incentives and incorporates further targeted incentives – an additional 1 year of regulatory data protection for products addressing UMN; 6 months of additional regulatory data protection for the conduct of comparative trials, which bring a more robust evidence base for the assessment of effectiveness of new treatments and facilitate decision-making downstream in the lifecycle of medicines; and a 6 month regulatory data protection incentive if a product is placed on the market in all Member States within 5 years of marketing authorisation (MA). Option B offers 6-years data protection and 2-year

market protection, marking a reduction in the current standard regulatory protection periods. New originator medicines with a demonstrated ability to address UMN would benefit from an additional 2 years of data protection, thus maintaining the current baseline. Standard regulatory protection under Option C would mimic that in Option B, with an additional 2 years of data protection if the product is placed on all EU markets within 2 years of authorisation and appropriately and continuously supplied where required. The special incentives in Option A for products addressing UMN and conducting comparative trials will also apply under Option C.

Options A and C aim to stimulate the development of **antimicrobials** through transferable exclusivity vouchers (transfer the right to extend the regulatory protection period to another product marketed by the same or another company). Instead of the voucher, Option B includes a 'pay or play' model – Either a company holds an antimicrobial in its portfolio, or it pays into a fund for financing the development of novel antimicrobials.

The three options also have different approaches and measures with regard to monitoring and mitigating medicine shortages, ensuring market launch of products more widely across the EU, and reducing the environmental footprint of pharmaceuticals. All options are complemented by a series of horizontal measures that aim to reduce regulatory burden and provide a flexible regulatory framework.

## The preferred policy option

Overall, Option C emerged as the preferred option in comparison to Options A and B. This option addresses the specific objectives of the revision most effectively, and has the most positive overall impact. Our multicriteria assessment showed that Option C is like to accrue more positive social and environmental impact than the other options and is likely to show positive economic impact (albeit to a slightly less extent than Option A). The latter is affected by some of the increased administrative burden and compliance costs for businesses and public authorities associated with changes in obligations in particular. Option C also emerges better than or equal to the other options in terms of internal and external coherence of the policy measures, proportionality of the policy measures with regard to addressing the trade-offs between the different objectives, EU-added value and subsidiarity as well as legal and political feasibility.

Option C will bring benefits to patients and citizens by increasing availability of and access to innovative medicines (through promoting innovation and market launch in all EU member states) and ensuring security of supply. No costs are expected as there are no associated obligations. Public sector researchers will also accrue benefits in terms of more opportunities to engage in research and development of medicines through measures to promote repurposing of off-patent medicines and to facilitate non-commercial entities to become marketing authorisation holders. For industry and public authorities, there will be a trade-off between benefits in terms of additional protected sales (for any additional regulatory protection period) and savings (owing to simplification, streamlining and better coordination) compared to additional administrative/compliance costs to fulfil new or more complex obligations. We estimate the benefits should be in the order of €2.19bn a year and €32.86bn over 15 years. We estimate the total costs to be in the order of €1.91bn a year of recurring costs which equates to €28.64bn over 15 years.

# 1 INTRODUCTION: POLITICAL AND LEGAL CONTEXT

This impact assessment (IA) report forms part of "the study in support of the Evaluation and Impact Assessment of the EU general pharmaceutical legislation" that was commissioned by the Directorate-General for Health and Food Safety and is being carried out by Technopolis Group with support of Ecorys BV, Milieu Law & Policy Consulting, Utrecht University (Centre for Pharmaceutical Policy and Regulation & Innovation Studies Group) and Informa Pharma Custom Intelligence. It includes all the chapters required of an IA report, as defined by the Better Regulation guidelines.

## *1.1 Political and legal context*

This impact assessment and its associated proposal for legislative reform builds on almost 60 years of successive European legislative actions designed to safeguard public health and promote harmonisation inside the European Union with the longer-term aim of creating a 'common market' for medicines.

The cornerstone of the European regulatory system for medicines was put in place in 1965 with Directive 65/65/EC,[7] which mandated the dual principles of public health protection and the free movement of products within the EU, which state that:

- Whereas the primary purpose of any rules concerning the production and distribution of proprietary medicinal products must be to safeguard public health
- […] this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community

In 1975, the criteria for admission were further detailed in Directive 75/318/EC and Directive 75/319/EC to facilitate the authorisation of medicines in two or more Member States.[8,9] The Committee on Proprietary Medicinal Products (CPMP) was established to facilitate the adoption of a common position by the Member States with regard to decisions on the issuing of marketing authorisations (MAs), which was the first mutual recognition procedure (MRP) based on voluntary endorsement of each other's initial evaluations. Directive 87/22/EEC introduced the 'concentration procedure' which is now known as the 'centralised procedure'.

The Council Regulation EEC/2309/93 resulted in the establishment of the European Agency for the Evaluation of Medicinal Products (EMEA) in 1995. The CPMP was re-established as a 'new' CPMP to help formulate the opinion of the Agency on questions relating to the submission of applications and granting MAs in accordance with the centralised procedure. Lastly, the most recent major revision of the general pharmaceutical legislation (Directive 2001/83/EC[10]) took place in 2004, when Regulation 726/2004[11] replaced the older regulation from 1993.[12]

In the 18 years since the last comprehensive review of the general pharmaceutical legislation, there have been wide-ranging developments in every socio-economic sphere touched by the legislation, whether that is advances in science, the globalisation of the pharmaceutical sector or public health systems' sharper focus on patient benefits and cost-effectiveness. Moreover, demographic change and rising expectations among citizens around access to and quality of health services are challenges facing all European countries.[13]

From this perspective alone, it is timely for this piece of fundamental legislation to be reviewed in terms of its continuing relevance and effectiveness to the health needs of European citizens.

The 2004 revisions were the subject of an evaluation that has been run back-to-back with this impact assessment, the report for which has been published separately.

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[7] European Commission (EC). Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31965L0065&from=EN.

[8] Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (75/318/EC). https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31975L0318&from=en.

[9] Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products (75/319/EEC). https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31975L0319&from=en.

[10] https://eur-lex.europa.eu/eli/dir/2001/83/oj

[11] https://eur-lex.europa.eu/eli/reg/2004/726/oj

[12] Council Regulation (EEC) No 2309/93/EC of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products, OJ L 214, 24.8.1993, p. 1.

[13] Hans Kluge, A new vision for WHO's European Region: united action for better health, The Lancet Public Health, Comment, Volume 5, ISSUE 3, e133-e134, March 01, 2020, doi.org/10.1016/S2468-2667(20)30003-7

### *1.2 Other relevant European strategies*

The Pharmaceutical Strategy for Europe, a central pillar for building a stronger European Health Union[14,15], was adopted on 25 November 2020 and is the principal EU strategy and action plan relevant to this impact assessment. The strategy is a key part of the European Health Union[16] and an important point of reference for this impact assessment. It defines a series of high-level objectives that may be addressed at least in part through further revisions to the EU general pharmaceutical legislation.

Specifically, the strategy aims to:

- Foster patient access to innovative and affordable medicines and fulfil unmet medical needs
- Support the competitiveness and innovative capacity of the European pharmaceutical industry
- Develop the EU's open strategic autonomy and ensure robust supply chains, including in times of crisis
- Ensure a strong EU voice on the global stage

The pharmaceutical strategy includes various 'flagship' initiatives and other actions to ensure the delivery of tangible results, including a targeted revision of the general pharmaceutical legislation to address the relevant problems as far as possible.

### *1.3 Relevance to the Sustainable Development Goals (SDGs)*

The impact assessment has considered the relevance of the proposed legislative actions to the UN Sustainable Development Goals (SDGs).[17]

Six of the 17 SDGs are likely to be addressed through the proposed changes to the EU general pharmaceutical legislation, with SDG3 and SDG9 being the most directly relevant, while four other SDGs are likely to be affected positively but to a lesser degree:

- SDG 3: Good Health and Well-Being for people. The general objective of the EU pharmaceutical legislation is to safeguard public health and its specific objectives include improved patient access to innovative and affordable medicines and the fulfilment of unmet medical needs. The proposed revisions will help to ensure the legislative framework continues to play a critical role in regard to safeguarding public health
- SDG 5: Gender Equality. The proposals may have a small positive impact on gender equality because of the commitment to address unmet medical needs (UMNs) and improve access – both of which can have a gender dimension – albeit this is most pronounced around access to and use of healthcare services rather than medicinal products more narrowly[18]
- SDG 8: Decent work and economic growth. The proposals may have some small impact on the quality of work and economy since new and improved access to effective medicines may improve citizens' abilities to manage chronic conditions and sustain more demanding / rewarding jobs. Moreover, legislative revisions have the capacity to further strengthen Europe's pipeline of new medicines and help to sustain growth rates of the innovative pharma and biotech industries if production occurs in Europe. Moreover, legislative measures designed to support earlier access to markets by the producers of generics and biosimilars may also help to sustain or even expand the EU's generics industry
- SDG 9: Industry, Innovation, and Infrastructure. The legislative proposals directly address a strategic industrial sector for Europe and will reward the pharmaceutical sector's investments in innovative medicines and novel manufacturing, helping to underpin the productivity and competitiveness of the EU industries facing increasingly fierce global competition from originators, generics, and suppliers in established (e.g. US) and emerging international

[14] A pharmaceutical strategy for Europe, European Commission. https://ec.europa.eu/health/human-use/strategy_en.

[15] Communication on a Pharmaceutical Strategy for Europe, COM(2020) 761, European Commission, November 2020. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020DC0761.

[16] https://ec.europa.eu/info/strategy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_en.
[17] https://www.un.org/sustainabledevelopment/sustainable-development-goals/
[18] https://eige.europa.eu/publications/gender-equality-index-2021-report/gender-and-intersecting-inequalities-access-health

industries (e.g. China and India). The proposed revisions in support of innovation (UMNs, antimicrobial resistance [AMR]) may be most consequential.

- SDG 10: Reduced Inequalities. The proposed revisions should contribute to wider policy efforts to reduce health inequalities as regards both improved market access and affordability (e.g. authorised medicines are made available more widely including among smaller EU member states) and unmet medical needs where millions of people live with debilitating diseases for which there is no effective treatment currently
- SDG 12: Sustainable consumption and production. The revisions to the legislation will help to improve the pharmaceutical industry's environmental performance in some limited degree, through more stringent environmental risk assessments and the expansion of the scope of the assessment to include manufacturing risks. This may encourage the use of less risky active pharmaceutical ingredients (APIs) and higher quality global supply chains, helping to reduce manufacturing-related releases of the most problematic substances to the environment. The revisions will also look to encourage member states to redouble their efforts in respect to the prudent use of antibiotics through the greater use of diagnostics, more cautious prescribing practices and more appropriate disposal regimes and infrastructure. These signals should help to reinforce trends towards less widespread use of antimicrobials as well as more informed disposal, both of which would help to reduce releases to the environment through excretion or poor waste management

## *1.4 Related initiatives*

### 1.4.1 Health related initiatives

There are several legislative initiatives, either upcoming or in preparation, that have relevance to the proposed revisions to the general pharmaceutical legislation. The most important of these are:

- The pending revision of the EU legislation on **blood, tissues and cells** (BTC) is relevant as some substances of human origin are starting materials for medicinal products. The revision will promote the safety of patients and donors, facilitate innovation and contribute to adequate supply of the relevant therapies. Particularly important for the pharma sector is strengthening the safety and quality requirements of BTC to align with the standards of the pharmaceutical framework for the highest risk preparations. It will also address the (re)emergence of communicable diseases, including lessons learnt from the COVID-19 pandemic, and is thus contributing to the European Health Union. Coherence between the two revisions is key to ensure clarity as to which legislation applies to some BTC based therapies.
- The proposed amendment to the Commission Implementing Regulation (EU) No 520/2012 **harmonising the performance of pharmacovigilance activities** by MA holders, national competent authorities and the European Medicines Agency.
- The **European Medicines Agency (EMA) fees legislation**[19] is currently under revision. The fees support EMA and national competent authorities and contribute to the sustainability of the EU regulatory system.
- The planned **revision of the EU's legislation on medicines for rare diseases (EC no. 141/2000) and children (EC No. 1901/2006),** also referred to as 'orphan ' and 'paediatric' medicines, respectively. According to the Commission work programme for 2022, the initiative would be put forward in December 2022. This initiative will address a number of shortcomings in the functioning of the existing framework detected during a recent evaluation of the current orphan medicinal product and paediatric medicine regulations.[20] The revisions echo several of the proposals for this IA of the general pharmaceutical legislation, for example, proving greater support to the development of products in areas of high unmet needs for patients. There is also an ambition to make the new legislation robust / adaptable enough to accommodate technological and scientific developments. Lastly, it will streamline and simplify existing

[19] Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products, OJ L 35, 15.2.1995, p. 1, and Regulation (EU) No 658/2014 of the European Parliament and of the Council on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use, OJ L 189, 27.6.2014, p. 112. These regulations set out fee amounts and allows for remuneration of the national competent authorities for the contributions to services provided by EMA to companies, e.g. assessment of application for marketing authorisation.

[20] https://ec.europa.eu/health/medicinal-products/medicines-children/evaluation-medicines-rare-diseases-and-children-legislation_en

procedures linked with the evaluation and authorisation of new medicines with a view to reducing the burden for both regulators and developers.

In addition, there are several important recent pieces of legislation that must also be considered, including most importantly:

- **The Clinical Trials Regulation (Regulation (EU) No 536/2014) (CTR)**, which came into force from 31 January 2022. It replaces the Clinical Trials Directive 2001/20/EC (CTD) and will streamline the registration, assessment and supervision processes for EU clinical trials. The CTD allowed for national rules around the assessment of the conduct of trials with such rules varying between member states. This leads in some cases to incoherence between the processes for MA (and the scientific advice given at European or Member State level) and the clinical trial authorisation process.
- **The Regulation on Health Technology Assessment (HTA)** was adopted in December 2021. The new rules will come into force in 2025 and should complement the efforts of the EU general pharmaceutical legislation to incentivise innovation. A strengthened and expanded HTA capacity will be better placed to assess and approve vital and innovative health technologies and improve the availability of evidence on safety, efficacy and effectiveness.[21]
- **Medical Devices Regulation[22]** (Regulation (EU) 2017/745) applies since 26 May 2021. Manufacturers must comply with the Regulation when placing new medical devices on the market. It sets the 'principal mode of action of the product' as the primary criterion to distinguish between medicinal products (which fall under the general pharmaceutical legislation) and medical devices. Difficulties arise when a medical device incorporates substances which if used separately can be considered medicinal products and thus would be relevant for the general pharmaceutical legislation.

### 1.4.2 Non-health related initiatives

There are several upcoming initiatives that fall outside the medicines and public health arena, which may have some relevance to the current impact assessment.

We looked specifically in the digital, green and innovation arenas:

- There are several initiatives in the digital space, which may be of some general relevance to medicines and healthcare, given the increasing digitalisation of the health economy and the central and critical role played by data – and especially patient-level data – at all points in the medicines lifecycle, from development through to use and disposal. These include
  - The European Health Data Space (the *EHDS*)[23]
  - Directive on the legal protection of databases[24]
  - The Directive on open data and the re-use of public sector information[25]
- In the energy, climate and environment realms, it is clear the EU Green Deal (2020) and Climate Change Strategy (2020) will have implications for the EU pharmaceuticals industry as it will for all industries. The EU pharmaceuticals industry contributes disproportionately to Europe's greenhouse gas emissions and waste streams, the EU commitments to achieving net zero by 2050, imply the industry will need to redouble its efforts to reduce emissions from manufacturing and distribution, while also strengthening its contributions to the circular economy. The proposals for revising the current legislation must therefore align with these more general EU policies to deliver net zero and enhance sustainability. Policy actions to mitigate the impact of medicinal products in water will be in place with the revision of the Environmental Quality Standard Directive (2008/108/EC as amended by 2013/39/EU), revision of the Groundwater Directive (2006/118/EC) and the revision of Waste Water Treatment Directive (91/271/EEC).
- We found no relevant upcoming initiatives in the competitiveness, research and innovation realms. However, as with the environment, there are pre-existing EU level initiatives that are

[21] https://ec.europa.eu/commission/presscorner/detail/en/IP_21_6771
[22] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. OJ L 117, 5.5.2017, p. 1–175.
[23] https://ec.europa.eu/health/ehealth-digital-health-and-care/european-health-data-space_en
[24] https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:31996L0009
[25] https://digital-strategy.ec.europa.eu/en/policies/legislation-open-data

relevant to the scientific and technological needs of the EU pharmaceutical industry. The most prominent of these existing initiatives is Horizon Europe and the €2.4bn Innovative Health Initiative (IHI) in particular,[26] which is the fourth successive European innovation partnership between the public and private sectors aiming to advance understanding and underpin breakthroughs in innovative medicines.[27] The IHI research strategy will address issues of direct concern to the EU Pharmaceutical Strategy, including addressing areas of UMN, AMR and green pharmaceuticals.[28] The IHI will contribute to a number of European policies of interest here, most notably Europe's Beating Cancer Plan, the new Industrial Strategy for Europe and the Pharmaceutical Strategy for Europe. The proposals for revising the current legislation must align with these more general EU policies to deliver advances in science and innovation relevant to medicines in Europe

An additional non-health related legislation that interacts with the general pharmaceutical legislation is Regulation (EC) No 469/2009 which establishes a **supplementary protection certificate** (SPC) for producers of pharmaceutical products and plant protection products to offset the loss of patent protections due to the compulsory lengthy testing and clinical trials. The SPC legislation applies without prejudice to the authorisation procedure laid down in Directive 2001/83/EC, in particular the regulation of generics and biosimilars, as well as falsified medicines, medical devices' unique identifiers, and also Good Manufacturing Practices *(*GMPs).

[26] https://www.imi.europa.eu/about-imi/innovative-health-initiative
[27] The origins of the Innovative Medicines Initiative (IMI) lie in the European Technology Platform (ETP) on Innovative Medicines (INNOMED, 2005-2009) that was supported under the European Commission's Sixth Framework Programme for Research (FP6). It was followed by the IMI1 (FP7, 2008-2013) and IMI2 (Horizon 2020, 2013-2020). https://www.imi.europa.eu/about-imi/history-imi-story-so-far
[28] https://www.imi.europa.eu/sites/default/files/uploads/documents/About-IMI/IHI/IHI_SRIA_DraftJune2021.pdf

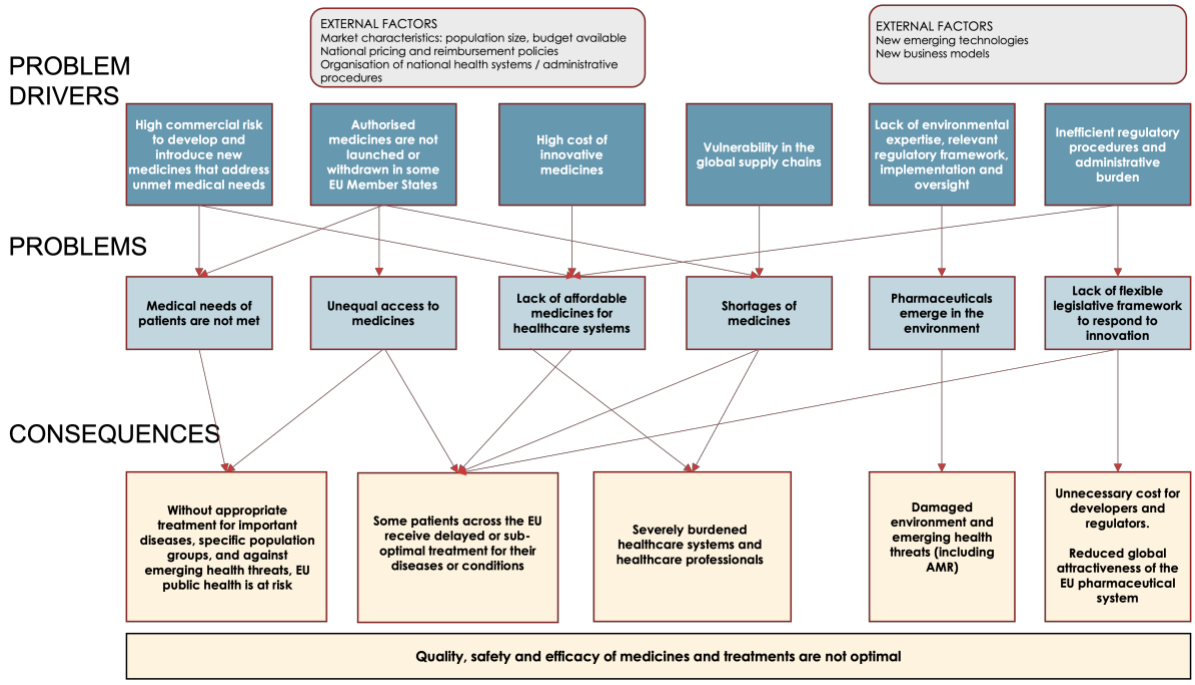
# 2 PROBLEM DEFINITION

## *2.1 What are the problems?*

While the EU general pharmaceutical regulation has improved the overall regulatory framework and underpinned strong progress in medical treatment in the last twenty years, and despite the strong foundations of the pharmaceutical sector, there are areas in need of improvement to ensure EU citizens optimal access to innovative and affordable medicines, to support the competitiveness and innovative capacity of the European pharmaceutical industry, and to develop the EU's open strategic autonomy and ensure robust supply chains.

The associated study to support the evaluation of the EU general pharmaceutical legislation, the Inception Impact Assessment and desk research has identified a series of outstanding problems where further regulatory action might be warranted. The problem tree for the revision of the general pharmaceutical regulation is presented in Figure 1. The problems, problem drivers and consequences are further elaborated below.

**Figure 1 Problem tree diagram for the revision of the pharmaceutical legislation**




While there have been numerous major medical advances in the past 20 years, many seriously debilitating conditions continue to exist with no or few treatment options, ranging from Alzheimer's disease through to muscular dystrophy and leukaemia. Together these conditions affect millions of EU citizens whose **medical needs are not being met**. Since 2005, between 13 and 43 medicines with new active substances have been authorised in the EU every year, and 4-20 of those medicines address unmet medical needs. While these novel medicines have improved survival rates and quality of life for EU citizens and many other patients around the world[29], other UMNs remain. In the public consultation[30], all stakeholders found that the legislation moderately promotes the development of medicines for unmet medical needs, with industry having the most positive view in that regard.

AMR is a key medical need that remains to be addressed. It is estimated that each year about 670,000 infections occur, and that 33,000 Europeans die as a consequence of antibiotic-resistant bacteria, with the burden being highest in the elderly and infants.[31] It is also estimated that AMR

[29] https://ec.europa.eu/health/system/files/2020-12/2020_healthatglance_rep_en_0.pdf
[30] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Evaluation-and-revision-of-the-general-pharmaceutical-legislation/public-consultation_en.
[31] https://pubmed.ncbi.nlm.nih.gov/30409683/

costs the EU €1.5 billion per year in healthcare costs and productivity losses.[32] The evaluation showed that the legislation has been less relevant to ensure development and authorisation of medicines addressing unmet medical needs, including novel antimicrobials.

Access to authorised medicines varies across Europe, with larger and/or wealthier nations more likely to benefit from available medicines. This creates **unequal access to medicines** across Europe and leads to some patient populations receiving delayed or sub-optimal treatment of their conditions. Patient access to medicines remains uneven across the EU[33], even for products that have been approved through the EMA's centralised procedure such as orphan medicinal products and oncology products[34]. Smaller and poorer countries in particular tend to see fewer product entries (smaller market potentials).[35]

At the member state level, most authorisations are for generic medicines[36], which can be marketed only after the expiry of regulatory and other intellectual property protection periods. Low volume markets also experience limited access to generics.

In the targeted survey, the legislation was seen to have underperformed in terms of access according to most stakeholder groups, except industry. Stakeholders agree that there is still room for improvement in this area.

**Lack of affordable medicines for healthcare systems** is also a challenge for many health systems. It has a complex set of drivers, including the cost of developing medicines and a lack of consensus on pricing principles. Many patients in the EU do not benefit from innovation as affordability of and access to medicines is not equitable across EU member states.[37] Innovative medicines are often costly and thus unaffordable for many EU citizens. Medicine prices also vary significantly between member states and are often not cheapest in poorer member states like Bulgaria or Romania.[38] Pharmaceutical budgets also put pressure on health systems, for example, they account for 20-30% of hospital expenditures and are growing[39].

Against this backdrop, generic and biosimilar entry creates competition, broadening patients' access to advanced treatments at more affordable prices and alleviating healthcare costs.[40] Generics are typically cheaper by 80%[41] on average and biosimilars by 20%[42] compared with originator products.

According to all stakeholder groups, the legislation has been less effective in enabling access to affordable medicines. The rising costs of medicines were key concerns for academics, healthcare professionals, public authorities and civil society stakeholders in the evaluation.

The evaluation showed that medicine shortages are an increasing problem in the EU; a problem that was also experienced during the COVID-19 pandemic. Over the last 10 years, there has been a strong increase in the number of shortages notified in the EU from a few in 2008 to nearly 14 000 in 2019[43]. The root causes include more complex and diversified global supply chains, quality and manufacturing challenges, commercial decisions and unexpected increase in demand. Medicine shortages are placing a significant burden on health systems, health professionals and, ultimately are putting patients at risk of sub-optimal care and health systems at risk of higher healthcare costs[44].

Medicine shortages have a global dimension due to the global supply chain, where external actions or events impact the supply of medicines in the EU, e.g. the Indian export restriction of certain active substances during the COVID-19 pandemic. Likewise, problems at a manufacturing site may cause shortages in several Member States or the whole of the EU, depending on the supply chain.

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[32] A European One Health Action Plan against Antimicrobial Resistance (AMR) (June 2017).
[33] Technopolis Evaluation study report, figure 10, 2022.
[34] Kyle, M. K. (2019). The Single Market in Pharmaceuticals. *Review of Industrial Organization*, *55*(1), 111–135. https://doi.org/10.1007/s11151-019-09694-6; Zamora, B., Maignen, F., O'Neill, P., Mestre-Ferrandiz, J., & Garau, M. (2019). Comparing access to orphan medicinal products in Europe. *Orphanet Journal of Rare Diseases*, *14*(1). https://doi.org/10.1186/S13023-019-1078-5; Bergmann, L., Enzmann, H., Thirstrup, S., Schweim, J. K., Widera, I., & Zwierzina, H. (2016). Access to innovative oncology medicines in Europe. *Annals of Oncology : Official Journal of the European Society for Medical Oncology*, *27*(2), 353–356. https://doi.org/10.1093/ANNONC/MDV547
[35] Newton, M., Scott, K., & Troein, P. (2021). *EFPIA Patients W.A.I.T. Indicator 2020 Survey*.
[36] Study on the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use, EY, January 2020, p. 103.
[37] https://ec.europa.eu/health/medicinal-products/pharmaceutical-strategy-europe/making-medicines-more-affordable_en
[38] Zaprutko T, Kopciuch D, Kus K, et al. Affordability of medicines in the European Union. *PLoS One*. 2017;12(2):e0172753
[39] European Commission, State of health in the EU: companion report 2019 (ISBN 978-92-76-10194-9)
[40] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective
[41] Mestre-Ferrandiz, J., Towse, A. & Berdud, M. Biosimilars: How Can Payers Get Long-Term Savings?. *PharmacoEconomics* **34,** 609–616 (2016).
[42] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilarsv
[43] Technopolis Evaluation study report
[44] European Commission, Directorate-General for Health and Food Safety, Jongh, T., Becker, D., Boulestreau, M., et al., Future-proofing pharmaceutical legislation: study on medicine shortages: final report (revised), 2021, https://data.europa.eu/doi/10.2875/211485.

The public consultation confirms the importance all stakeholders (in particular civil society organisations and healthcare professionals) place on medicine shortages. In the targeted survey, civil society, public authorities and health service stakeholders considered the legislation least effective in addressing issues related to security of supply and medicine shortages.

Pharmaceuticals may enter the environment during their manufacturing, use by patients and disposal. Residues of **pharmaceuticals in the environment** can not only damage our environment and ecosystem, but also cause new health threats and exacerbate existing ones such as AMR. Residues of several pharmaceuticals have been found in surface and ground water, soil, and animal tissues, with traces of some pharmaceuticals found in drinking water.[45] The monitoring of pharmaceuticals in the environment is very limited and the ability for wastewater treatment in eliminating pharmaceutical residues varies. Therefore, it is important to be able to identify the risks posed by individual pharmaceuticals on the environment.

In the targeted consultations, industry, civil society and public authority stakeholders ranked reducing the environmental footprint of medicines among the objectives where the general pharmaceutical legislation had been the least effective. In the public consultation, stakeholders felt that the legislation has performed moderately in terms of ensuring that medicines are manufactured, used and disposed of in an environmentally friendly manner with citizens, healthcare professionals and public authorities being the most critical.

Lastly, there is a **lack of flexibility in the EU legislative framework to respond to innovation,** which is needed if the EU pharmaceutical system wants to maintain its global attractiveness and continue to develop and enable the early launch of innovative and generic medicines. The evaluation showed that regulatory requirements for medicines can be very complex, with low levels of digitalisation, and sometimes duplicative processes within and between regulators. Inefficiency in regulatory procedures causes administrative burden and imposes unnecessary cost on developers and manufacturers. In particular, the 'sunset clause' was found to be ineffectual, and the renewal requirement after 5 years was judged to be inefficient.

Advances in science and technology have the potential to address UMN, improve public health and quality of life. However, novel types of medicines and medicines produced using novel technologies can create regulatory challenges where they do not meet the scope or definitions of the legislation and therefore find themselves unregulated or subject to unintended barriers to innovation, development, production, or MA. Challenges are particularly evident around regulation of gene therapy medicinal products, borderline products and novel technologies and approaches (e.g. personalised medicines, novel manufacturing processes and artificial intelligence) to medicines.[46–47]

The consultations showed a consensus between academia/research organisations, patient/consumer organisations, healthcare professionals and industry that the legislation was not flexible enough to accommodate scientific advances, such as ATMPs and real-world data in healthcare. Public authorities noted that medicines regulators need more resources to keep up with the speed of scientific and technological developments and to assess complex therapies appropriately.

An assessment of the current authorisation system[48] identified the need for rationalisation and simplification which the consultations echoed. Stakeholders noted the need for strengthened coordination between bodies responsible for marketing authorisation procedures, clinical trial authorisations, HTA and pricing and reimbursement. Several industry respondents stated that regulatory burden can be costly, duplicative and thus hinder innovation, in particular for innovative SMEs who may struggle with high fee costs, though fees incentives exist for SMEs[49].

### *2.2 What are the problem drivers?*

Europe's ageing population and changing lifestyles are contributing to an increasing health burden, which continues to have strong socio-economic dimensions, with the less well-off having higher levels of morbidity and reduced mortality[50]. While the EU has a world-leading, research-intensive

[45] European Commission, 2019. European Union Strategic Approach to Pharmaceuticals in the Environment.
[46] Beattie, S. 2021. Call for More Effective Regulation of Clinical Trials with Advanced Therapy Medicinal Products Consisting of or Containing Genetically Modified Organisms in the European Union. Human Gene Therapy 32(19–20), pp. 997–1003. doi: 10.1089/hum.2021.058.
[47] Anklam, E. et al. 2022. Emerging technologies and their impact on regulatory science. *Experimental Biology and Medicine* 247(1), pp. 1–75. Available at: https://journals.sagepub.com/doi/full/10.1177/15353702211052280 [Accessed: 1 April 2022].
[48] COM(2021) 497 final.
[49] Commission Regulation (EC) No 2049/2005 provides for specific support for SMEs, including an SME Office in the EMA and fee reductions and deferrals. Further fee incentives for SMEs are provided in the Rules for implementation of the EMA fee regulation (Council Regulation (EC) No 297/95) and in the EMA pharmacovigilance fee regulation (Regulation (EU) No 658/2014).
[50] https://www.euro.who.int/en/data-and-evidence/european-health-report/european-health-report-2021

pharmaceutical industry[51], the rising cost and complexity of medicines research is affecting medicine pipelines, forcing companies to invest more heavily in R&D, while also increasing the price of many new treatments[52]. This has increased the **commercial risk of developing and introducing new medicines** that address UMN.

The UMN of AMR is widely documented, driven by several factors including the overuse and misuse of antimicrobials on the one hand and a growing problem with releases into the environment through use and poor disposal practice on the other.[53,54] The challenge is made worse by a weak global pipeline of major new classes of antimicrobials. This situation is not expected to change without substantive public support, as there are evident and growing market failures, with an evident gap between the typical cost and scale of the scientific challenge involved in developing new antimicrobials and the typical income and profit that can be derived from sales of these products as healthcare systems work on reducing antimicrobial use as a way to limit AMR.

Another key problem driver is that **authorised medicines are not launched or withdrawn (after launch) in some EU Member States**. Factors beyond the authorisation process such as market size, purchasing power, national pricing and reimbursement policies and tax rates[55] impact companies' decisions in that regard. Access problems due to selective marketing also occur with generic medicines. During the stakeholder consultation, an industry association described how increasing use of policies that put pressure on the prices of generic medicines necessitates 'low price – high volume' models. In low volume markets, generic companies find it challenging to operate profitably and may decide not to market their product.

**New, highly innovative medicines are costly**, placing pressure on public budgets. The prices of medicinal products are influenced by factors such as research costs incurred (also for unsuccessful R&D), return on investment estimates (considering the target population for the product), and national pricing and reimbursement policies and tax rates.[56] Among these factors, research costs are partially influenced by the pharmaceutical legislation and its documentation/evidence requirements. However, there is a lack of transparency on R&D costs or public contributions to these costs. While R&D costs are not relevant for the assessment of a medicine's benefit-risk balance, information on such costs is relevant for the downstream actors.

There is a **vulnerability in global supply chains** arising from the consolidation of the global industry that has produced narrow but complex pharmaceutical supply chains, in which many different intermediate suppliers may be connected. An increasing focus on cost reduction has furthermore increased the EU's reliance on oversees suppliers and manufacturers. For generic medicines in particular, the vast majority of all products sold in the EU is produced in countries such as India and China. Together, these forces have weakened the resilience of EU supply chains against supply disruptions or sudden spikes in demand. In addition, the implementation of provisions related to continuity of supply of medicines, such as notification requirements and obligation to ensure appropriate and continued supply, varies across Member States, e.g. Italy requires notification of shortages 4 months in advance while Romania requires them at least 6 months in advance[57].

There is an increasing number of novel technologies and approaches emerging that are transforming the development and production of medicines.[58] For example, genetically modified organism (GMO)-containing medicinal products such as gene-based and cell-based therapies, will increasingly become more important as they have great potential to treat a range of diseases, including areas of UMN. However, the regulatory system does **not sufficiently cater for innovation** and the **current medicines framework lacks agility** to respond appropriately to these rapidly advancing technologies. These regulatory challenges are driven in many cases by **inefficiencies in the regulatory framework**, e.g. redundant requirements like the 5-year renewal of marketing authorisation, leading to unnecessary administrative burden. In the accompanying evaluation study, several NCAs reported increases in costs relating to additional enforcement obligations introduced in the 2004 revisions to the general pharmaceutical regulation. Operational and staff expenditure for the EMA has also increased almost four-fold since 2004 to €168m and €115m in 2020. Industry actors also incur costs with regard to filing MA applications, complying with pharmacovigilance and good manufacturing practice/good distribution practice (GMP/GDP) requirements and fulfilling other

[51] https://www.efpia.eu/media/602709/the-pharmaceutical-industry-in-figures-2021.pdf
[52] https://www.frontiersin.org/articles/10.3389/fmed.2021.760762/full
[53] https://pubmed.ncbi.nlm.nih.gov/26603922/
[54] https://pubmed.ncbi.nlm.nih.gov/35338063/
[55] Zaprutko T, Kopciuch D, Kus K, et al. Affordability of medicines in the European Union. *PLoS One*. 2017;12(2):e0172753.
[56] Zaprutko T, Kopciuch D, Kus K, et al. Affordability of medicines in the European Union. *PLoS One*. 2017;12(2):e0172753
[57] European Commission, Directorate-General for Health and Food Safety, Jongh, T., Becker, D., Boulestreau, M., et al., *Future-proofing pharmaceutical legislation: study on medicine shortages : final report (revised)*, 2021, https://data.europa.eu/doi/10.2875/211485.
[58] Anklam et al., 2022

obligations such as MA renewals. In addition, there is duplication of assessment by the medicines authorities, for instance when different companies apply for authorisation of the same product with the same clinical trial in different procedures. There is inadequate pan-European digital infrastructure and insufficient legal basis for optimal use of electronic tools for companies or medicine authorities.

Another important problem driver is **the lack of relevant environmental expertise, regulation and oversight**. For example, if risk associated with API discharges from manufacturing sites is included in the Environmental Risk Assessment (ERA) accompanying MA applications, it would increase the relevance of the assessments.[59] However, predicting environmental concentrations of pharmaceuticals and thus environmental risk for emission routes such as production of APIs and formulation is difficult, [60] and the full extent of any risk will only be known once full scale production happens, but this requires an MA. Moreover, for some pharmaceuticals, as high as 90% of the active ingredient is excreted or washed off into the environment in its original form during use by patients.[61] This means conditions of use of medicines may need to be tightened and enforced, requiring oversight from public authorities. It should also be noted however that other policy instruments beyond the general pharmaceutical legislation may also play a role to reduce the environmental footprint of industry and environmental residues.

### *2.3 How likely is the problem to persist?*

The Pharmaceutical Strategy for Europe (2020) is an attempt to respond to current problems and problem drivers. The strategy also foresees evaluation of the performance of the current regulatory system to substantiate any potential changes needed to make the future system more patient-centred, future-proof, and crisis-resistant[62,63]. The European Commission has started building a stronger European Health Union, in which all EU countries prepare and respond together to health crises; innovative, safe and effective medicines are available at an affordable cost; and countries work together to improve prevention, treatment and aftercare for diseases such as cancer. Alongside this more general appreciation of a fast-changing world, our consultations and desk research have considered the likely future evolution of the specific problems identified.

Without incentives to address UMN and developing appropriate treatments (including against antimicrobial resistant pathogens), future **EU public health is at risk**. The current EU general pharmaceutical legislation includes no specific incentives or obligations to encourage the development of or prudent use of antimicrobials. The WHO Global Observatory on Health Research and Development monitors antibacterial products in development, and its April 2021 dashboard[64] shows that as of September 2020, there was a total of 41 antibiotics and 27 non-traditional antibacterial agents in clinical development globally. Those 68 products are distributed across the three phases of clinical trials. Overall, the WHO concludes that the clinical pipeline and recently approved antibiotics are insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance. Drug-resistant diseases already cause at least 700,000 deaths globally a year, including 230,000 deaths from multidrug-resistant tuberculosis, a figure that could increase to 10 million deaths globally per year by 2050 under the most alarming scenario if no action is taken[65]. Furthermore, demographic changes and environmental challenges could create new unmet medical needs and public health burdens, so interventions are needed on several fronts, including the general pharmaceutical legislation, to address market failures in this area.

Despite the presence of an EU internal market, more is needed to reduce the highly uneven access to medicines in the EU. As already discussed, smaller and low-price markets typically experience the greatest problems with access as these markets are commercially unattractive to marketing authorisation holders (MAHs). It is expected that without intervention, such problems will persist and may even worsen. The result is that **some patients across the EU will receive delayed or sub-optimal treatment for their diseases or conditions**. The COVID-19 pandemic demonstrated this when sudden high demand for products used in the treatment of COVID-19 patients, coupled with disruptions to global supply chains, temporarily threatened access to critical medicines. As such, authorised medicines may continue to be inaccessible if prices are unaffordable.

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[59] Eeb. (2018). Policy options for regulating pharmaceuticals in the environment.
[60] Marlene Ågerstrand, Cecilia Berg, Berndt Björlenius, Magnus Breitholtz, Björn Brunström, Jerker Fick, Lina Gunnarsson, D. G. Joakim Larsson, John P. Sumpter, Mats Tysklind, and Christina Rudén (2015). Improving Environmental Risk Assessment of Human Pharmaceuticals. *Environmental Science & Technology 49* (9), 5336-5345
[61] European Commission, 2019. European Union Strategic Approach to Pharmaceuticals in the Environment.
[62] Ratanawijitrasin, S. and E. Wondemagegnebu (2002). Effective Drug Regulation: A Multicountry Study. Albany, Switzerland, WHO.
[63] Coglianese C. Measuring regulatory performance. Evaluating the impact of regulation and policy. Organisation for Economic Co-operation and Development (OECD). Expert Paper No. 1; August 2012. Available at http://www.oecd.org/gov/regulatory-policy/1_coglianese%20web.pdf.
[64] https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antibacterial-products-in-clinical-development-for-priority-pathogens
[65] No time to wait: Securing the future from drug-resistant infections, Report to the UN Secretary-General, April 2019

However, many complementary actions outside this legislation have to be taken to address these problems[66].

The pandemic also focused attention on the EU's ability to forecast demand, secure supplies and manage shortages of critical medicines going forwards[67]. There is an assumption that public health crises are highly likely to occur in future and that against the backdrop of a growing problem with medicines shortages more generally, there is a clear case for more concerted action at the EU level. Moreover, learning from this exceptional experience, the EU has identified two issues that are more generally applicable, one of which tends to reduce effective capacity and the other amounts to a potential missed opportunity: there is a concern over the implications for EMA resourcing and timeliness of immature MAH applications; and a recognition of the potential value in earlier dialogue with developers through rolling review regulatory assessments for innovative new products of relevance to unmet needs. To strengthen the resilience of pharmaceutical value chains many EU countries are looking for strategies to encourage diversification and potentially reshore pharmaceutical manufacturing to Europe. Without action, lack of affordability and shortages of medicines will **severely burden healthcare systems and healthcare professionals** through unsustainable healthcare costs and inability to offer medicines to EU citizens that need them.

The **damage to environment and emerging health threats (including AMR)** will also become worse without action. Studies have shown direct effects on wildlife, even at a low concentration, from some pharmaceuticals that persist in the environment, but there is not enough evidence to directly link pharmaceutical residues found in drinking water to human health.[68] However, the potential effect of long-term exposure on EU populations and the environment cannot be ignored.

Biomedical research and innovation are happening at a blistering pace. Gene editing, pharmacogenomics, artificial intelligence and big data-driven precision medicine, to name a few, are greatly advancing the promise of and opportunities in health and life sciences.[69] However, society will not harvest the benefits of these technological and scientific advances at a pace consonant with their promise without a simultaneous advance in the development of the regulatory framework. In a world of fast paced technology and rapidly changing conditions, regulatory systems too must be flexible so they can adapt and respond to changes in the systems they seek to control.[70] Importantly, the regulatory system should continue to enable the availability of innovative medicines, with a view to improve public health, but also to foster economic growth. More flexible regulatory approaches, where regulatory density is adapted according to complexity and uncertainties about medicinal products have been proposed as ways forward.[71] Without addressing these problems, **unnecessary costs for developers and regulators** (as outlined in the previous section) will continue to occur, ultimately **reducing global attractiveness of the EU pharmaceutical system**.

[66] E.g. best practice exchange between Member States on pricing, payment and procurement policies.
[67] https://www.ema.europa.eu/en/documents/other/reflection-paper-forecasting-demand-medicinal-products-eu/eea_en.pdf https://www.ema.europa.eu/en/documents/other/reflection-paper-forecasting-demand-medicinal-products-eu/eea_en.pdf
[68] Eeb. (2018). Policy options for regulating pharmaceuticals in the environment.
[69] EMA (2018) "EMA Regulatory Science to 2025 Strategic reflection (EMA/872479/2018), London: European Medicines Agency.
[70] Duit, A., V. Galaz, K. Eckerberg and J. Ebbesson (2010). "Governance, complexity, and resilience." Global Environmental Change 20(3): 363-368.
[71] Klein L, Stolk P, De Bruin ML, Leufkens HG. Regulatory density as a means to refine current regulatory approaches for increasingly complex medicines. Drug Discov Today 2021; 1359-6446.

# 3 WHY SHOULD THE EU ACT?

## *3.1 Legal basis*

The cornerstone of the European regulatory system for medicines was put in place in 1965 with Directive 65/65/EC,[72] which mandated the dual principles of public health protection and the free movement of products within the EU. The general pharmaceutical legislation is based on Articles 114 and 168 of the Treaty on the Functioning of the European Union (TFEU). These articles provide the legal basis for the EU to adopt measures which have as their object the establishment and functioning of the internal market (Article 114(1)) as well as setting high standards of quality and safety of medicinal products (Article 168(4)(c)). While the internal market and common safety concerns in public health matters fall within the shared competence of the EU and Member States, a harmonised EU legislation, such as the general pharmaceutical legislation, means that Member States can no longer exercise their own competence. Any future legislative proposals will also be based on Articles 114(1) and 168(4)(c) TFEU. They will also consider Article 35 of the EU Charter of Fundamental Rights that provides that the Union is to ensure a high level of human health protection in the definition and implementation of Union policies.

The pan-European regulatory system for medicines has evolved in line with changing social and technological developments and its scope has been expanded over time, aimed at ensuring a high level of protection of public health. It is based on the principle that the placing of a medicine on the market is subject to the granting of a marketing authorisation by the competent authorities.

The European Medicines Agency (EMA) is the principal EU-level regulatory body for medicines. Its Committee for Medicinal Products for Human Use (CHMP) is responsible for the scientific evaluation of applications for EU marketing authorisations, which it does in part using the resources of Member States.[73] Ultimately, the European Commission (EC) is responsible for the granting of EU marketing authorisations. The EC has also taken a lead in defining policy in this area, which it does in consultation with the EU Pharmaceutical Committee, which consists of senior experts in public health matters from the Member States' administrations and is chaired by a Commission representative.[74]

The EU legislation works in concert with member states' National Competent Authorities (NCAs) and a portfolio of related national legislation in areas ranging from health technology assessment (to determine the (cost-)effectiveness of new medicines against standard treatments in the specific national context) to reimbursement. NCAs regulate medicines approved by national procedures, the decentralised procedure and the mutual recognition procedure, and are also largely responsible for enforcement of the conditions set out in the EU general pharmaceutical legislation.

## *3.2 Subsidiarity: Necessity of EU action*

Member States (MSs) would struggle to achieve equivalent levels of safety and efficacy of authorised medicines were they to act by themselves, and this would be especially challenging given the longstanding investments made in EU structures and coordination mechanisms. It would be extremely costly for individual MSs to build up their national structures to anywhere near the capacity and quality of the EU infrastructure. Moreover, such a policy would likely result in significant unevenness across MSs, with the larger EU countries more likely on average to be able to fund the establishment of equivalent national regulatory systems. Smaller MSs may struggle disproportionately, as there would be minimum requirements for new investment and capability development that may be harder to fund. Smaller MSs already rely to some extent on their larger neighbours, through the Mutual Recognition Procedure / Decentralised Procedure (MRP / DCP). Perhaps more importantly, switching to a more distributed approach would run counter to recent developments within the current regulatory system, with a probable increase in the application of different standards, losses of overall system efficiency and a likely backward step in the safety and quality of medicines.

While the EU market for medicines falls some way short of being a 'single market,' a move back to national legislation would be likely to make matters worse rather than better. There have been important economies of scale through harmonisation; whereby the regulatory objectives can be met more efficiently through EU level actions. While the legislation respects Member States' exclusive

[72] European Commission (EC). Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31965L0065&from=EN.
[73] https://www.ema.europa.eu/en/about-us/what-we-do/legal-framework
[74] https://ec.europa.eu/health/medicinal-products/pharmaceutical-committee-veterinary-pharmaceutical-committee-and-expert-groups_en

competence in the provision of health services, including pricing and reimbursement policies and decisions as well as prescription of medicines, common provisions for the authorisation of medicines constitute a cross-border issue for public health that affects all Member States and thus can effectively be regulated only at EU level. National actions are likely to lead to fragmentation, and possibly exacerbate some of the problems, distort competition and increase administrative burden for the pharmaceutical companies, which often operate in more than one Member State. An example of fragmentation is the additional and non-harmonised measures introduced by Member States to prevent and mitigate medicines shortages[75].

### *3.3 Subsidiarity: Added value of EU action*

In terms of added value, the evaluation revealed that the 2004 revisions to the legislation had delivered important benefits as a result of EU level actions that would not have been realised through the efforts of NCAs working alone or in smaller groupings. The major improvements include:

- The expansion in the scope of the centralised procedure (CP) and resulting enhancement in the overall speed and consistency of assessments and improved access to high level scientific expertise. The CP is compulsory for high-technology medicinal products, particularly those resulting from biotechnical processes, in order to maintain the high level of scientific evaluation of these medicinal products in the European Union and thus to preserve the confidence of patients and the medical professions in the evaluation. This is particularly important in the context of the emergence of new therapies, such as gene therapy and associated cell therapies, and xenogenic somatic therapy. This approach should be maintained, particularly with a view to ensuring the effective operation of the internal market in the pharmaceutical sector.

- The European Medicines Agency (EMA) has been key actor in the unification and coordination of the regulatory system across the EU. In particular, coordination of EU regulatory networks has provided valuable exchange of experience and access to a wide range of scientific and technical expertise, which would not be available in one country or region alone. Furthermore, the establishment of EMA has greatly improved transparency on how the regulatory system works and decisions are made, thus building trust and consistency across the EU regulatory system.

- EU-level coordination and cooperation has helped establish the EU has a global leader in regulatory practices, exemplified by the EU establishing the first science-based regulatory framework for authorisation of high-quality, safe and effective biosimilar medicines: resulting in a comparative advantage for the EU which accounted for approximately 70% of the world's biosimilar authorisations between 2006 and 2010. Biosimilar medicines have created competition in the internal market, broadening patients' access to advanced treatments at more affordable prices and alleviating healthcare costs.

- EU action during the COVID-19 crisis was a particularly value-added intervention, enabling quicker and concerted action compared to what MSs would have been able to achieve independently. The EU-level cooperation prevented duplication of efforts and facilitated rapid mobilisation of resources, capabilities, and expertise across the EU to tackle the pandemic ensuring supply chains continued to function and EU citizens had timely access to vaccines and medicines.

The problems researched for this impact assessment all have an EU dimension, where a further EU policy response can be expected to mitigate or resolve that problem more effectively and more efficiently than would be the case were the response left to individual MSs alone. However, it must be noted that national pricing and reimbursement decisions as well as business decisions about R&D and where to launch their products will modulate the effect achieved by EU action. Areas where EU level action can bring added value are listed below.

- The overarching regulation by the EU of new medicines means the provision of EU-level regulatory incentives can catalyse innovation to a degree that is not possible through national support measures alone.[76]

[75] European Commission, Directorate-General for Health and Food Safety, Jongh, T., Becker, D., Boulestreau, M., et al., Future-proofing pharmaceutical legislation : study on medicine shortages : final report (revised), 2021, https://data.europa.eu/doi/10.2875/211485
[76] https://ec.europa.eu/health/medicinal-products/pharmaceutical-strategy-europe_en

- The EU has been working to combat the growing challenge of antimicrobial resistance since the 1990s and continues to coordinate EU-wide actions through the EU One Health Action Plan against AMR.[77] Moreover, the EU has played an important role in helping to coordinate global efforts.[78] In addition, the 2020 Pharmaceutical Strategy for Europe highlights the importance of AMR in the context of unmet medical needs (UMN) and commits to review the pharmaceutical legislation with the aim of restricting and optimising the use of antimicrobial medicines.
- In principle, the provision of health care – including pharmaceutical care – is a national competency for the EU Member States. National factors that influence a market's commercial attractiveness for MAHs, such as market size, pricing and reimbursement policies or procurement practices, are outside of the mandate of the EU. Nonetheless, the EC can encourage greater access by making access to EU instruments or incentives conditional on fulfilment of certain market placement criteria.
- EU level action can promote faster market entry of generics and biosimilars via actions associated with marketing authorisations (i.e. streamlined pathways, shorter approval times), incentives for developers and measures such as the Bolar exemption that promote R&D activity in the context of regulatory and intellectual property protection.
- The EU, in particular through the EMA, plays a role in facilitating the exchange of information about shortages between countries. This, in turn, enables countries to better understand the underlying causes of shortages, as well as have an overview of available supplies. For essential and critical medicines, the EC could also play a role in coordinating joint procurement and warehousing of supplies.
- The revision provides opportunities to align (and thus create synergies) with actions proposed in the European Union Strategic Approach to Pharmaceuticals in the Environment.[79]
- While GMP inspections are conducted by NCAs, greater guidance, coordination, and work sharing at the EU level can help to harmonise practices and make them more consistent. It also helps in reducing duplication, facilitating data sharing/transparency and saving resources while enhancing supervision.
- The EMA and the Committee for Advanced Therapies (CAT) is best placed to address classification issues around Advanced Therapy Medicinal Products (ATMPs) that are highly innovative and complex medicines based on genes, tissue or cells. The classification challenges are further complicated by the fact that the *donation* of blood, tissues and cells (BTC) always falls under the BTC legislation; whereas for the subsequent steps of processing and application, there can be difficulties/differences at MS level distinguishing between BTC and medicines partly on the basis of the presence or not of an industrial process, no definition of which currently exists[80] [81]. The recent evaluation and impact assessment of the EU legislation on Blood Tissues and Cells (BTC) recently[82] described the high magnitude of concerns on legal clarity, how these issues are driven by the borderline criteria set in the pharmaceutical legislation ('industrial process,' intention to place on the market', hospital exemption) and the possible impact of these issues including on cost and access. This BTC impact assessment underlined that it is critical that there are alignments between these 2 legal frameworks.
- Regulatory efficiency is a key aim in the Pharmaceutical strategy for Europe. With the dual system for MAs, the Commission is able to explore with Heads of Medicines Agencies (HMA) and the EMA options to streamline and harmonise MA procedures. Moreover, through the HMA networks and working with other Directorate Generals, there are opportunities for the Commission to lead on harmonisation of procedures, creating coherence between different legislations, looking for areas for work-sharing with NCAs, etc., thus helping to decrease duplication, legal/regulatory uncertainty and inefficiencies.

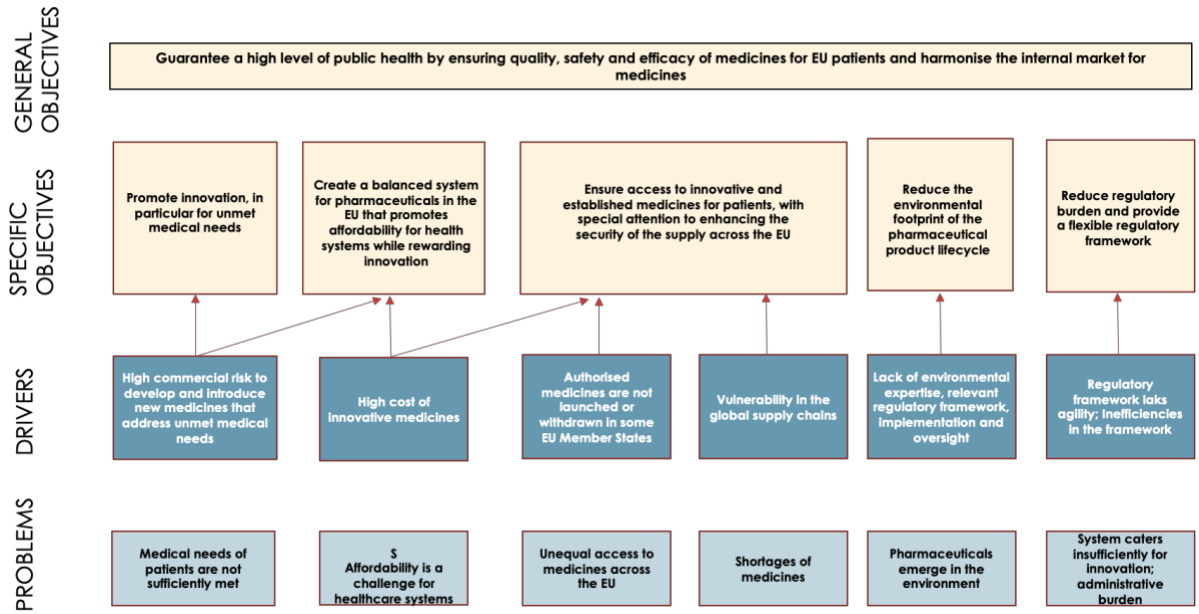
[77] https://ec.europa.eu/health/antimicrobial-resistance/eu-action-antimicrobial-resistance_en
[78] https://eu-jamrai.eu/
[79] European Commission, 2019. European Union Strategic Approach to Pharmaceuticals in the Environment
[80] (European Commission & Directorate-General for Health and Food Safety, 2018)
[81] (Anker Mikkelsen et al., 2020)
[82] (European Commission & Directorate-General for Health and Food Safety, 2018)

# 4 OBJECTIVES: WHAT IS TO BE ACHIEVED?

## *4.1 Introduction*

This chapter sets out the general and specific objectives as well as the intervention logic (Figure 2) for the revisions to the legislation, which will address the problems identified, and provide a focus for assessing and comparing the likely cost-effectiveness of the selected policy options. The two legislations constituting the general legislation make up a single intervention logic in this policy area.

**Figure 2 Intervention logic for the general and specific objectives, problem drivers and problems**




## *4.2 General objectives*

The general objective of the revision is unchanged from previous versions in that the general pharmaceutical legislation aims to "guarantee a high level of public health by ensuring the quality, safety and efficacy of medicines for EU patients" and harmonise the internal market.

## *4.3 Specific objectives*

The specific objectives of the revision will be to

**(1) Promote innovation, in particular for unmet medical needs**

This objective aims to promote the development of medicines that address UMN. It aims to incentivise innovation to enable major therapeutic advances that tackle conditions that are not yet addressed and represent a significant EU health burden. This will not only ensure a pipeline of innovative new medicines for use across the EU is maintained, but will also support pharmaceutical R&D and hopefully strengthen the competitiveness of the research-based EU pharmaceutical sectors.

**(2) Create a balanced system for the pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation**

This objective aims to promote affordability of medicines across the EU healthcare system such that there is competition and healthcare costs are sustainable for Member States. However, affordability should not be promoted at the expense of innovation. Thus, the underlying ambition is to create a balance in the EU pharmaceutical system where innovation is rewarded, for example through incentives such as added regulatory data protection which allows greater return on investment for originators over a specified period through exclusive prices. On the other hand, the ambition is also to facilitate faster market entry of generics and biosimilars as a means to improve competition across the EU and drive down the costs for medicines beyond regulatory or patent protection, while also strengthening the EU generics and biosimilar industry.

**(3) Ensure access to innovative and established medicines for patients, with special attention to enhancing security of the supply across the EU**

This objective aims to promote equal access to medicines for all EU citizens, with a strong focus on preventing and addressing shortages of medicines. A combination of incentives to increase placement of medicines on all, or a majority of, EU markets, obligations to support market placement for centrally authorised products, and disincentives for limited market placement through removal of protections against competition are interventions that could facilitate authorised medicines being launched across the EU and prevent their withdrawal. Improving the quality and quantity of data on medicine shortages, through adoption of common definitions and standardised data collection across all EU Member States is expected to help safeguard the continued and sufficient availability of medicines to patients.

**(4) Reduce the environmental footprint of the pharmaceutical product lifecycle**

This objective aims to enhance environmental sustainability of pharmaceuticals through minimising emission of pharmaceutical through their production, use, and disposal. This would entail strengthening the environmental risk assessment (ERA) and robust assessment of the environmental risks of pharmaceuticals as well as promoting prudent use of pharmaceuticals such as antimicrobials, supporting sustainable consumption and manufacturing.

**(5) Reduce the regulatory burden and provide a flexible regulatory framework**

This objective aims to create a flexible regulatory framework to futureproof innovation and reduce regulatory burden. Through simplifying regulatory requirements and pathways and creating reducing burden for industry and public authorities alike, this objective aims to increase the regulatory attractiveness of the EU. Where possible, the goal is to provide clarity on the appropriate regulatory pathway, reduce regulatory approval times and regulatory costs while maintaining the high standards and robust assessment of the quality, safety, and efficacy of medicines. Leveraging digital technology and the use of electronic product information could support this objective.

It is envisaged that objectives 1, 2 and 5 will work in synergy and promote innovation while objectives 2, 3 and 5 through a range of measures will help to achieve access to affordable medicines. Trade-offs have to be considered between interventions under objectives 4 and 5 as measures to reduce the environmental footprint are likely to increase the administrative burden. Similarly, trade-offs will also have to be considered between measures undertaken to achieve objectives 3 and 5 as new or modified obligations with regard to reporting or mitigating medicine shortages may increase administrative burden for businesses and regulators. Trade-offs are also inherent in objective 2 between rewarding innovation in medicines through extra regulatory protection and achieving affordability through generic/biosimilar competition as well as achieving access (objective 3) possibly through additional market launches, which might involve additional costs and thus impact affordability (objective 2).

The specific objectives are consistent with Green Deal and Digital agenda and with the right of access to preventive health care and the right to benefit from medical treatment set out in the EU Charter of fundamental rights. The objectives provide the reference point for our proposals for monitoring and evaluating the legislative actions that are expected to be implemented to accompany the preferred option.

# 5 WHAT ARE THE AVAILABLE POLICY OPTIONS?

## *5.1 What is the baseline from which options are assessed?*

The baseline is represented by the business-as-usual scenario, that is, the situation if no policy changes were made. All current incentives, policies and procedures would be retained.

Currently, regulatory protection in the form of 8 years data protection and 2 years of market protection is the standard incentive with additional 1 year of data protection for new indications representing significant public health benefits. These protections allow developers to recoup their investment by delaying the entry of generic or biosimilar medicines.

The current legislation also provides an additional 1 year regulatory market protection for a new indication with a significant clinical benefit, allowing thus a maximum of 11-year regulatory protection. The current revision does not consider changing this incentive. Therefore, this incentive is not presented in the options.

There are no special incentives or obligations for the development of or prudent use of antimicrobials, development of new antimicrobials or prudent use of existing ones, neither for conducting or to be transparent about public contribution to R&D costs.

At present, there are no incentives or obligations on MAHs to place their products on markets that, on their own, do not offer a sufficient business case for doing so. The only legal provision, known as the 'sunset clause', is that the MA will cease to be valid if a medicine is not placed on any EU market within three years of the authorisation being granted or if the medicine is removed from the market for three consecutive years. This provision, however, is satisfied by placement on a single EU market.

The EU pharmaceutical legislation currently has two provisions that directly connect to security of supply. The first (Article 23a) places an obligation on MAHs to notify NCAs in the relevant MSs if they expect a temporary or permanent withdrawal of an authorised medicine from an EU market. The second (Article 81) obliges MAHs and wholesalers to ensure appropriate and continued supplies of authorised medicines. Both articles need to be transposed into national legislation by the Member States, who may opt to add more specific requirements. To improve the collection and standardisation of information on shortages across the EU, in 2019 the EMA/HMA published a 'Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)[83]. The guidance includes a template detailing what information should be included. However, many elements are not mandatory and, thus far, are not required by NCAs.

The ERA is the main mechanism within the current legislation for ensuring environmental sustainability of pharmaceuticals. It is required for all new MA applications whether through a centralised, mutual recognition, decentralised or national procedure and ensures the potential environmental risks of pharmaceuticals are adequately assessed. While the outcome of the ERA does not affect the decision to award an MA, it serves as the basis for minimising the amount of pharmaceuticals released into the environment (using appropriate measures), identification of specific risk-minimisation activities to be undertaken by the user of the medicine and appropriate labelling to ensure correct disposal.[84]

## *5.2 Description of the policy options*

The policy options represent a range of policy measures covering policy dimensions such as innovation, particularly for UMN; antimicrobial resistance (AMR); improving access, security of supply and competition for medicines; addressing challenges related to the environmental footprint, quality and manufacturing of medicines; and future-proofing the regulatory system. The main differences in the policy options and the measures therein are described in the sections below. There are key pivotal measures among these that represent the greatest change and impact compared to the current system which will be the focus of this impact assessment (Table 1). The Policy Options address the specific objectives and the underlying problem drivers to different extents, which is also discussed in the sections below. How the pivotal measures map on to the specific objectives is shown in Table 1.

[83] European Medicines Agency. (2019). *Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)*.
[84] EMA. (n.d.). Environmental risk-assessment of medicines.

**Table 1 Mapping of pivotal measures to objectives**

| Objective | Baseline | Option A | Option B | Option C |
|---|---|---|---|---|
| Promote innovation, in particular for unmet medical needs | 8 years DP +2 years MP (+1 year additional DP for new indication with significant benefit)<br><br>No special incentives for the development of antimicrobials | 8 years DP +2 years MP for all medicines<br><br>Special incentive bonus for medicines that address UMN (+1 year DP) or include comparative trials (+6 months DP)<br><br>Transferable vouchers for antimicrobial products | Standard protection for all originators: 6 years DP +2 years MP<br><br>Special incentive for originators that address UMN (+2 years DP)<br><br>Pay or play model for antimicrobial products | Standard protection for all originators: 6 years DP +2 years MP if all EU markets covered<br><br>Special incentive bonus for medicines that address UMN (+1 year DP) or include comparative trials (+6 months DP)<br><br>Transferable vouchers for antimicrobial products |
| Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation | Not applicable | No provision | Require public transparency on any relevant public contribution or funding, including of research and development costs | Require transparency on public contribution to R&D costs in relation to clinical trials included in the MA application |
| Ensure access to innovative and established medicines for patients with special attention to enhancing security of supply across the EU | Currently no obligation or incentive to launch in a particular or group of MS<br><br>Obligation to notify a withdrawal 2 months before the interruption in market supply of the product | Additional protection period if centrally authorised product is placed on market in all MSs within 6 years of the MA (milestone incentive); and allow generic competition if not launched in majority of MS within 5 years of MA (disincentive)<br><br>Notification requirement same as in baseline | Obligation to place a centrally authorised medicine on the market in the majority of MS (small markets included)<br><br>Notification requirement same as in baseline | If a medicinal product is appropriately and continuously supplied in all EU markets within 2 years after MA (and not withdrawn before the additional exclusivity kicks in), the product receives additional 2 years of DP (milestone incentive)<br><br>Notification period of 12 months for withdrawals for all medicines that have been on the market for more than 2 years and of up to 6 months or as soon as a serious shortage risk is identified for all other shortages<br><br>Shortage prevention and mitigation plans for all medicines<br><br>Stockpiling requirement for critical medicines<br><br>Increase transparency of the supply chain, and provide detailed information upon request of national authorities or EMA<br><br>Monitoring of shortages is reinforced but remains with MS with establishment of a mechanism of information exchange |
| Reduce environmental footprint of the pharmaceutical product lifecycle | An ERA is required for all new MA applications for a medicinal product through a centralised, mutual recognition, decentralised or national procedure. Potential risks from medicines to the environment are assessed by regulators and precautionary measures or recommendations are issued | Same as baseline ERA | No legislative change; Continue the implementation of the actions under the EU Strategic approach to pharmaceuticals in the environment | Strengthen the ERA requirements and conditions of use for medicines<br><br>Include assessment of the environmental risk of manufacturing into ERA<br><br>Include AMR aspects in GMPs |

Notes: AMR=antimicrobial resistance; DP=data protection; EMA/HMA= European Medicines Agency/Heads of Medicines Agencies; ERA= environmental risk assessment; GMP=good manufacturing practice; MA= marketing application; MP=market protection; MS=member state; R&D=research and development; UMN=unmet medical needs

### 5.2.1 Policy Option A

Option A keeps the incentives at the same level as the current legislation and uses additional ones to address UMN and to support public health objectives. The main difference compared to the other two options is that this option addresses challenges through stronger enforcement of existing obligations and informational requirements rather than setting further obligations.

Support for innovation under Policy Option A would maintain the current system of regulatory incentives (8 years data + 2 years market protection), supplemented by targeted incentives (such as additional 1 year of regulatory data protection for products addressing UMN) to stimulate innovation. It also foresees the introduction of a new bonus incentive to stimulate developers to conduct comparative trials, which will tend to provide a more robust evidence base for the assessment of the safety and effectiveness of new treatments.

The measures to stimulate the development of antimicrobials include novel incentives, including transferable vouchers (transfer right to extend regulatory protection period for another product marketed by the same or another company), a measure proposed widely by industry as a way to underpin the substantial R&D costs of bringing new classes of antimicrobials to the market and previously explored as an instrument in the Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections.[85] This will be supported by a measure to harmonise the summary of product characteristics for nationally authorised antimicrobials to support prescription practices.

Policy Option A promotes access with a targeted bonus of an additional 6 months of regulatory protection if a product is placed on the market in all MSs within 5 years of MA (milestone incentive). The rationale behind the measure is that MAHs can be encouraged to increase the number of markets in which they launch products or accelerate the time frame within which they do so, by offering them a reward in exchange. The proposed incentive takes the form of extended regulatory protection that delays generic competition.

Measures on security of supply retain the current requirement for notifications of withdrawals (at least two months in advance). No changes are envisaged in terms of changes to the Bolar exemption or duplicate marketing authorisation regimes to increase choice and competition and thereby improve access, security of supply and affordability of medicines.

The current ERA regime continues with an obligation to include the information on the environmental status of supply chain actors in the application dossier. The latter proposal is part of the package of suggestions to support quality and manufacturing aspects for medicinal products along with a harmonised system of sanctions and accommodating new manufacturing methods within the legislation.

Option A will also support voluntary inclusion of new indications (repurposing) for off-patent medicines by companies through the pro-active assessment by regulators of promising data coming from academia and NGOs that is put at the disposition of the marketing authorisation holder.

Overall, Option A addresses all of the specific objectives, but since it does not mark a major departure from the baseline it is expected to be comparatively less effective in addressing the problem drivers that currently exist in the landscape except for the barrier to development of new medicines to address UMNs. Through longer standard regulatory protection and a special incentive bonus for addressing an UMN or conducting comparative trials and transferrable vouchers for developers of new antimicrobials, Option A offers attractive incentives to promote innovation, particularly for UMN.

### 5.2.2 Policy Option B

Option B uses more obligations to address the specific objectives rather than incentives. This option explores stronger monitoring mechanisms and increased obligations with interventions at different milestones of the lifecycle of a medicine with the aim of fostering access, affordability and security of supply of medicines. Incentives are adapted to reward innovation in areas of unmet needs and to promote transparency of investment costs.

Policy Option B introduces a modulated system of incentives, with a reduction in the current standard regulatory protection periods. Under this option, standard protection for all originator medicines would consist of 6 years of data protection and 2 years of market protection. New originator products with a demonstrated ability to address UMN can avail of strengthened protection (additional 2 years of data protection) compared to the standard. Other medicines will be entitled to strengthened protection only if they can demonstrate no return on investment in view of investment costs,

[85] https://eu-jamrai.eu/wp-content/uploads/2021/07/1.3.1_Policy_brief_Improving_access_to_essential_antibiotic.pdf

including for research and development. Furthermore, all MA applicants will be required to publicly disclose any relevant public funding received (transparency).

Option B also encourages development of antimicrobials through novel incentives. It introduces a pay or play model. Either a company holds an antimicrobial in its portfolio, or it pays into a fund for financing the development of novel antimicrobials. It includes measures for prudent use of antimicrobials including monitoring consumption, optimising package sizes and stricter rules for the use and disposal of human antimicrobials.

Access measures in Option B consist primarily of an obligation to launch centrally authorised medicines on the market in a majority of MSs (small markets included) within a 5 years. If the obligation is not fulfilled, the medicine loses its regulatory protection, and generics are allowed to enter the market.

Measures on security of supply encourage EU coordination for exchange of information and use existing guidelines and systems, such as the EU medicines verification system (EMVS; developed for the Falsified Medicines Directive) to track supply, and measures to increase manufacturers' responsibilities to ensure supply. The notification period for withdrawals remains identical to the baseline and MAHs are obliged to offer their MA for transfer to another MAH in case of withdrawals from the market.

The ERA requirements remain the same with no legislative change but this will be complemented by stronger overall responsibilities of MAHs vis a vis suppliers and improving oversight of sites through modification of provisions on inspections and a mandatory joint audit scheme for member state GMP and GDP inspections.

Other measures incorporated in Option B include possibility for regulators to impose a post-authorisation obligation for comparative studies on the effectiveness of a given medicine compared with the standard of care, codification of rolling reviews beyond crisis-related medicines, and measures to future-proof the regulatory system by reviewing the scope and definition of products that need to be accommodated under the general pharmaceutical legislation and simplifying/clarifying the regulatory framework for certain categories of medicinal products (e.g. borderline products).

Within this option, additional measures have been introduced to support competition and thereby improve access to and affordability of medicines. Anti-competitive practices such as introducing by the originator a copy of a biological medicine (auto-biological) through duplicate marketing authorisations are restricted or no longer possible, interchangeability of biosimilars with their reference product will be scientifically assessed as part of the product assessment and the Bolar exemption will be broadened to more actors and beyond generics.

Option B addresses a greater number of problem drivers (and thus specific objectives) more directly than Option A. Measures to improve transparency of R&D costs and competition target the high cost of innovative medicines, while regulatory protection periods (standard and strengthened) and the 'pay or play' promote innovation. Environmental challenges are addressed to a greater extent compared to the baseline through prudent use measures for antimicrobials, while future-proofing measures provide greater flexibility to the regulatory framework. Security of supply measures do not mark a great departure from the baseline but involve more coordinated monitoring and exchange of information on shortages, while access is promoted through an obligation to put a product on the market rather than an incentive or penalty. As such, Option B could be considered less effective in addressing the specific objective related to ensuring access to medicines.

### 5.2.3 Policy Option C

Option C applies a modulated 'quid pro quo approach.' The incentives systems in options B and C are similar. However, unlike option B, access and availability will be addressed with disincentives and rewards rather than obligations. Measures supporting innovation include stronger incentives targeting unmet needs, increased obligations and strengthened market conditions for competition to foster access, affordability and security of supply of medicines. Transparency on public contribution to the costs of clinical trials will be required for all medicines.

The standard protection for originator products in option C is as in option B (6 years data protection and 2 years market protection). The strengthened protection (additional 1 year data protection) applies to originator medicines addressing an UMN and there is a special bonus incentive (6 months) to stimulate developers to conduct comparative trials.

On AMR, option C is similar to option B, with a strong emphasis on prudent use measures with some differences – (1) no mandatory use of diagnostics prior to use of antimicrobials or stricter rules for disposal, but (2) introduction of requirement for AMR management plan from MAHs. To incentivise development of new microbials, there is a possibility to introduce transferrable vouchers (transfer right to extend regulatory protection period for another product marketed by the same or another company) for developers.

Access is promoted by incentivising market placement in all Member States. If a product is placed on all EU markets within 2 years of authorisation and appropriately and continuously supplied, unless it is demonstrated a MS does not wish to be supplied, the product receives 2 years of additional data protection. This incentive is granted only if the product is not withdrawn prior to the expiration of the normal exclusivity period. The option also foresees a requirement to include small markets in national authorisation procedures, as in option B.

With respect to security of supply, in addition to an EU definition of shortages, critical shortages and critical medicines, option C measures include a balance of EU-level and Member State-level actions to mitigate and prevent shortages and build on the shortage provisions in the EMA reinforced role legislation (EU 123/2022). The approach to reporting shortages is harmonised across the EU, while monitoring of supply remains with Member States and only critical shortages are escalated to EU-level. As with option B, support to the management of shortages is increased through earlier, harmonised reporting on shortages. There is information sharing by Member States on critical shortages and supply chain vulnerabilities. More action by stakeholders is required through shortage mitigation and prevention plans, diversification of supply chains and requirements for maintaining reserve stocks for unfinished critical medicines, as appropriate. Requirements for increased transparency of supply chains are introduced.

The ERA requirements and conditions of use for medicines are strengthened. This option also foresees the inclusion of AMR environmental aspects into GMP and assessment of the environmental risk of manufacturing in the ERA.

On quality and manufacturing, option C foresees stronger oversight of manufacturing supply chains through changes to inspections (both scope and provisions), enhanced Member State cooperation (joint audits), introduction of new IT tools for regulatory cooperation and increased EMA coordination of inspections. Key measures to promote competition in Option B are retained in Option C such as provision of information on and scientific assessment of interchangeability of biosimilars as well as the broadening of the Bolar exemption and restricting duplicate MAs to cases of intellectual property protection or co-marketing.

The changes to the scope, definitions and classification advice with regard to medicinal products would be similar to option B. However, with regard to the regulatory framework, this option foresees the inclusion of a legal basis to explore sandbox environments (i.e. a structured form of testing before formal regulation) which would more readily accommodate innovation in breakthrough areas and create a more flexible regulatory environment.

Option C could be considered the most effective in addressing the specific objectives of the revision of the general pharmaceutical legislation. It offers incentives to promote development of originator products addressing UMN and AMR (similar to Option A), measures to promote transparency of R&D costs (at least for clinical trials) and competition (similar to Option B), and incentives for promoting access to medicines in all EU MSs. It introduces more measures to address security of supply issues and environmental challenges compared to the other two options. For instance, there are more obligations to support prevention and mitigation of medicine shortages including a longer notification period for withdrawals as well as other types of shortages, and strengthens the ERA requirements.

### 5.2.4 Horizontal measures

Whichever Policy Option is preferred, it will be complemented by the implementation of a series of horizontal measures to improve the effectiveness and efficiency of the regulatory system overall. Such horizontal measures include streamlining, more coordination and empowering new concepts in the regulatory system. The horizontal measures respond to the specific objective "to reduce regulatory burden and provide a flexible regulatory framework".

Actions will be taken to streamline procedures and avoid duplicative assessments of the same data. This is particularly relevant for generic applications, to ensure there is only one assessment carried out and to facilitate the sharing of the relevant files and data across different applications for the authorisations of medicines containing the same active substance. A more efficient repeat use procedure[86] will be provided to reduce administrative and cost/burden and prevent medicine shortages. Another proposal is to abolish the sunset clause and renewal of MAs after five years as they represent unnecessary duplication and a burden on MAHs and regulators. Likewise, the envisaged reduction in the number of notifiable variations could potentially reduce the administrative costs uncured by MAHs and regulators.

The provisions of the legislation will be reviewed with regard to combination products to ensure complementarity with the medical devices regulation in relation to benefit/risk assessment, responsibilities of the medicine developer, and joint scientific advice. Where necessary, the revisions will look to streamline procedures as regards the authorisation of medicines, to facilitate efficient

[86] See glossary.

interaction and synergies between different but related regulatory frameworks e.g. interplay with BTC framework, medical devices (for certain types of products) and health technology assessments.

In addition, delinking the environmental risk assessment of medicines that contain or consist of GMOs from the GMO legislation and replace it with GMO environmental risk assessment requirements and procedures adapted to the specificity of medicines under the general pharmaceutical legislation is considered but not a complete derogation from the GMO legislation.

Adaptations to accommodate new concepts and regulatory processes such as adaptive clinical trials, real world evidence (RWE), and new uses of health data within the regulatory framework, making use of more IT-driven processes and greater digitalisation across the lifecycle of medicines, notably electronic submissions of applications or registrations by companies, variations to MAs and electronic product information are also being considered.

The provision of authorised electronic product information for EU medicinal products has been identified as an important means by which to facilitate dissemination of medicines information to patients and healthcare professionals, enable easier access to data contained within the product information by regulators and stakeholders, and potentially increase efficiencies in the administration of product information.

The working methods of EMA and the European Medicines Regulatory network will be adapted, especially with regard to functioning of the centralised procedure and the decentralised procedure, the approval of generics, the use of expert assessment teams and multi-expert inspections teams to ensure a better use of the available network resources. Measures also introduce an EU-wide centrally coordinated process for early dialogue and more coordination among clinical trial, marketing authorisation, health technology assessment bodies, pricing and reimbursement authorities and payers for integrated medicines development and post-authorisation monitoring, pricing and reimbursement.

### *5.3 Options discarded at an early stage*

Two additional options were considered at an early stage. The first discarded option considered measures to address the objectives in a system where all marketing authorisations for medicinal products would be granted by the EMA with no authorisations at MS level. This option was discarded because of the additional, unsustainable burden it would place on the EMA. The second discarded optional considered an authorisation system that operated only at MS level. This was rejected at an early stage owing to the fragmentation and inefficiencies that would be introduced by the absence of a centralised authorisation mechanism. It would have also meant disbanding the EMA and losing all the efficiencies, knowledge and guidance that have been accumulated at the EU level and have benefited MS NCAs over the years.

# 6 WHAT ARE THE IMPACTS OF THE POLICY OPTIONS?

## *6.1 Economic impact*

### 6.1.1 Changes in regulatory protection

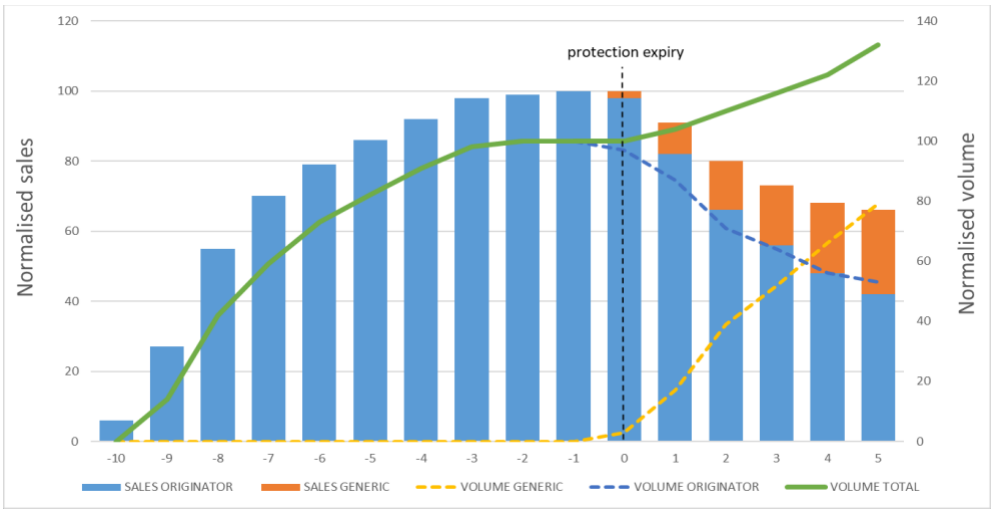
The general pharmaceutical legislation incentivises innovation through **regulatory data and market protection**. Regulatory protection protects data on the safety and efficacy of the product generated for the purpose of the MA and guarantees that during the protection period no abbreviated MA may be granted referring to the originator's regulatory data. This protects innovators from generic or biosimilar competition for 10 or 11[87] years after authorisation. Apart from regulatory protection, medicines are also protected from generic or biosimilar competition by patents (20 years from patent filing) and supplementary protection certificates (SPCs, 5 year extension of primary patent). Medicines for rare diseases also benefit from 10 years market exclusivity (+2 years if paediatric studies were carried out). The longest protection period after entering the market may be provided by any of these instruments.

Regulatory protection is the last layer of protection for 35% of the medicines. Consequently, changes to the regulatory protection period would concern only around 1/3 (i.e. 35%) of the newly approved medicines, which have a 23% share among all originator medicine sales in the EU.

### 6.1.2 Baseline

We used a conceptual model to explain the impacts of the changes in the regulatory protection, including on different stakeholders. The model is based on the commercial lifecycle of a representative innovative medicine, an analogue, for which regulatory protection is the ultimate protection. To create this analogue, historical data[88] were examined, and the evolution of sales followed from MA until protection expiry, and 5 more years from then, along with generic/biosimilar sales (Figure 4). The model uses normalised units to represent prices and volumes across different products, where 100 is equal to originator's peak sales, at year -1.

**Figure 4 Normalised sales and volume for products with 8+2 years of regulatory protection (baseline)**




The SPC evaluation[89] highlighted that generic competition is not uniform across medicines. High-sales medicines, small molecule medicines are more likely to be contested and by more competitors, leading to quick erosion of the price and the innovator's premium. On the other hand, biological medicines, medicines for rare diseases and low revenue products are less likely to be contested, resulting in slower price erosion, or even maintaining a monopoly position. To account for this variability, the model took a cross-section of medicines protected by regulatory protection, even including some medicines that was not contested by generics after protection expiry. The model represents the real-life scenario at systemic level, however individual medicines might show a much steeper erosion, or the opposite, a constant high sales after expiry.

[87] An extra year is granted for an additional indication with significant clinical benefit. Historically around 1 in 8 medicines qualify for that.
[88] A cohort of medicines approved between 2004 and 2011, where RP is the last defence. Further explanation of the inputs used for the model is provided in Annex 4.
[89] SWD(2020) 292 final.

From year 0, the generic medicines enter the market with a lower price, carve out a growing market share and force the originator to offer discounts[90]. The volume of generic medicines steeply increases, partly because some users substitute the originator medicine with generics and partly because the total volume rises with increased affordability. For healthcare systems, the price drop following generic competition means cost savings. In our analogue, the price drop is 50% on average at year +5. The lower price extends eligibility and more patients and from more Member States can have access to the medicine either in its original or generic form. Even with the 32% more patients served at year +5, health systems pay 34% less than at peak sales in year -1.

To account for the impacts of modifying the regulatory protection, we use the above baseline and the 16 years observation period, which we consider as the commercial lifetime of a medicine protected by regulatory protection. This allows us to understand how the stakeholders' positions change in different scenarios.

We measure economic impacts for key stakeholders as follows:

- For **health payers** we measure the impact of changes by the change in the **cost of medicines**, which can be directly deducted from total sales of originator and generic medicines in IQVIA data.
- For **patients**, we measure the impact of change by the change in the **volume of medicines**. The more the volume, the more patients could benefit from therapy, either using originator or generic product.
- For **originator** and **generic industry** the key measure of impact is **the profit** that they can realise from their business operations.

There is no readily available dataset on profits, in fact a product level profit margin is a highly confidential business information. Our best proxy to profits is sales but only if products with similar profit margins are compared. We also distinguish three different categories of sales and caution against a head-to-head comparison of sales data across the different categories.

- Protected originator sales: this is the most profitable category during the protected period of new medicines, the monopoly price can include up to 80-90% profit margin
- Contested originator sales: once generics enter the market, originator products are forced into price competition. Still, originator products can maintain up to 30% price premium, which can mean 1,5-3x higher profit margins than generic products
- Generic sales: generic industry operates on a high volume, low margin basis. With low product development risk, a 10-20% product level profit margin can be sustainable.

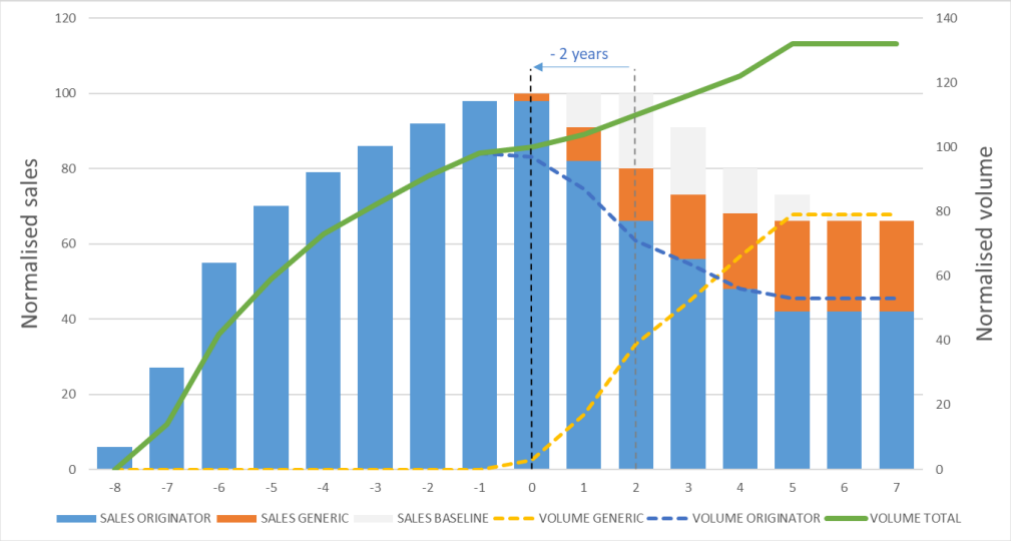
Thus a unit of protected sales may be 2-10x more valuable than a unit of generic sales.

### 6.1.3 Decreasing standard regulatory protection (Option B)

To model for a regulatory protection of 6+2 years instead of the 8+2 years in baseline, we removed from our analogue the original year -1 and -2, enabling earlier generic competition. To keep the same 16 years of observation period, we have added year +6 and +7 in the model, which we assumed to be equal to year +5[91] (**Figure 5)**.

[90] The evaluation (Annex 5) found that originator products can maintain a 30% premium over their generic competitors
[91] More on the assumptions in Annex 4

**Figure 5** - Normalised sales and volume for products with 6+2 years of RP protection




At systemic level, due to other existing protections, such as SPC, patent and orphan exclusivity this measure would only be applicable for 30%[92] of all new medicines. Moreover, Option B would exempt medicines addressing UMN and medicines with no return on investment from the measure (as they can maintain the baseline protection), resulting in 20-25% of new medicines affected by the measure, or 8-13 medicines annually. Using the average peak sales of €160m for medicines protected by regulatory protection, Table 3 summarises the impacts at product and systemic level.

**Table 3 Changes between baseline and regulatory protection (6+2 years) per stakeholder**

| | Product level change | % change | Systemic change (8-13 medicines) |
|---|---|---|---|
| Originator protected sales | -€320m | -28% | -€2.5-4.1b |
| Originator contested sales | +€134m | | |
| Originator medicine's commercial value | | -22% | |
| Generic sales | +€77m | +56% | +€0.6-1b |
| Cost to public payer | -€107m | -6% | -€0.9-1.4b |
| Patients served | | +5% | |
| Patients + payer monetised gain/loss | +€178m | +9% | +€1.4-2.3b |

Compared to the baseline, affected **originators** would lose their two highest-sales, most-profit years, but would be somewhat compensated by additional years of remaining sales in a contested market. Accounting for this, the product would still **lose 22% of its commercial value**. For the innovator industry this sums up to €2.5-4.1 billion loss annually in protected sales in the EU. More than 75% of originators who expressed an opinion in the targeted consultation said that a reduction of the protection period would have a negative impact.

The losses of the innovators are captured by the generic industry, the public payers and patients. The measure would generate €0.6-1 billion extra sales for generic industry, and €0.9-1.4 billion direct cost reduction for health payers. Even with the lower price, 5% more patients could benefit from the affected medicines and accounting for the extra patients served in a monetised form, the total benefit for the public is €1.4-2.3 billion, or 0.6-1.0% of the total EU pharmaceutical expenditure. An additional benefit would be a higher proportion of UMN among newly approved medicines[93], due to the relative higher reward.

In summary, **a 0.6-1.0% of saving for payers and patients, would leave 75-80% of regulatory protection-protected medicines unaffected and reduce by 22% the commercial value for the remaining**.

[92] Some of the Regulatory protection-protected medicines are eligible for SPC protection between year 8 and 10 from MA, this is discounted, hence not 35% but only 30% of the Regulatory protection-protected medicines would be affected.
[93] As a result of decreasing non-UMN medicines

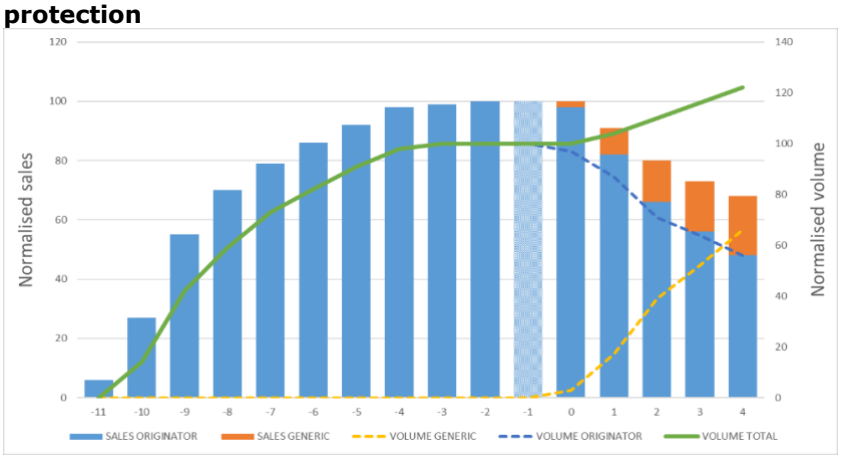
Apart from the imbalanced impact, the measure would have additional costs. With a lower reward, some developer will decide not to enter the EU market, or delay entry and seek return on other markets first. Moreover, an estimated **€510-830 m will be lost for innovation**[94], equal to the development cost of 8-12 new medicines over 15 years, or more incremental innovation (new indication of existing products, improved formulation or combination) that could benefit patients.

Even though in the consultation, civil society organisations in principle supported a reduction of regulatory protection, patients would pay the highest price for the lost innovation, in that their medical needs could not be met. But innovation is important for health payers too if new products offer cost-effective health solutions, and a continuous stream of innovative medicines is needed for the generics industry for new business opportunities.

### 6.1.4 Special incentives through increasing regulatory protection (Option A and C)

Following the same model, the impacts of an increased regulatory protection (either offered for UMN, comparative trials or market launch) can also be shown (Figure 6).

**Figure 6 Normalised sales and volume for products with 8+2+1 years of regulatory protection**




| | |
|---|---|
| Medicine's commercial value | **+11%** |
| Generic sales | **-28%** |
| Cost for payers | **+2.9%** |
| Patients served | **-2.4%** |

In this case, an additional protected year[95] is added at peak sales, extending the protection. The originator captures 14% increase of its protected and thus most profitable sales. The benefits are offset to some extent by losing one year of contested sales, still resulting in an overall **11% increase of the product's commercial value**.

On the other hand, the cost to public payers increases by 2.9% compared to baseline, while 2.4% less patients would be served. The generics industry loses €38m sales on average per rewarded product.

Overall, payers, patients and the generic industry share the burden of allowing longer streams of monopoly revenues to the innovator, to compensate for extra costs occurred (comparative trial, market launch), or to reward and incentivise innovation of high public health benefit (UMN).

Special incentive: 1 year extension of regulatory protection for medicines addressing UMN (Option A, C)

This measure affects regulatory protection-protected medicines and medicines with orphan market exclusivity as last protection, altogether 40% of all new medicines. Of these we expect 15-20% to address UMN. Applying these rates on the 40-50 annual new authorised medicines as per our dynamic baseline, **2-4 special UMN incentives per year is expected**. It is worth noting that for orphan medicines for the highest unmet needs, the corresponding modulation of market exclusivity, under the revision of that regulation, will have a higher impact than the modulation of the RP for those products.

For affected medicines, the innovator's protected sales will increase by 14% or an average €160m, or €320-640m at industry level. The expected impact is that **medicines addressing UMN will become 11% more attractive commercially** for developers, and their proportion among the newly authorised medicines would increase from 20% to 25% among Regulatory protection-protected medicines. The improved proportion translates into more public health benefits at society level.

The cost of this incentive is shared among generic industry, health payers and patients. With 2-4 such incentives annually, the generic industry would lose €77-154m a year and the health payers

[94] 20% of lost protected sales, the typical R&D rate of revenue for originator companies.
[95] Impacts can be proportionated if the extension is longer or shorter than a year

would need to pay €109-218m more. Accounting for the unserved patients too, the **public cost would rise to €163-326m.** The consultations showed that both public authorities and patients support modulating the RP periods around factors such as UMN. Industry on the other hand said that if incentives were limited to UMN only, that would disregard the reality of science and incremental innovation and also would introduce uncertainty.

Special incentive: 6 month extension of regulatory protection for comparative clinical trials (Option A, C)

Similar to the previous incentive, this measure could benefit regulatory protection-protected medicines and some medicines for rare diseases. Around **40% of all new medicines would be eligible**. Conducting comparative trials should be feasible for many medicines, but not for some, especially UMN medicines[96]. We expect that half of the regulatory protection-protected products could benefit from it, or **8-10 medicines annually**.

With this incentive, benefiting originator companies could obtain a **7% more protected sales**, or €80m on average, **€640-800m at industry level**. Of course, higher sales medicines would have a higher compensation, regardless the cost of the trial. For 8-10 medicines a year, comparative trial data would be available helping public authorities making better informed reimbursement decisions, and saving cost down the line. Data from trials would also accelerate pricing and reimbursement decisions, allowing faster access to patients.

The cost of the incentive is borne by generic industry, health payers and patients. Generic industry would lose €154-192m in sales, and the direct **cost for the public** budget would be €218-272m, accounting also for unserved patients, it amounts to **€326-408m** for the public.

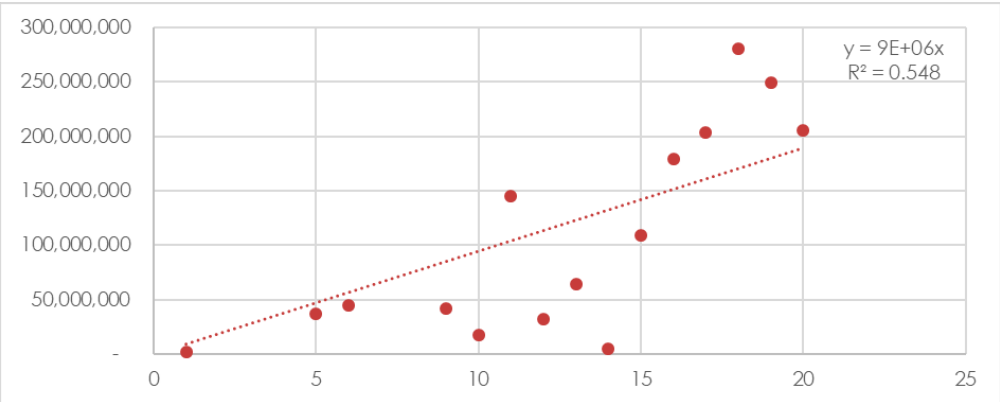
In the consultations, industry supported that comparative data is already provided at authorisation stage when possible and expressed concern that some products (e.g. ATMPs, products for ultra-rare diseases) will not benefit from this incentive. Patients and public authorities on the other hand supported comparative clinical trials (even as an obligation in the case of the latter).

### 6.1.5 Measures to improve market access (Option A, B and C)

All policy options address the challenge of unequal market access to new medicines across the EU but with different measures. Option A offers a +6 months extension of regulatory protection for medicines launched in all EU markets within 5 years of market authorisation. Option B instead requires companies to launch their product in the majority of all EU countries within 5 years, otherwise they lose their regulatory protection and generics are allowed to the market. On the other hand, Option C links the market launch with the standard regulatory protection period as modulation. It requires market launch in all EU MS[97] and within 2 years of authorisation as a conditionality to parts of the protection period. Non-complying medicines would lose the 2 years conditional part of their RP (or 1 year in the case of the variation of Option C).

We have also observed a strong correlation between a medicine's peak sales and its access across EU countries (Figure 7). The magnitude of the incentive or the loss of protection is commensurate to the peak sales, meaning that for high sales medicines the motivation is very high to comply. Since high-sales medicines are launched already in most of the markets, for them the compliance cost is small. The opposite is true for low sales medicines.

**Figure 7 Average annual peak sales of products per number of country launch**




Based on the size of the incentive (or potential loss in option B and C), the compliance is estimated as the percentage of medicines fulfilling the market launch requirements. From this, the costs or

[96] In case of UMN, there are no satisfactory therapeutic options. Consequently, a new therapy would have no comparator.
[97] Except those not willing to be served.

savings to the public have been calculated (Table 4). For option A, we used the same model as for the special incentive for comparative trials, but expecting that only the higher sales medicines would comply, a higher average peak sales was used in the model (detailed in Annex II).

In options B and C the concept is reversed. If a medicine complies with the requirements, the stakeholders' position would not change. But non-complying medicines would face earlier generic competition, resulting in losses for originators and in gains for the public and generics. To calculate public savings stemming from non-complying medicines we used the model of the decreasing standard regulatory protection. Again, the average peak-sales value was adjusted, assuming that the low-sales medicines will be the ones not complying.

**Table 4 Comparative table of measures improving access**

| Option | Expected compliance | Originator's reward/loss | Cost/benefit for public |
|---|---|---|---|
| Option A<br>+6 months, if in all EU | 50% (6-8 medicines) | +5.5% commercial value | €390-520m public cost |
| Option B<br>-5 years, if not in majority of MS | 75% (11-13 medicines)<br>But not all markets | -20-60% commercial value | €270-360m gain from non-complyi medicines |
| Option C<br>-2 years, if not in all EU | 66% (10-12 medicines) | -22% commercial value | €360-440m gain from non-complyi medicines |

In consultations, industry was concerned about regulatory 'penalties' to ensure access. For industry access depends on factors that are not in their control (e.g. variations in national reimbursement decisions) however it agreed that the measure can be a financial incentive to launch in smaller markets. Civil society organisations, patients, researchers and public authorities considered this measure as very important. Points stressed were providing 'real' effective access to continuous supplies and some public authorities arguing that this measure should be an obligation.

### 6.1.6 AMR addressing measures

Antibiotic development is not attractive commercially because new antibiotics are kept on the shelf and only used as a last resort, to delay or avoid the evolution of resistant bacteria. The lack of use translates to low sales and a broken business model, which can only be tackled by public intervention. Pull incentives[98] reward successfully developed medicines, either by creating markets for them, or by giving a prize to the developer. There are several models considered at EU level, some of them under the realm of research and crisis preparedness policies, such as the subscription model (guaranteed revenue delinked from volume) and the innovation partnership (funding for research + guaranteed purchase of the product). These models require commitment and direct funding contributions from the Member States. There are other models discussed below, that can be implemented through the general pharmaceutical legislation.

*Transferable exclusivity vouchers for novel antimicrobials (Options A and C)*

A transferable regulatory protection voucher (or transferable exclusivity voucher) allows the developer of an antimicrobial product to benefit from an additional year of regulatory protection period on another product in their portfolio or sell the voucher to another company that would use the voucher for their own benefit. This mechanism could provide the developer a reward (or an incentive) for developing an antimicrobial product and meet (partially) the high related investment needs. The cost of the voucher would be met by payers for products developed for other diseases. By adjusting the additional protection period and eligibility of products that can use the voucher, the calibration of the voucher value to the desired level can guide the legislators.

According to EFPIA[99], the value of such voucher in the EU should be between €280 and €440 million per product, based on assumptions around a "fair European share", a proportionate contribution to product development that would benefit the global population.

*Cost and benefit of transferable exclusivity vouchers*

The buyers and thus users of the vouchers would be companies the hold the products with the highest sales among the regulatory protection-protected medicines. The commercial lifecycle of these products differs from the average, as their market is more attractive for generic/biosimilar competitors. It results in a faster erosion of price and originator's sales, therefore an additional year of protection has a higher value for the originator, and has a higher cost for the other stakeholders. We have examined over a 10-year period the highest selling regulatory protection-protected medicines, and identified the champions for each year[100]. The average peak annual sales of these

[98] As opposed to push incentives that provide funding for research and development
[99] Representative of innovative industry: A new EU pull incentive to address Anti-microbial Resistabce (AMR) Recommendations from EFPIA, available at https://www.efpia.eu/media/636464/a-new-eu-pull-incentive-to-address-anti-microbial-resistance-amr.pdf.
[100] More details on data and inputs to the model in Annex 4

champions is € 545 m, this was used in our model. Table 5 summarises the changes caused by the voucher to the various stakeholders.

**Table 5 Changes to baseline with the voucher and value of voucher**

| Stakeholder | change | change % |
|---|---|---|
| Originator protected sales | **+€545 m** | +14% |
| Generic sales | **-€164 m** | -23% |
| Cost to public payer | **+€283 m** | +4.7% |
| Patients served (normalised volume) | | -3.8% |
| Patient + payer monetised gain/loss | -€441 m | -7.3% |

| | |
|---|---|
| Extra monopoly revenue | +545 M |
| Production, distribution cost | 20% |
| Cost of capital | 10% /year |
| **Value of voucher** | **360 M** |

The €545 m gain of the originator in protected sales is not equal to the value of the voucher for the originator, because the revenue contains the cost of manufacturing and distribution, as well as the cost of capital. We assume that the originator can only use the voucher 2 years after buying it, to ensure that generic competitors can prepare for a delayed entry. Assuming 20% cost of sales and 10% annual cost of capital over 2 years, the **value of the voucher for the originator is € 360m** at a **cost of € 441m for payers and patients** (or €283 m in nominal value, disregarding patients' loss).

*Sharing the value of the voucher between buyer and seller*

We were able to identify the likely average value of the voucher, however it remains uncertain what proportion of the value will be transferred to the seller – the actual developer of the rewarded antimicrobial, often an SME. The negotiating position of the seller will depend on the second highest selling medicine, the next potential buyer, similar to an auction where the winner has to pay only a little more than the second highest bidder. The situation is further complicated if there are more vouchers on the market and the EFPIA paper estimates 1-3 vouchers per year. Each additional voucher drives down the price for all vouchers in that year, as they generate competition for each other. For instance, if there are 3 vouchers, the price for all vouchers will fall between the value of the voucher for the 3rd and 4th best seller medicine. Using historic data on the second, third and fourth best-selling Regulatory protection-protected medicines in a given year, we can visualise the impact. (Figure 8, Table 6).

**Figure 8 Distribution of buyer and seller advantage if 1 or 3 vouchers issued a year**


**Table 6 Share of value among buyer, seller and the public**

| 1 voucher | |
|---|---|
| Seller rent | €205 m |
| Buyer rent | €154 m |
| Cost to public in nominal value | €283 m |
| Cost to public incl. unserved patients | €441 m |

| 3 vouchers | Voucher 1 | Voucher 2 | Voucher 3 | Total |
|---|---|---|---|---|
| Seller rent | €89 m | €89 m | €89 m | €267 m |
| Buyer rent | €270 m | €97 m | €50 m | €417 m |
| Cost to public in nominal value | €283 m | €147 m | €109 m | €539 m |
| Cost to public incl. unserved patients | €441 m | €228 m | €170 m | €839 m |

In the model, based on historic sales data, **the buyer captures 43% of the voucher's value** if there is one voucher per year, and 61% if there are three vouchers annually. The buyer's share is sensitive to the gap in the voucher's value between one buyer and the next. The smaller the gap, the higher proportion of the value remains with the developer (seller). Appropriate safeguards and modulation of the voucher system could potentially improve the buyer/seller value-sharing ratio.

Aside from the problem that the voucher generously rewards the buyer without merits, there is a question of effectiveness: what is the price the public has to pay for 1 euro award to the developer.

We present this in **Table 7** both in nominal value (the net budgetary effect for payers) and with a cost that takes into account the lost volumes and thus unserved patients.

**Table 7 Cost for the public payer to reward the developer with 1€**

| Scenario | 1 voucher | 2 vouchers | 3 vouchers |
|---|---|---|---|
| Cost to public in nominal value | 1.38 € | 1.40 € | 2.02 € |
| Cost to public incl. unserved patients | 2.15 € | 2.18 € | 3.14 € |

If it were possible to add safeguards, ensuring that 90% of the value of the voucher is captured by the seller (developer), the ratio of the award and the cost would significantly improve. In this case, it would cost €87 m to the health payers to give a €100 m reward, but this payer cost does not account for the unserved patients' loss[101].

Regardless of the cost calculation method, the public has to pay more than 1€ for each euro awarded to the developer. However, it would be a feasible way to pool sizeable resources and incentivise antibiotic development, which so far have proven ineffective with other incentives. These costs should be reflected taking into the current €1,5bn in health care costs and productivity losses from AMR [102] and the risk from the high levels of antimicrobial resistance in bacteria from human infections, a silent pandemic that is not subsiding, and its economic consequences.

In the consultations, some civil society organisations concurred that company profits would rise as a result of a transferable voucher and would therefore address the issue of AMR. However they recognised that if this is done the system should be fine-tuned to meet the needs of patients. Others oppose this incentive as it would delay the entry of generics for other medicines and could increase substantially costs for public health systems. Alternative solutions should be considered. In the public consultation innovator industry defended the benefits of transferable exclusivity extensions. Public authorities and the generics industry expressed opposing views citing arguments linked to overcompensation, high cost to health systems and loss of competitiveness for generics.

*Pay or play model (Option B)*

In this model, a company co-finance the innovation and either holds an antimicrobial in its portfolio or it pays to a fund that is destined to finance the development of novel antimicrobials. The analysis found that a pay or play model would impose additional costs on EU pharmaceutical businesses. Undoubtedly the increased fees on other therapeutic areas will be passed on health systems (insurers and/or patients) through higher prices[103] and while a minority may look to avoid a levy by developing antimicrobials or acquire businesses with an antimicrobial in the portfolio, the majority would be likely view the surcharge as an unavoidable additional cost to be factored into their wider pricing policies. In addition, the fund would generate only limited amount of money therefore only partial return of investment and/or limited number of rewards can be ensured. The results of this model could be seen only after several years (when the fund collects enough capital). Finally, other therapeutic areas that also suffer lack of investment may need/request to be included, making the scheme unsustainable.

The pay or play model would not directly increase the number of novel antimicrobials and may risk increasing prices, creating substantial social costs. The benefits of the incentive would depend on the use of the collective fund, beyond the scope of the general pharmaceutical legislation.

This measure was supported by patients and other civil society organisations in the public consultation. Industry was the least supportive. In a workshop industry participants raised concerns that the 'pay or play' model would unfairly penalise companies (particularly SMEs) with no expertise in AMR product development.

### 6.1.7 Administrative burden on business

An evolving regulatory landscape has the potential to add significantly to the administrative burden of businesses if additional regulatory requirements are introduced or requirements are made more complex. Conversely, streamlining, simplification and automation of regulatory processes can also reduce administrative burden.

**Baseline**

In recent years, shortage notification systems have been improved. Given the need for data collection and notification of shortages, there are associated administrative costs for MAHs and wholesalers to

[101] Unserved patients refer to those patients that were not served due to the delayed entry of generics, ie. the lost volume
[102] 201020_EUJAMRAI_policy-brief_WP7_appropriate-use-of-antibiotics-one-health-perspective.pdf (eu-jamrai.eu)
[103] (https://academic.oup.com/cid/article/71/8/1994/5736365?login=true).

fulfil their obligations related to detecting and reporting shortages. Similarly, there are administrative costs associated with ERA submissions for MA applications. In our research, we have not been able to find data to quantify these specifically.

Harmonisation of summary of product characteristics (SmPCs) for nationally authorised antimicrobials to support prescription practices may require reassessment in order to prepare a new SmPC and Product Leaflet for sharing with member states that could amount to many tens of thousands of Euros for up to 5 MAHs every year.

**Option A**

Changes to regulatory data protection periods for medicines to make them contingent on market placement should be expected to make the system considerably more complex. It will require regular reporting by MAHs on market launches resulting in higher administration costs.

Whilst possible that, compared to the current situation, encouraging the use of the HMA/EMA reporting template would increase the information requirements in some MS, standardisation of requested information is more likely to facilitate central coordination of shortage reporting, thereby reducing transactional costs. Elements to address security of supply of medicines in Option A imply limited burden on industry players as they are non-binding and do not represent drastically onerous requirements compared to the baseline.

**Option B**

For developers that need to demonstrate the absence of a return on investment (ROI) from their R&D to secure a period of additional regulatory protection, there would be increased administrative costs associated with the data-hungry and exacting ROI methodology that businesses would need to follow. In terms of transparency requirements, the link between R&D grants / tax reliefs and individual medicines is complex and would demand the development of new costing models and assessment frameworks with additional administrative costs for firms needing to prepare the required information.

Obligations on MAHs to place centrally authorised medicines on the market in a majority of MS, presumably at risk of penalty in case of non-compliance, may carry substantial costs to the MAH. They may either be required to operate in markets where they cannot generate a sufficient ROI or incur fines if they refuse to do so. The MAH will also have to provide additional information to regulators to demonstrate their compliance with obligations. This implies increased administrative costs. These obligations will also increase the costs to MAHs for interacting with regulatory agencies and HTA bodies in MSs.

**Option C**

Additional regulatory data protection period for medicines contingent on appropriate and continuous supply will require regular data reporting by MAHs resulting in higher administration costs. Similarly, an increase in notification period for withdrawals (12 months) and shortages (6 months) will increase the complexity and administrative burden of reporting shortages for MAHs. Introduction of a common template for reporting withdrawals and shortages could help reduce the additional administrative burden to some extent and promote harmonised data collection. Keeping monitoring at Member State level will not lead to additional burden for MAHs as it builds upon existing systems. MAHs will also incur greater costs due to requirements for stockpiling and development of shortage prevention and mitigation plans for all medicines. The horizontal measures however (discussed in chapter 8) would significantly cut red tape.

Increased transparency around public support for clinical trials is narrower than the proposal under Policy Option B, where all aspects of public support for medicines development, including various tax reliefs, have to be considered. Hence, this option would be simpler to implement as information on support of specific clinical trials through publicly funded R&D grants is more likely to be in the public domain already and thus will incur less substantial administrative costs.

### 6.1.8 Conduct of business

The general pharmaceutical legislation has a significant impact in the conduct of business, from medicine development to distribution. Businesses adapt to cope with changes to regulatory requirements and incentives as well as other contextual factors to fulfil their regulatory obligations and capture profits in an efficient manner.

**Baseline**

The current system provides incentives for innovation in terms of data (8 years) and market (2 years) protection to give time to developers to recoup their investment by delaying the entry of generics or biosimilars. These are without prejudice to intellectual property protection and specific rewards and market exclusivity for orphan and paediatric indications. The evaluation found the harmonised incentives of the current regulatory system had contributed to the growing numbers of applications for new and innovative medicines received by the EMA.

**Option A**

Retention of the current period of regulatory protection for all new medicinal products and special bonus incentives for UMN, and EU-wide product launch would have a positive effect on businesses that can benefit from the incentives. However, this could negatively impact the generic and biosimilar industry as it would further delay their access to the market. Measures on security of supply retain the current requirements hence they would bring no additional burden.

**Option B**

For originators, a reduction in the period of regulatory protection will reduce overall income and profitability from new medicines would be significantly reduced (22% loss in commercial value). It is expected that developers would adjust / increase prices to counter the loss or otherwise rebalance their portfolios towards those market segments with greater commercial potential. The threat to EU-based originators will be offset to some degree by giving a boost to EU's generic industries, broadening their portfolios and potentially creating a prime-mover advantage in global markets. Similarly, developers of products addressing UMN will be exempt from the negative impacts of the measure.

A pay or play model would impose additional costs on EU pharmaceutical businesses, and while a minority may look to avoid a levy by developing antimicrobials or acquire businesses with an antimicrobial in their portfolio, the majority would be likely to view the surcharge as an unavoidable additional cost to be factored into their wider pricing policies. The pay or play model may encourage developers willing to avoid the fees to broaden their product portfolios through commercial activities (e.g. mergers, acquisitions, licences, etc. with smaller biopharmaceutical companies that develop antimicrobials).

**Option C**

Under this option, companies will be able to obtain the same protection period as in the baseline, but subject to compliance with certain conditions on which the eligibility for those "conditional" periods depend. Access to additional incentives for market launch and supply in all Member States, innovation for UMN and AMR as well as comparative trials will grant MAHs a longer period of exclusive prices compared to the minimum period being introduced, representing increased revenue and potentially changing behaviour of the sector. For companies not complying with the criteria for the conditional periods, impacts to conduct of business will be similar to those for Option B with reduction in overall income and profitability for new medicines.

As regards shortages, submission of shortage prevention plans and additional reporting requirements to increase transparency of the supply chain would be acceptable to industry stakeholders if the information remains confidential, as this could be commercially sensitive. In consultations, industry stakeholders have strongly opposed applying these measures to all authorised medicines rather than limiting it to critical medicines and those medicines at high risk of shortage.

### 6.1.9 Public authorities

Changes to the legislation will have implications directly for the actions and budgets of both European institutions (the EMA) and national competent authorities (NCAs) and indirectly for national health technology assessment agencies and, critically, health payers.

**Baseline**

Many MSs have invested in recent years in setting up and/or improving shortage notification systems. In addition, there are costs associated with administratively processing notifications for NCAs, reviewing MA applications, and paying and reimbursement (healthcare costs).

**Option A**

Incentives providing longer data protection periods in general (whether to promote innovation or market launch across all MSs) may carry a significant cost to national health systems and payers by potentially delaying generic entry. There may also be additional administrative burden for the EMA and NCAs involved in the assessment of the additional applications, UMN criteria and verification of product market launch information to determine whether a MAH has fulfilled all the conditions to be eligible for longer data protection. On the other hand, a special incentive bonus for comparative trials would offset an additional period of high prices for payers against a more straightforward and robust assessment by regulators and a better evidence base for HTAs and payers.

The cost of a transferable voucher given to developers of novel antimicrobials could amount to €0.5bn (borne by healthcare payers across the whole of the EEA). This cost needs to be considered in the context of the health costs related to AMR and possible savings from novel antimicrobials to combat resistant bacteria.

**Option B**

Health payers may benefit from lower average lifetime costs for medicines due to earlier generic entry (because of a reduced data protection period). The extent of these benefits will depend on originators' response to the reduced incentives, and it is possible that average prices will be adjusted upwards to some degree to offset the shortened protection period.

Greater transparency around public support for medicines development may strengthen payers' position when negotiating with MAHs, helping to place a downward pressure on prices and thereby helping to maintain or improve access to medicines. Auditing the claim of developers demonstrating the absence of return on investment can be time consuming for authorities; the global development and the complex accounting systems raise questions on the overall feasibility of the exercise.

The measures to increase patient access to medicines are expected to improve the situation in particular in smaller markets, and thus the cost-effectiveness of the health systems.

Creating the infrastructure and processing the information from monitoring shortages will require a significant investment from authorities. However the shortages avoided reduce the burden of finding substitutes or alternative suppliers.

**Option C**

Incentives providing longer data protection periods in general (whether to promote innovation or market access across all MSs) may carry a significant cost to national health systems and payers by potentially delaying generic entry and increasing the period for premium pricing. However, early generic entry as standard for newly authorised products that do not fulfil UMN criteria, do not involve comparative trials or are not supplied in all MSs within 4 years would represent savings for payers and health systems.

There may also be additional administrative burden for the public authorities involved in the assessment of UMN criteria and verification of product market supply to determine whether a MAH is eligible for longer data protection. Similarly, an increase in notification period for withdrawals and non-withdrawals will increase the complexity and administrative burden of monitoring shortages for MS authorities, although use of a common template for reporting could enable cost savings in the long term. Monitoring of supply at MS level is economically advantageous for NCAs as it builds upon the existing system of national monitoring.

Greater transparency around public support for clinical trials may strengthen pricing and reimbursement agencies' negotiating position with MA holders, helping to reduce prices and thereby improve access to medicines.

The EMA and NCAs may require additional capacity or incur greater administrative burden in reviewing and assessing products based on the additional requirements for ERA (environmental risk of manufacturing) and GMP (AMR aspects). The EMA would also need to recruit expertise and set up a new structure for providing advice on ERA and green manufacturing aspects and quality.

### 6.1.10 Sectoral competitiveness, trade and investment flows

The legislation has impacts on the EU's regulatory attractiveness and competitiveness of the EU-based pharmaceutical industry internationally.

**Baseline**

The evaluation accompanying this impact assessment showed that the EU has a strong second position globally following the US. Any additional burden that may have been introduced by the 2004

revisions, such as ERAs and improved pharmacovigilance and manufacturing practices, did not disadvantage EU-based pharmaceutical companies when compared with their international competitors, either within the EU or when exporting to other regions outside the EU. The EU has a large trade surplus in pharmaceutical products and is a leading exporter in developed markets.[104]

**Option A**

The special incentive bonus for UMNs and transferable vouchers are expected to improve competitiveness and attractiveness of the EU pharmaceutical sector and support increased investment in medicine development to address UMNs and AMR respectively.

**Option B**

Reduction in the standard regulatory protection could weaken the global competitiveness of EU based originators overall, compared with the current situation. The proposed pay or play model and access obligation would raise the cost of doing business in EU. This could affect the competitiveness of pharmaceutical companies in EU relative to non-EU companies.

**Option C**

As in option A, retaining the standard regulatory protection period, and providing additional incentives (UMN, AMR, comparative trial) would make the EU pharmaceutical sector more attractive. The conditional EU-wide market launch, the greater obligations and requirements to monitor and prevent shortages (including more reporting and stockpiling requirements) and to address environmental challenges could affect the competitiveness of the EU pharmaceutical sector negatively, but the overall balance of the measures on competitiveness would still be positive.

### 6.1.11 Research and innovation

The legislation expressly promotes research and innovation for medicines in the EU and thus has repercussions for innovators and researchers in the public and private sector.

**Baseline**

Current regulatory data protection arrangements have supported innovation for new medicinal products with the number of medicines in the Biopharma pipeline (Phase I to regulatory submission) going from 1,492 in 2006 to 1,966 in 2021 (country share from 31% to 25%) for companies headquartered in Europe.[105]

The WHO Global Observatory on Health Research and Development's April 2021 dashboard[106] shows that as of September 2020, a total of 41 antibiotics and 27 non-traditional antibacterial agents were in clinical development globally. Those 68 products are distributed across the three phases of clinical trials. Thus, the current clinical pipeline and R&D activity is insufficient to tackle the challenge of increasing emergence and spread of AMR.

**Option A**

The special incentives will support increased return on investment for developers and bring additional investment into R&D for UMN, including AMR. Comparative trials will contribute to better understanding the clinical benefits of the studied medicines and their comparators.

**Option B**

The reduction of the standard regulatory protection would cause an estimated annual €510-830 m loss for R&D, equal to the development cost of 8-12 new medicines over 15 years.

**Option C**

Impacts on research and innovation would be similar to those for Option A.

### 6.1.12 Functioning of the internal market

[104] Guinea, O., & Espés, A. (2021). International EU27 pharmaceutical production, trade, dependencies and vulnerabilities: a factual analysis.
[105] 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022
[106] https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antibacterial-products-in-clinical-development-for-priority-pathogens

The general pharmaceutical legislation can have some limited effects on the internal market of medicines in the EU through its interplay with national laws and practices on the approval, pricing and sale of medicines.

**Baseline**

In the market access and pricing environment the current trend is towards increasing use of 'gatekeeping' measures and price controls[107]. Such measures may have the effect of further limiting the number of markets in which products are launched or causing longer delays between authorisation and availability.

**Option A**

The slight increase in the number of new innovative medicines owing to incentives provided and the increase in access to innovative medicines through the market launch incentive improve the functioning of the internal market. On the other hand, delayed generic entry would hinder competition, and keep prices high for a longer period compared to the baseline. Overall, option A would make more harm to the functioning of the internal market than benefit.

**Option B**

Earlier generic entry due to lowering of the standard data protection period for most new medicines (except those addressing a UMN) and increase in access to medicines through market launch obligations improve access to medicines and the functioning of the internal market. Reduced number of new innovative medicines would offset parts of the benefit.

**Option C**

Increase in the number of new innovative medicines owing to incentives provided (including additional data protection and transferable voucher), and the increase in access to medicines through the market launch measure will improve patient coverage and functioning of the internal market. Transferable vouchers introduce an element of unpredictability for the start date of the competition.

### 6.1.13 Position of SMEs

Micro and small businesses are an important sub-group driving innovation in medicines. Pharmaceutical and biotechnology SMEs face additional market barriers as compared with their larger counterparts. The challenges are particularly significant given the very large cost, lengthy timelines and regulatory hurdles associated with the development of new medicines (e.g. 10 years from pre-clinical research through to regulatory approval with high attrition rates at each stage).

**Baseline**

SMEs and emerging biopharma companies[108] accounted for 59% of products in the pipeline (Phase I to regulatory submission) in 2021.[109]

**Option A**

The transferable exclusivity voucher is intended to reward antibiotic developers that are often SMEs. Thanks to the transferability, they can monetise the value of the voucher by selling it. Fulfilling the conditions for the market launch incentive is more challenging for SMEs compared to big companies that may have offices and staff in all Member States.

**Option B**

SME originators may find it more difficult to invest in riskier novel medicines given the reduction in future returns on investment owing to reduction in the standard data protection period and their relatively weaker market position when it comes to negotiating prices.

[107] Deloitte Centre for Health Solutions. (2019). *Patient access to innovative medicines in Europe A collaborative and value based approach*.

[108] Companies having less than $200 million (€186 million) in estimated annual spending on R&D, or under US$500 million (€466 million) in global revenue

[109] 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022

Obligations for market placement in a minimum number of MSs, including smaller markets, may be more challenging to meet for SMEs that do not yet have market presence or distribution channels in such markets.

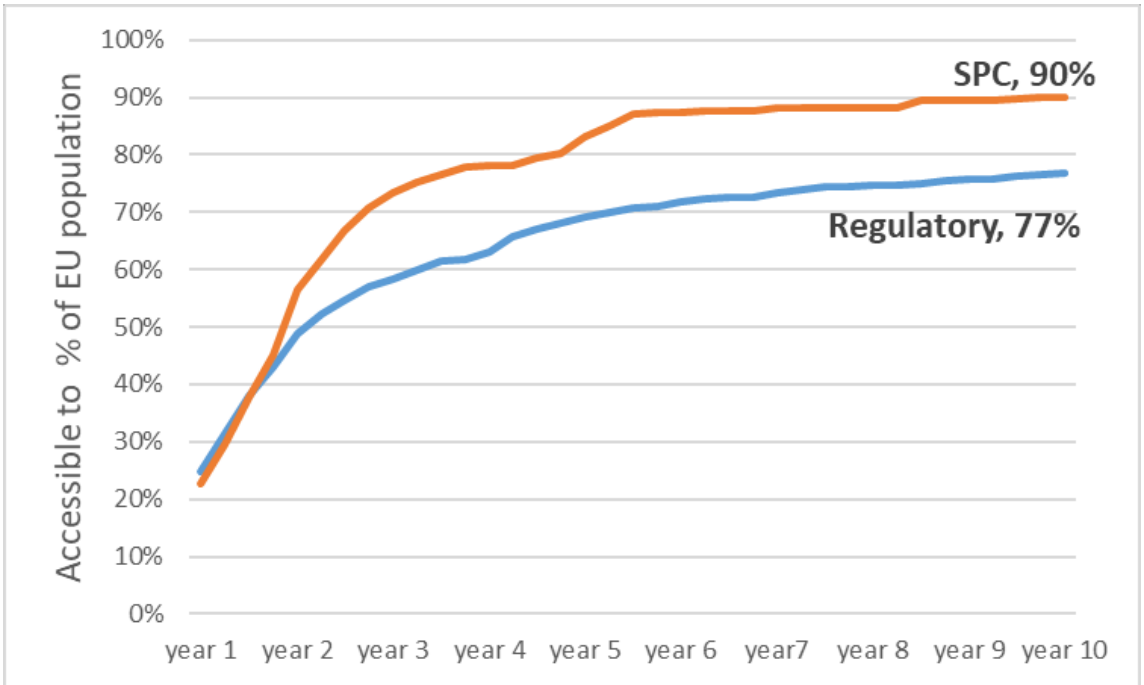
**Option C**

There may be additional burden on SMEs to meet the new requirements for ERA either in terms of administrative costs or need for specialised expertise. The greatly expanded obligations and requirements for withdrawal/shortage reporting and management would also put a much larger burden on SMEs compared to their larger counterparts.

### *6.2 Social impact*

Public health and safety is the key impact dimension assessed as social impact from the legislation and includes patients' and health system interests. Analysis of historical data[110] reveals that access to newly authorised medicines in the EU is unequal and even among citizens having access to a medicine, there is a large variation in time to access. Moreover, medicines whose last layer of protection is SPC are more accessible than those where regulatory protection is the last layer (Figure 9).

**Figure 9 Average product accessibility to EU population over time, by protection type**




**Baseline**

Given the long-run nature of medicines development cycles, we can assume historical growth rates – in the numbers of innovative medicines – will continue to hold in the medium term with an increase in the absolute number of active programmes (from 1,492 to 1,966 i.e. 32%) in the EU pipeline over the last 15 years.[111] As such, EU health care systems and patients would continue to see an expanding pool of novel medicines and treatment options in the next five years with some fall off in the rates thereafter.

It is estimated that each year about 670,000 infections occur, and that 33,000 Europeans die as a consequence of antibiotic-resistant bacteria. With the burden being highest in the elderly and infants[112]. It is also estimated that AMR costs the EU €1.5bn per year in healthcare costs and productivity losses. Without new antimicrobials coming onto the market, the AMR burden would remain unchanged or even grow.

[110] See Annex 4 (analytical methods and methodology) and Annex 5 (evaluation SWD)
[111] 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022
[112] Cassini, A., Högberg, L. D., Plachouras, D., Quattrocchi, A., Hoxha, A., Simonsen, G. S., Colomb-Cotinat, M., Kretzschmar, M. E., Devleesschauwer, B., Cecchini, M., Ouakrim, D. A., Oliveira, T. C., Struelens, M. J., Suetens, C., Monnet, D. L., Strauss, R., Mertens, K., Struyf, T., Catry, B., … Hopkins, S. (2019). Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *The Lancet Infectious Diseases*, *19*(1), 56–66. https://doi.org/10.1016/S1473-3099(18)30605-4

Although a 2018 study by Ferrario found that, for medicines launched between 2010 and 2014, the time between authorisation and first use of cancer medicines had shortened[113], analysis by IQVIA has suggested that between 2014 and 2018 in several countries the average delay had increased. Thus, with continuation of the baseline scenario, the problems of selective market entry and delayed patient access to innovative medicines could remain or even worsen.

Available evidence suggests that across the EU the frequency of shortages and their impact on patients and healthcare providers is increasing.[114] While MSs have already introduced a variety of actions at the national level to help protect their security of supply, the impact of these measures on preventing and mitigating the impact of shortages is not yet sufficiently understood.[114]

**Option A and C**

The special incentives under Options A and C should support increased R&D investment and this should flow through to an increase in treatment options and benefit more patients, particularly through products that address an UMN. Comparative trials may provide a better evidence base for reimbursement decisions, potentially leading to cost-effective medicines becoming more readily available to those that need them. Such trials also tend to assess patient relevant parameters, such as their quality of life (pain, daily functioning) and provide better information to healthcare providers for evidence based treatment decisions.

The transferable exclusivity voucher in Option A and C would help develop new antibiotics. While those novel antibiotics need to be used selectively, i.e. as a last-line therapeutic instrument (to avoid bacteria developing resistance against them), they serve as an 'insurance' scheme for the EU and global population. The growing threat of antimicrobial resistance means that routine hospital procedures such as a hip replacement or a caesarean section can turn fatal, or a small injury during a holiday trip can end with an amputated limb. So far these events are sporadic within the EU, but can develop into a dangerous public health emergency in the future. New antibiotics on the shelf can protect citizens from such a crisis and the cost of inaction may be much higher than any of the models considered. The use of transferable exclusivity voucher to address this challenge will be after all a matter of political choice.

**Option B**

The reduced regulatory protection in Option B would allow faster generic/biosimilar entry, lower prices and thus a quicker expansion of eligibility to the concerned innovative medicines. The positive impacts would be somewhat offset by reduced innovation, and the delayed or no entry of some innovative products to the EU market.

The impacts of an obligation to place centrally approved products on the market will scale with the number of countries and patients reached and with the importance of the medicine. Increased access to effective and safe medicines including new medicines to address UMN and AMR will have a positive impact on the health status and wellbeing of patients and citizens. Prudent use measures will promote tighter prescription practices and ensure patients only use antimicrobials when they need them, potentially reducing the selection pressure for antimicrobial resistance and reducing negative impacts on public health.

Added coordination at EU level and use of an EU-wide system for monitoring shortages will allow for improved decision-making to prevent and mitigate the impact of shortages. If successful, this will in turn result in greater continuity of supply for medicines that are needed to offer appropriate healthcare to patients.

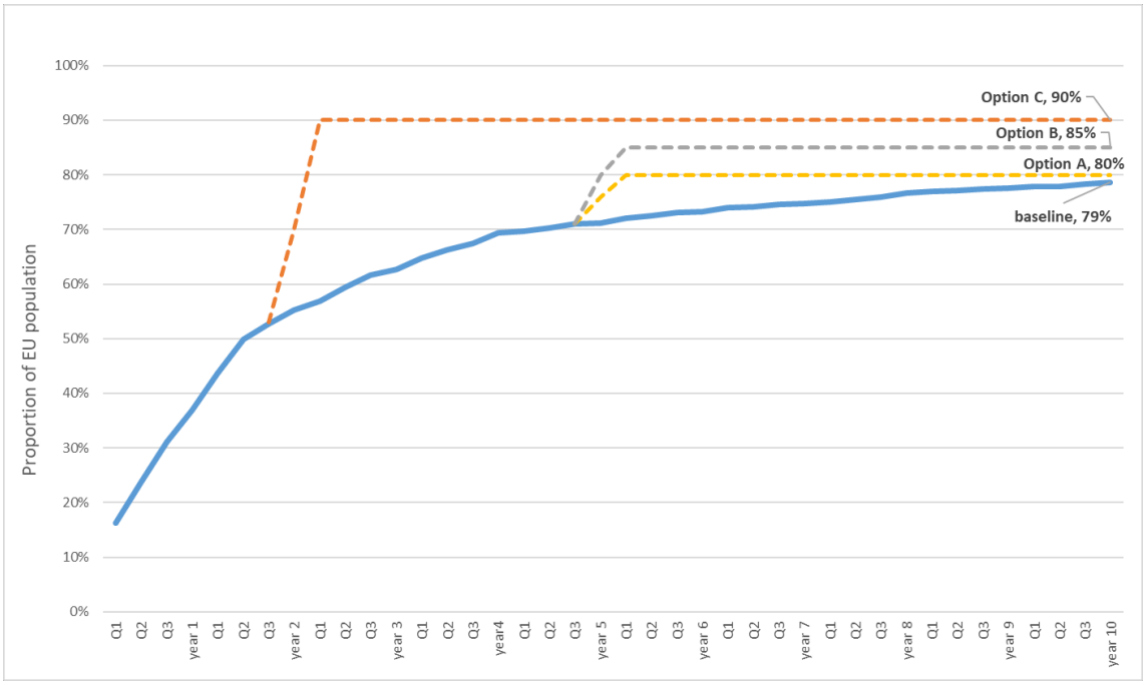
**Overall comparison**

All policy options seek to address this objective, using either incentives or reducing protection in case of non-compliance. Figure 10 shows the likely social impact of the various options. We compared the options to the baseline in terms of time to access and proportion of EU population gaining access to a model regulatory protection-protected medicine.

[113] Ferrario, A. (2018). Time to Entry for New Cancer Medicines: From European Union-Wide Marketing Authorization to Patient Access in Belgium, Estonia, Scotland, and Sweden. *Value in Health : The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, *21*(7), 809–821. https://doi.org/10.1016/J.JVAL.2018.01.003

[114] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages* (Issue December).

**Figure 10 Proportion of EU population gaining access over time in various options**




In this respect, Option C outperforms all options, by providing access on average to 80% of EU population over the 10 years protected period, 15% higher than in the baseline. Also options A and B offer a higher access than the baseline (67,6% and 70.2% respectively). In other words, in Option A 11 million, in Option B 22 million and in Option C 67 million more EU citizens would have access to a typical RP protected medicinal product, should they need it[115] compared to the baseline.

In the public consultation, stakeholders rate access to medicines in the EU as 'moderate' or 'poor' (64.1%). The favoured policy responses differ between respondents; industry placing the root causes as factors outside the control of the legislation, and public authorities and patients advocating for obligations or conditions as incentives for access or stronger notification requirements (e.g. for shortages and withdrawals).

### *6.3 Environmental impact*

Environmental impact was assessed in the context of sustainable consumption and production impacts for citizens and industry actors.

**Baseline**

If no changes are made to current requirements, the ERA would continue to be performed by companies when applying for an MA. A 0.01 µg/L threshold value for predicted environmental concentration in surface water ($PEC_{SW}$)[116] would continue to be used and any active substance with $PEC_{SW}$ greater than this threshold would undergo further assessment as to its fate in the environment and potential effects on representative organisms. Thereafter precautionary measures or recommendations to minimise risk would be provided if necessary. Continued review of potential risks to environment from medicinal products and increased awareness of and promotion of prudent use of pharmaceuticals (outside the legislation e.g. based on the European Union Strategic Approach to Pharmaceuticals in the Environment[117]) could help drive down emissions of pharmaceuticals in the environment and improve waste management to some extent, at least for medicines requiring new MAs.

**Option A**

More prudent prescription of antimicrobials should result in fewer antibiotics entering the environment (whether through lower levels of manufacturing activity, better stewardship or

[115] The medicines that were modelled with the average medicine, can be manifold in fact. They may address a small or big patient population, can offer higher or lower therapeutic value, therefore we refrained from converting the coverage rate into QALYs or other similar indicator that could thus compromise the integrity of the analysis.
[116] Whomsley, R., Brendler-Schwaab, S., Griffin, E. *et al.* Commentary on the draft revised guideline on the environmental risk assessment of medicinal products for human use. *Environ Sci Eur* **31,** 17 (2019).
[117] European Commission, 2019. European Union Strategic Approach to Pharmaceuticals in the Environment

improved disposal practices). On the other hand, with no change in ERA compared to the baseline there should be no impacts on sustainable consumption and production.

**Option B**

More extensive prudent use measures for antimicrobials should result in fewer antibiotics entering the environment resulting in greater sustainable consumption impacts compared to Options A and C. In terms of ERA, the requirements are not changed compared to the baseline but there are synergies with the implementation of actions under the EU Strategic approach to pharmaceuticals in the environment which should result in additional impacts on sustainable consumption and production compared to Option A.

**Option C**

Prudent use measures for antimicrobials should result in fewer antibiotics entering the environment resulting in sustainable consumption impacts intermediate between Options A and B. Strengthened ERA requirements and conditions of use of medicines, including assessment of the environmental risk of manufacturing and including AMR aspects in GMP will allow a more holistic assessment of environmental risk along the pharmaceutical lifecycle. Identification of relevant risks and strategies to mitigate these should considerably improve the sustainability of pharmaceutical consumption and production. Stockpiling requirements however may have negative impacts on sustainability.

In the consultations, stakeholders have pointed out that the introduction of new rules at an EU level has been known to be a trigger for other regions, leveraging EU actions. There is variable stakeholder support to the extent of strengthening of the ERA which ranges from support for it to cover all stages of pharmaceutical manufacturing, from raw materials to end-product (public authorities and patients) to views considering existing measures (controls, benchmarking on the manufacturing and disposal of products in the environment) stringent enough (industry).

# 7 HOW DO THE OPTIONS COMPARE?

This section compares the three policy options with the baseline scenario in terms of their overall effectiveness, efficiency, coherence, feasibility, EU-added value and proportionality.

The comparison has focussed on the pivotal measures as these are likely to contribute the most significant impacts and will allow clear differentiation between the options. We have not included a separate assessment of the pivotal horizontal measures here as these are common across the three options and are unlikely to impact on the performance of the pivotal measures (no significant overlap between the specific objectives and problem drivers targeted by the horizontal measures and pivotal measures). The overall comparison of the options against the relevant criteria and compared to the baseline is presented in Table 2 below.

**Table 2 Overall comparison of policy options**

| Criteria | Policy Option A | Policy Option B | Policy Option C |
|---|---|---|---|
| Effectiveness: contributing to achieving the policy objectives | | | |
| Promote innovation, in particular for unmet medical needs | +++ | - | +++ |
| Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation | - | ++ | + |
| Ensure access to innovative and established medicines for patients with special attention to enhancing security of supply across the EU | + | ++ | +++ |
| Reduce environmental footprint of the pharmaceutical product lifecycle | + | ++ | +++ |
| Reduce regulatory burden and provide a flexible regulatory framework | +++ | ++ | ++ |
| Effectiveness: other impacts | | | |
| Economic impact (Competitiveness, research and innovation, SMEs and Internal Market) | +++ | + | ++ |
| Social impacts (public health and safety) | ++ | + | +++ |
| Environmental impacts (sustainability) | + | ++ | +++ |
| Efficiency | | | |
| Administrative and compliance costs (administrative burden and conduct of business, public authorities) | +++ | + | ++ |
| Savings and benefits | + | ++ | +++ |
| Coherence | | | |
| Internal coherence | ++ | + | +++ |
| External coherence | ++ | ++ | ++ |
| Legal and political feasibility | + | - | ++ |
| EU added value | ++ | ++ | +++ |
| Proportionality | + | + | ++ |
| Overall | + | + | +++ |

## *7.1 Effectiveness*

### 7.1.1 Effectiveness in achieving the policy objectives

Our assessment of the effectiveness of the three policy options to achieve the 5 specific objectives of the revision is based on a qualitative assessment of the extent to which the relevant pivotal measures in each option address the specific objectives and/or their underlying problem drivers. Our assessment is discussed in more detail in Section 5.2 and considers firstly whether pivotal measures in an option target a specific objective or its problem drivers and secondly whether they represent a change from the baseline situation and if so the nature of the measure. For example, whether the measure involves an incentive or an obligation with an incentive considered more effective and the extent to which different aspects of the problem are being targeted.

### 7.1.2 Effectiveness to generate the desired impacts

Analysis in this section uses a common framework based on a multi-criteria assessment (MCA) approach with the choice of criteria encompassing the main impact types (those that reflect costs/savings will be included in the assessment of the efficiency of the options) that have been researched through the impact assessment:

- Economic impact (for effectiveness): Position of SMEs, Global competitiveness of the EU pharmaceutical industry, Functioning of the internal market and competition, Research and innovation
- Economic impact (for efficiency): Conduct of business, administrative costs on businesses, public authorities
- Social impact: Public health and safety (including impact on patients/citizens)
- Environmental impact: Sustainability (i.e. sustainable consumption and production)

For each impact type and policy area, we assessed the likely impact on a 7-point scale (-3 to +3) considering the direction (positive, neutral or negative) of impact and performance (or scale of impact) compared to the baseline. The assessments were initially performed for each proposed policy measure and were aggregated for each policy area by impact type considering internal synergies and trade-offs within the pivotal elements in the same area. The assessments are based on qualitative data (mostly) and where available quantitative data obtained from the literature, other secondary sources (e.g. IQVIA) and stakeholder consultations conducted for this impact assessment. There were some areas with data gaps where we used our best judgement.

Based on the MCA of individual policy areas, we created aggregate MCA scores by impact type (see Table 3). This analysis suggests the likelihood of positive economic impacts is greatest for Option A, followed by Option C and then B. Option C is most likely to generate positive impacts on sustainability (followed by Option B and A) and public health and safety (followed by Options A and B). Thus, overall Option C emerges as the most effective when all three major impact types are considered.

**Table 3 MCA of policy options across key impact types and pivotal measures**

**Policy Option A**

| Policy Block | Innovation incentives | AMR | Transparency | Market launch | Security of Supply | Environment | |
|---|---|---|---|---|---|---|---|
| **Impact types** | | | | | | | **Overall** |
| Conduct of business | 1 | 2 | 0 | -1 | -1 | 0 | 1 |
| Administrative costs | -1 | -2 | 0 | -3 | 0 | 0 | -6 |
| SMEs | 0 | 3 | 0 | 0 | 0 | 0 | 3 |
| Competitiveness | 1 | 2 | 0 | -2 | -1 | 0 | 0 |
| Internal market | 0 | 1 | 0 | 1 | 0 | 0 | 2 |
| Innovation and research | 1 | 3 | 0 | -1 | 0 | 0 | 3 |
| Public authorities | -1 | -3 | 0 | 2 | 0 | 0 | -2 |
| Public health and safety | 1 | 2 | 0 | 3 | 2 | 0 | 8 |
| Sustainability | 0 | 1 | 0 | 0 | 0 | 0 | 1 |

**Policy Option B**

| Policy Block | Innovation incentives | AMR | Transparency | Market launch | Security of Supply | Environment | |
|---|---|---|---|---|---|---|---|
| **Impact types** | | | | | | | **Overall** |
| Conduct of business | 0 | -2 | -1 | -3 | -1 | 0 | -7 |
| Administrative costs | -2 | -2 | -2 | -2 | 0 | 0 | -8 |
| SMEs | -4 | -2 | -1 | -2 | 0 | 0 | -9 |
| Competitiveness | -1 | -1 | -1 | -1 | -1 | 0 | -5 |
| Internal market | -1 | 0 | 0 | 1 | 0 | 0 | 0 |
| Innovation and research | -2 | 1 | -1 | -1 | 0 | 0 | -3 |
| Public authorities | 0 | -2 | -1 | 2 | 0 | 0 | -1 |
| Public health and safety | 0 | 1 | 0 | 3 | 3 | 0 | 7 |
| Sustainability | 0 | 1 | 0 | 0 | 0 | 1 | 2 |

**Policy Option C**

| Policy Block | Innovation incentives | AMR | Transparency | Market launch | Security of Supply | Environment | |
|---|---|---|---|---|---|---|---|
| **Impact types** | | | | | | | **Overall** |
| Conduct of business | 1 | 2 | -1 | -1 | -2 | -1 | -2 |
| Administrative costs | -1 | -1 | -1 | -1 | -2 | -1 | -7 |
| SMEs | -2 | 3 | -1 | 0 | 0 | -1 | -1 |
| Competitiveness | -1 | 2 | 0 | -2 | -1 | -1 | -3 |
| Internal market | -1 | 0 | 0 | 1 | 0 | -1 | -1 |
| Innovation and research | -1 | 3 | 0 | 0 | 0 | 0 | 2 |
| Public authorities | 1 | -4 | 1 | 2 | 2 | -1 | 1 |
| Public health and safety | 1 | 3 | 0 | 2 | 3 | 1 | 10 |
| Sustainability | 0 | 1 | 0 | 0 | 0 | 2 | 3 |

The main points to note with regard to effectiveness of different policy options in the key policy areas are as follows:

- **Innovation Incentives** – Options A and C both offer the same incentives for innovation, in particular for UMN and AMR. Overall, Option A is slightly more generous towards innovators, as in this option incentives can be freely cumulated, whereas in Option C the maximum period of regulatory protection is capped. Option B keeps the baseline protection period for UMN medicines, whereas for other regulatory protection protected originator medicines there will be a 22% loss in commercial value, resulting in €510-830 m less funds for innovation annually.

- **AMR** – Option B's pay or play model is less effective than the transferable exclusivity voucher of Option A and C in stimulating AMR related innovation.

- **Transparency** – The R&D transparency requirements in option B and C are expected to indirectly contribute to affordability, better equipping national bodies for price negotiations.

- **Market launch** – All measures in this area will result in more and quicker market access of new medicines, compared to the baseline. The market launch obligations in options B and C are synergistic with affordability. In these options, if a company fails to comply with the market launch obligations, it will lose part of its regulatory protection, meaning earlier

generic competition and more affordable prices. The gain in access is highest with option C, thanks to the shorter deadline for compliance (2 years) and to the all-EU launch requirement (vs majority of EU in B).In option A, the market launch incentive would come with an extra €390-520m cost to the public.

Options A and C offer additional incentives for UMN, and for the transferable exclusivity voucher, which come with additional costs. This is a trade-off between innovation and affordability. Options A and C also offer an incentive for comparative trials, however the cost of that incentive may be offset by savings to the health systems by more informed pricing and reimbursement decisions, with an expected overall neutral/positive impact on affordability. However, this could not be quantified.

- **Security of supply** – Option A does not represent a significant change to the baseline in terms of shortages management, whereas Option B proposes a more coordinated reporting system, and option C goes beyond Option B, requiring earlier notification for shortages and withdrawals. As such, Option C has the highest positive impact on shortages, followed by Options B and A. There is a trade-off between the extra reporting needed to address shortages and the additional administrative costs associated with that. Stakeholder feedbacks from industry suggest that these costs could be tolerable.

- **Environment** – Option A does not impose additional requirements for the ERA beyond current measures (baseline), whereas Option B obliges companies to report the environmental risks of manufacturing too. Option C also includes this additional requirement along with more stringent conditions of use for medicines than the baseline. Option C offers the highest safeguards against uncontrolled release of pharmaceutical residues into the environment. All options feature prudent antibiotic use measures to reduce antibiotics in the environment and lower the risk of AMR. However, here too there is a trade-off between inclusion of additional measures for environment protection and the resultant administrative burden.

More details of the expected impacts for each option and the baseline have already been presented in Chapter 6. The choice for best option also depends on the stakeholder type. For originator companies, Option A offers the most benefits, whereas for the generic industry, Option B would the preferred one. From a patient/public health perspective, Option C is the most advantageous by far, with that option representing a fair compromise between originator and generic industry, along with public authorities and payers.

### *7.2 Efficiency analysis*

Analysis shown in Table 3 suggests the likelihood of efficiency is greatest for Option A, followed by Option C and then B. This potentially reflects the nature of the policy options where Option A is closest to the current scenario with the fewest additional obligations and Option B includes the most changes with more stringent obligations for industry and more changes to the regulatory system implying more administrative costs and burden for public authorities.

For example, Option A maintains the current standard regulatory protection periods (unless the product is not launched) and avoids significant additional obligations (particularly for industry) beyond what currently exists. This option would provide greater continuity, maintain regulatory attractiveness and minimise negative impacts on conduct of business and administrative costs unlike the other policy options, which have minimum guaranteed regulatory protection periods lower than the current one.

Policy Option B links a shorter standard regulatory protection period with a variety of obligations related to prudent use of antimicrobials, transparency of R&D costs, access, and reporting and addressing medicine shortages. Policy Option C also combines incentives and obligations in a similar way. The administrative burden and budget impacts on businesses and public authorities are on a similar scale. However, the mix of obligations and incentives in Option C represent a more positive impact on conduct of business compared to Option B.

In carrying out this impact assessment, we have sought to prepare an economic analysis for pivotal elements in the legislative proposals, which will complement the more qualitative assessment presented in the preceding sections. For a detailed description, see models for assessing impact of pivotal policy measures in Annex II.

**Table 4 Overview of the costs and benefits associated with Incentive system compared to baseline**

| Incentive system | Industry (originators) | Industry (generics) | Healthcare payers | Patients |
|---|---|---|---|---|
| **Option A:** Baseline regulatory data protection of 8+2 years | 0 | 0 | 0 | 0 |
| **Option A:** Incentive bonus +1 years for addressing UMN | Benefit of €93m - €186m per year<br>(15 years: €1.4bn - €2.8bn) | Loss of €38m - €76m per year<br>(15 years: €576m - €1.1bn) | Cost of €80m - €160m per year<br>(15 years: €30.9bn - €40.4bn) | Lower coverage for protected product of €51m - €102m per year<br>(15 years: €768m - €1.5bn) |
| **Option A:** +6 months for generating comparative trial data | Benefit of €278m - €418m<br>(15 years: €4.2bn - €6.3bn) | Loss of €115m - €130m per year<br>(15 years: €1.7bn – €3.4bn) | Cost of €240m - €360m per year<br>(15 years: €3.6bn – €5.4bn) | Lower coverage for protected product of €154m - €230m per year<br>(15 years €2.3bn – €3.5bn) |
| **Option B:** Standard protection period 6+2 years | Loss of €2.4bn – €3.1bn per year<br>(15 years: 37.5bn - €46.5bn) | Benefit of €998m - €1.3bn per year<br>(15 years: €15bn - €20bn) | Nominal saving of €2.1bn -€2.7bn per year<br>(15 years: €30.9bn - €40.4bn) | Benefit of greater coverage of €1.3bn - €1.7bn per year<br>(15 years: €20bn - €26bn) |
| **Option B:** Incentive bonus +2 years for addressing UMN/ROI | 0<br>Combined with RDP 6+2 no effect compared to baseline | 0<br>Combined with RDP 6+2 no effect compared to baseline | 0<br>Combined with RDP 6+2 no effect compared to baseline | 0<br>Combined with RDP 6+2 no effect compared to baseline |
| **Option C:** Standard protection period 6+2 years | Loss of €2.4bn – €3.1bn per year<br>(15 years: 37.5bn - €46.5bn) | Benefit of €998m - €1.3bn per year<br>(15 years: €15bn - €20bn) | Nominal saving of €2.1bn -€2.7bn per year<br>(15 years: €30.9bn - €40.4bn) | Benefit of greater coverage of €1.3bn - €1.7bn per year<br>(15 years: €20bn - €26bn) |
| **Option C:** Incentive bonus +1 years for addressing UMN | Benefit of €93m - €186m per year<br>(15 years: €1.4bn - €2.8bn) | Loss of €38m - €76m per year<br>(15 years: €576m - €1.1bn) | Cost of €80m - €160m per year<br>(15 years: €30.9bn - €40.4bn) | Lower coverage for protected product of €51m - €102m per year<br>(15 years: €768m - €1.5bn) |
| **Option C:** +6 months for generating comparative trial data | Benefit of €278m - €418m<br>(15 years: €4.2bn - €6.3bn) | Loss of €115m - €130m per year<br>(15 years: €1.7bn – €3.4bn) | Cost of €240m - €360m per year<br>(15 years: €3.6bn – €5.4bn) | Lower coverage for protected product of €154m - €230m per year<br>(15 years €2.3bn – €3.5bn) |

### 7.2.1 Reviewing the standard period of regulatory protection

The centrepiece of this work has related to our review of the costs and benefits of a possible change in the standard period of regulatory protection, which is the basis for several proposed policy measures, including a potential multi-year special bonus for new medicines that address an unmet medical need and a 6-month special bonus for the inclusion of the results from a comparative trial within the data dossier.

To estimate the likely costs and benefits of a future change in the standard period of regulatory data protection, the study team has worked with IQVIA-sourced sales data to model the speed and degree to which the prices and revenues of protected medicinal products are eroded by the entry of generics. Our methodology and detailed analysis are presented in Annex II.

The analysis of IQVIA data revealed that the regulatory data protection period is the 'last line of defence' for around 40% of all medicines and that reducing the regulatory data protection period by one year would result in a combined reduction in overall income for EU originators on the order of €1.9bn. This is as a result of generics companies entering the market a year earlier than they would have done otherwise, and a resulting reduction of around 80% in average prices. The model suggests there would be a small reduction in the numbers of innovative medicines being developed. This earlier switch to open competition would produce estimated net savings for health payers across Europe on the order of €1.5bn, based on the procurement of the same mix and volume of medicines from generics manufacturers rather than the premium-priced medicines of the originators. This saving may be used to offset financial pressures on health systems overall or may alternatively be invested in an additional quantum of medicines, which would deliver additional patient benefits.

### 7.2.2 Transferable vouchers

The second important piece of modelling work relates to the proposed transferrable voucher (which is a central proposal for addressing the AMR related objectives under Policy Option A, and Policy Option C.

Our analysis estimates that transferrable vouchers would be strong enough to mitigate evident market failures and incentivise a meaningful expansion of private sector interest and investment in the antimicrobial area. This would feed forward into a stronger global antimicrobial pipeline and increase the likelihood of new classes of antimicrobial being developed, which would have immediate benefits for the more effective treatment of certain diseases as well as helping to combat the growing global threat of AMR.

While the social costs for each voucher awarded may run into the hundreds of millions of Euros across all EU health systems combined, which will be an unwelcome additional pressure on hard-pressed healthcare budgets across Europe, these high costs should be mirrored by equally large additional private investments in R&D and an equally beneficial improvement in treatment options and patient benefits. Our overall analysis of the potential direct and indirect costs and benefits associated with this measure, based on a conservative 'claim' against the policy measure's potential to reduce deaths in Europe relating to AMR, shows a positive return on investment overall, of 1:1.2.

### 7.2.3 Administrative costs

The third economic element we have been working on is the likely value of the administrative costs associated with the various measures proposed, and here we have struggled to get to any view of matters beyond the broadest directional statements. Which is to say industry has been prepared to indicate where they would expect to see additional costs and whether those would be smaller or larger costs.

The evaluation component of this back-to-back study provided some figures we could reuse in the Impact Assessment. For the 2004 revisions, we estimated that industry had incurred one-off costs amounting to around 0.5% of annual sales, albeit that was driven in large part by new IT systems that would have delivered additional benefit to companies. The industry estimated that the ongoing additional administrative costs amounted to an increase of around 5-10% of regulatory costs. However, this lacks the granularity needed to support discussions of the "one in one out" principle or indeed comparison of the policy options.

## *7.3 Coherence*

### 7.3.1 Internal coherence

There is a good degree of internal coherence within each of the three policy options with pivotal elements closely aligned with each other in terms of the guiding principles for each option – current

level of incentives and limited obligations for Option A, reduced incentives with additional obligations for Option B and reduced incentives with 'quid pro quo' obligations for Option C.

The incentive system is internally coherent for the standard and special incentives for each of the three options in terms of the length and types of incentives. There is consistency and potential for synergy among the special incentive bonuses for UMN and comparative trials, transferable vouchers and milestone incentive for market launch in Options A and B with additional periods of data protection on offer. There is also synergy and coherence between prudent use measures for antimicrobials and inclusion of AMR aspects in GMPs under Option C. Thus, Option C offers the widest internal coherence following by Options A and B in that order.

### 7.3.2 External coherence

The pivotal measures being compared do not represent major changes in external coherence compared to the baseline. Option B has coherence with the EU Strategic approach to pharmaceuticals in the environment. The policy options all are coherent with the EU Action Plan on Antimicrobial Resistance[118].

All three options also have coherence with the SDGs 3, 9 and 10[119] as described in Chapter 1. With additional measures, particularly for the development and prudent use of antimicrobials and addressing environmental challenges, the options are also coherent with SDGs relevant to sustainable consumption and development such as

- SDG 1: End poverty in all its forms everywhere – AMR could push around 28 million people into extreme poverty by 2050 due to high costs of treatment and chronic infections[120], and hence introduction of AMR-related measures may have a positive impact on poverty (coherent with all options)
- SDG 6: Clean water and sanitation (coherent with all options)
- SDG 12: Ensure sustainable consumption and production patterns (is coherent with Option C to a greater extent owing to specific measures that address this aspect)

## *7.4 Legal and political feasibility*

All three options are consistent with the EU's right to act under the Treaty of the Functioning of the EU and Directive 65/65/EC (covering public health protection and the free movement of products within the EU). Moreover, all three options propose actions that will allow the objectives of the revision to be addressed to a greater extent than if Member States were acting alone.

Option C includes a Member State level action in the form of monitoring of shortages, but this is the current system and the measure in addition includes establishment of a mechanism of information exchange to allow harmonisation and improve transparency of data collection. An area that may that generate feasibility concerns is the market launch incentives and obligations. Paying and reimbursement decisions fall under Member State competence and follow national policies. In this case it will be important to clarify what "placing on the market" and "market launch" means considering there may be different interpretations in different Member States. This concern applies more for Options A and B as in Option C the milestone incentive is linked to supply which could be monitored as part of the system for monitoring shortages and withdrawals.

## *7.5 EU added value and subsidiarity*

All three options address areas where EU level action would present added value, particularly in terms of coordination, efficiency, clarity of requirements, standardised instruments, and harmonisation across the EU (see Chapter 3). Member State action would create additional burden, complexity, uncertainty and fragmentation. Option A could be considered to have the least EU added value as it has fewer mechanisms that make use of EU level coordination and knowledge to support Member States. Option B makes use of existing EU level infrastructure (European Medicines Verification System) and EU coordination for monitoring and exchanging information on medicine shortages. Similarly, Option C proposes having an EU-wide definition of shortages, critical shortages and critical medicines as well as a central mechanism for information exchange across Member States for medicine shortages.

[118] Available at: https://ec.europa.eu/health/system/files/2020-01/amr_2017_action-plan_0.pdf
[119] https://ec.europa.eu/eurostat/documents/4031688/14665125/KS-06-22-017-EN-N.pdf/8febd4ca-49e4-abd3-23ca-76c48eb4b4e6?t=1653033908879
[120] IACG (2018) AMR Indicators and their relevance to the global indicator framework for SDGs and targets for the 2030 Agenda for sustainable development

With regards to subsidiarity, all three options pursue the objectives of the revision and provide a clear demarcation between EU level and MS level actions. At the same time, the content and form of Option C shows that in both qualitative and quantitative terms, it promotes the revision's objectives at Union level better and does not exceed what is necessary to achieve these objectives.

### *7.6 Proportionality*

The principle of proportionality is strongly reflected in the discussion of certain trade-offs to be made between the different objectives. Option A includes only marginal changes compared to the baseline. As such it provides limited levers to address current problems (as shown in the problem tree), which the current legislation has not wholly addressed according to the evaluation. Moreover, Option B considerably adds to burden for businesses and public authorities in terms of multiple additional obligations and enforcement of the obligations and hence could be considered disproportionate in comparison of what needs to be achieved. Trade-offs are also inherent between the objectives of innovation, access and affordability and thus measures to incentivise innovation versus those to incentivise generic/biosimilar competition. The incentives for innovation have to be adapted to take into account the fact that medicines are not sufficiently accessible by patients in all Member States. This is reflected in Option C which modulates incentives to reward innovation, especially for UMN, but also make the regulatory protection period conditioned to market launch in all Member States. If this condition is not fulfilled generic competition will start earlier, resulting in increased affordability.

The proposal for a MA to be offered for transfer to another MAH before a permanent withdrawal which is present in all three options is seen as conflicting with the proportionality requirements of EU treaties by the EU trade association for the generics industry (Medicines for Europe). It indicates that permanent withdrawals for commercial reasons are often necessitated by national market conditions, such as pricing and reimbursement policies (e.g. price cuts, reference pricing, claw backs and rebates), that are imposed by Member States and over which the MAH has no control. Mandating that the MAH offers the authorisation to another party before allowing it to withdraw is therefore in their view a form of regulatory expropriation in violation of Art. 16 of the European Charter of Fundamental Rights.

### *7.7 Limitations of the comparison*

There is a level of potential uncertainty in the findings described in this chapter owing to the influence of other contextual factors such as developments in the pharmaceutical sector, other relevant legislations (e.g. upcoming HTA legislation, Urban Waste Water Directive) and policies at MS level (e.g. for paying and reimbursement). There is also a level of uncertainty owing to the limitations and assumptions involved in assessing and quantifying the likely impacts of the options provided. One key factor is the use of pivotal measures to focus the comparison under the assumption that these represent the key aspects and major impacts of the legislation. Any of these factors might affect the overall findings and thus the choice of a preferred option.

# 8 THE PREFERRED OPTION

## *8.1 Costs and benefits of the preferred option*

The impact assessment of the three policy options indicates that policy option C is the strongest option to address all the objectives of the revision of the general pharmaceutical legislation. It proposes a modulated trade-off between incentivising innovation (for both unmet medical needs and antimicrobial resistance) and improving access, transparency, and security of supply of medicines as well as reducing the environmental footprint of pharmaceuticals. The costs and benefits of Policy Option C for different stakeholder types are described below.

Taken together, we estimate the benefits should be in the order of **€2.19bn a year** and €32.86bn over 15 years. We estimate the total costs to be in the order of **€1.91bn a year** of recurring costs which equates to €28.64bn over 15 years. It should be noted that these aggregate figures represent the benefits and costs across all stakeholder types where data allowed quantification. Hence, these numbers should be interpreted with caution in light of the benefits and costs that could not be quantified/monetised as well as differences in benefits and costs across stakeholder types.

### 8.1.1 Patients, Citizens and Healthcare services

Policy Option C will bring **benefits to patients and citizens** by facilitating the work of healthcare professionals, pharmacies, hospitals and strengthening health systems. Increase in availability of new innovative and generic medicines owing to additional incentives for addressing UMN and AMR as well as promoting access across all Member States in parallel with reduced standard regulatory protection will benefit patients. Our analysis estimates that a 2-year regulatory data protection reduction would result in additional volume of medicine reaching patients that amounts to benefits of €1.3bn to €1.7bn per year, compared to baseline. Prudent use measures for antimicrobials and transferable vouchers for development of new antimicrobials will also benefit patients. Transferable vouchers would give access to additional antimicrobials (estimated additional 1,533 QALYs per year) and reduce EU deaths due to AMR (estimated reduction of 330 per year).

Future proofing measures in Option C will ensure patient safety in areas of rapid technological change such as personalised medicines, bedside manufacturing and pharmacoprinting as well as products of new manufacturing methods. Regulatory sandboxes will also increase the chance of faster patient access to cutting edge medicinal products. While this policy will also reduce uncertainty over borderline products, Member State level processes will remain and thus diverging interpretations could lead to negative impact on patient safety in some countries. Security of supply measures will improve availability of both critical and non-critical medicines, which will significantly benefit patients and healthcare services. Citizens will also benefit from strengthened and more holistic ERAs. Lastly, introduction of the legal basis for electronic product information will bring advances to readability for patients and opportunities for healthcare professionals to communicate information more effectively.

### 8.1.2 Industry

For industry stakeholders, reducing the period of regulatory protection and increasing obligations would bring significant changes. There would be additional costs to MAHs and reduced return on investment, leading originators to shift focus to more commercially promising areas. The reduction in regulatory protection may cause relatively more problems for SMEs and also reduce the nature and volume of R&D carried out by the EU pharma industry, though the special incentives for comparative trials, addressing UMN, post-authorisation studies and market launch and continued supply to all MSs would counter this effect to some extent, by offering a longer period for charging premium prices and thus a larger ROI. We have estimated that a 2-year reduction of regulatory data protection is equivalent to loss of €2.4bn–€3.1bn per year to originator industry, as it reduces revenues at exclusive prices. On the other hand, measures to incentivise addressing UMN have the potential to provide benefits amounting to an average of €480m per year, and generating comparative trial data of €720m on average annually. Our analysis also shows that developers granted a transferable voucher in return for developing a novel antimicrobial could have approximately €545m in direct benefits every year, due to the additional income at premium price for the product, as well as the additional income at premium prices for medicines where the voucher has been applied.

Reduction in the standard data protection period would strengthen the EU generics sector and the internal market for medicines. This measure would benefit generics industry at 998m - €1.3bn per year. On the other hand, incentives involving extension of data protection would delay generic entry and keep generic manufacturers out of the market for longer. In the case of UMN incentive of an additional 1 year to originators, it represents a loss of €77m - €154m per year for generic companies, and €154m - €192m for comparative trials. They would also have increased costs from the obligation to include smaller markets in their own mutual recognition procedure (or decentralised procedure)

applications. On the other hand, there should be an increase in R&D activity for generics/biosimilars with a streamlined and clearer regulatory pathway and broadened Bolar exemption.

Policy option C also brings greater certainty for businesses by adding clarity and predictability to the regulatory system. For example, it will adapt definitions of medicinal products and delink scope from industrial processes, establishing risk-based classification for less complex cell-based medicinal products, avoid duplicative process such as current GMO requirements and create a centralised classification tool for borderline products. These measures should promote innovation and shift investment: in 2021, around €20 billion was invested in cell and gene therapies globally, but the EU attracted only €2.9 billion of this (even though down 8% compared to the previous year)[121]. SMEs should also benefit from the introduction of regulatory sandboxes to support development of innovative products, and improvements to the hospital exemption should encourage innovation in the field of advanced therapy medicinal products (ATMPs).

Greater use of multi-country packs is also expected to facilitate the movement of medicines within the EU internal market, which will help all businesses. In terms of security of supply, policy option C introduces several obligations and requirements on MAHs and wholesalers that likely will carry significant costs to these parties including costs associated with warehousing (for stockpiling), operations and capital. Stakeholder consultations estimated that increasing warehouse capacity to accommodate 10% additional stock will have a cost of EUR 500k – 1million per warehouse. This policy option will also bring more transparency and obligations regarding supply chain actors and environmental risk assessments, which will result in additional costs for businesses for inspections, compliance and other additional responsibilities. This will likely represent a very substantial burden on SMEs in particular.

### 8.1.3 Public authorities, agencies and payers

The reduced regulatory data protection period for new medicines will support early generic and biosimilar entry resulting in a decrease in prices, improving access to medicines across MSs and reducing costs for health systems. Our analysis estimates that 2-year regulatory data protection reduction would result in a nominal saving of €2.1bn -€2.7bn per year for the healthcare payers. On the other hand, a reduced regulatory data protection period may cause industry to apply a higher premium on prices of new medicines during the protection period. Similarly, incentives involving additional data protection periods will also lengthen the period in which health systems can be charged higher prices for medicines. For example, transferable vouchers would have indirect healthcare costs for the healthcare payer, although there would be a positive return on investment of 1.2.

Public authorities will require additional budget and expertise for reviewing MA applications (larger number of applications, change in ERA requirements, etc.), enforcement of obligations (e.g. for market launch, lifecycle management of antimicrobials), inspections of manufacturing sites, increased commitments to provide advice (e.g. on interchangeability of biosimilars, ERA, green manufacturing, classification of borderline products etc.) as well as setting up of new centralised infrastructure for information exchange (e.g. for shortage monitoring; one-off costs). Additional costs for EMA in assessing the application for new antimicrobials and the associated voucher are estimated at €2m per year. The workload of pricing and reimbursement agencies would also increase with incentives for market placement driving up the number of applications. Similarly, broadening of bolar exemption and shorter approval timelines may increase the number of MA applications, adding costs for regulators who might need to increase assessment capacity.

Health payers would also benefit from measures to promote post-authorisation studies and comparative trials, which would enable access to evidence that supports paying and reimbursement decisions for HTA bodies. The option to reject immature marketing authorisation applications at time of validation would reduce workload of regulators. We have estimated that refusing immature marketing applications could save the EMA and NCAs 3% of annual costs.

Measures to improve security of supply will facilitate information exchange between Member State authorities and improve strategies to tackle shortages. Both aspects should reduce long-term costs to authorities. However, public authorities will also need to increase capacity to assess shortage prevention plans provided by MAHs, and, depending on the cost and risk-sharing agreements for reserve stock, authorities may also incur direct costs for storage. While measures to improve quality, manufacturing and environmental sustainability of pharmaceuticals will increase workload for EMA

[121] Alliance for Regenerative Medicine. (2022). *Cell & Gene State of the Industry Briefing*. https://alliancerm.org/arm-event/sotibriefing/; Lambot, N., Awigena-Cook, J., Reimer, T., Persson, A., Romanetto, J., Friedeberg, B., Acha, V., Dandapat, S., Ruppert, T., Correas, C., Wonnacott, K., Fleischmann, T., Holzhauser, C., Galaup, A., Montes, F., Garcia, S., Tellner, P., & Beattie, S. G. (2021). Clinical trials with investigational medicinal products consisting of or containing genetically modified organisms: implementation of Clinical Trials Regulation EU 536/2014. *Cell and Gene Therapy Insights*, *7*(9), 1093–1106. https://doi.org/10.18609/CGTI.2021.143

and NCAs as discussed above, increased coordination, joint audits and data sharing could also result in efficiencies.

#### 8.1.4 Academic/research institutions

Policy Option C will bring benefits for clinical researchers and academics in the form of opportunities to be more involved in the development work and trials, as a binding system for scientific assessment of evidence for repurposing off-patent medicines will be established, and obligations will be simplified to facilitate non-commercial entities (e.g. academic) to become marketing authorisation holders. This policy option also brings increased requirements of efficacy and safety for use of hospital exemption (e.g. trial data and good manufacturing practices capability), which will increase costs to academic researchers and research institutions involved in ATMP development. Academics and research institutions will also benefit from streamlining 'horizontal' measures such as fee reduction and more advice to help non-commercial entities to bring innovative products to market.

### *8.2 Horizontal measures*

#### 8.2.1 Balance of costs and benefits for the pivotal horizontal measures

We have prepared an overview of the costs and benefits associated with each of the three major categories of horizontal measures identified through the impact assessment. This analysis has been carried out in line with the better regulation guidelines, with the costs presented in line with the standard cost model. It is presented in the annexes to this report.

It shows estimated total costs for the pivotal streamlining measures combined fall in the range €1.1bn to €2.5bn across the next 15 years. We estimate the total benefits will fall somewhere in the range €2.8bn-€5.8bn across the same period.

Our overall estimates are likely to be understated slightly, as there are likely to be further indirect benefits associated with the horizontal measures, and in particular the likelihood of shortening average times for the assessment of applications should flow through to marginally earlier access to new medicines and generic competitors for large numbers of EU citizens and patients. We were unable to push these estimates to the point where we were able to quantify the likely benefits to patients, which are likely to be relatively limited in depth but wide-ranging.

#### 8.2.2 Pivotal horizontal measures and regulatory fitness and performance (REFIT)

The proposed horizontal measures are intended to deliver wide-ranging improvements to the efficiency and effectiveness of the EU pharmaceutical regulatory system. This is a matter of good public management: it aligns closely with the European Commission's regulatory fitness and performance programme (REFIT), which aims to ensure that EU laws deliver on their objectives at a minimum cost for the benefit of citizens and businesses.

Table 5 presents a qualitative assessment of the benefits for each of the 10 pivotal horizontal measures, rating the likely benefits – against the baseline – on a 3-point scale (H, M, L) for each stakeholder group. From this perspective, the most promising horizontal measures – overall, for all stakeholder groups – are the proposals to improve the governance of the European medicines regulatory network, the development of an integrated, pan-EU data architecture for the regulatory system and an EU-wide, centrally coordinated process for early dialogue.

**Table 5 Qualitative assessment of the benefits of pivotal horizontal measures, by key stakeholder group**

| | Business | EMA | NCAs | SMEs | Health Systems | Environment |
|---|---|---|---|---|---|---|
| Streamlining and de-duplication | | | | | | |
| #1 Streamlining of procedures | H | M | M | H | L | L |
| #2 Accelerated MRP and more efficient RUP | H | L | H | L | M | L |
| #3 Efficient governance of the European Medicines Regulatory Network | H | H | H | H | M | L |

| | Business | EMA | NCAs | SMEs | Health Systems | Environment |
|---|---|---|---|---|---|---|
| #4 Facilitate more efficient interaction across regulatory frameworks | M | H | M | M | M | L |
| Digitalisation | | | | | | |
| #5 Legal basis to allow network to create an integrated, pan-EU health regulatory data service | M | M | H | H | H | M |
| #6 Legal basis for setting up ePIL system for healthcare professionals | L | M | M | L | M | M |
| #7 Electronic submission of applications | H | H | M | H | L | M |
| Enhanced support and regulatory flexibility | | | | | | |
| #8 Optimise regulatory support to SMEs and non-commercial organisation | L | M | L | H | H | L |
| #9 Adaptation of the regulatory system to support the use of new concepts | H | M | M | H | M | L |
| #10 EU-wide centrally coordinated process for early dialogue | H | M | H | H | M | L |

### 8.2.3 Simplification and burden reduction to support the one in one out approach

The pivotal horizontal measures are designed to simplify the regulatory system and reduce burden on industry and regulators alike. This is done for reasons of good governance but also in part to create the financial headroom to introduce new legislative actions and procedures that will inevitably bring additional costs in pursuit of additional social benefits. As a case in point, the strengthening of the environmental risk assessment within the overall assessment process (e.g. in consideration of manufacturing and supply chain issues) will add costs, compared with the current situation, as will the inclusion of environmental issues within post-market authorisation monitoring and reporting activities.

The identification of the specific cost savings has been designed to support the EC in its application of one in one out approach.

We have presented our cost estimates in Annex III for the two horizontal measures that relate most directly to simplification and burden reduction, specifically streamlining and digitalisation measures. The table summarises the balance of costs and benefits, and suggests that the measures as proposed may deliver a reduction in compliance costs and administrative burden in the range of €1.2bn-€2.4bn for industry.

More specifically:

- The proposed streamlining procedures will yield useful cost savings for European pharmaceutical businesses, with estimated cost savings falling in the range of €15m-€30m annually (€225m-€450m over 15 years)
- The streamlining procedures are estimated to be cost neutral for regulators with the balance of costs and benefits estimated to fall close to zero
- The proposed digitalisation measures will provide some financial savings to industry, given the primary focus is on the integration of regulatory systems and platforms across the EU and support for the re-use of data (e.g. the 'Once Only' principle of the EU digital strategy). Electronic submission will deliver industry cost savings. These are estimated at €112m-€225m over 15 years

- The proposed digitalisation measures will provide relatively larger financial savings for regulators, with NCAs accruing a larger proportion of the benefits with the EMA shouldering more of the substantial costs involved in the design and development of the new systems. The savings across the whole EU regulatory network are estimated at €1b-€2b over 15 years

For citizens/patients, many improvements are foreseen in all areas of importance[122] but there are no obligations and therefore costs induced by the legislation.

[122] The legislation aims at improving the flow of cutting-edge treatments available for conditions for which there are no effective treatment options currently (UMN), reversing the decline in investment in antimicrobial research and encircling the issues driving AMR, incentivising access in all Member States, a broader repurposing, and the generic and biosimilar entry. A more robust ERA will also support environmental goals. Measures on security of supply will moreover improve access to medicines.

# 9 HOW WILL ACTUAL IMPACTS BE MONITORED AND EVALUATED?

## *9.1 Defining the monitoring and evaluation requirements*

Monitoring is necessary to allow policy makers and stakeholders to (i) check if policy implementation is 'on track' and (ii) to generate information that can be used to evaluate whether it has achieved its objectives. It is run continuously to generate information for current management and to feed into future evaluations and impact assessments. The framework also needs to be clear about data sources, including instructions as to where data can be accessed or might need to be collected through regulatory processes or periodical surveys, and how those data will be used in the context of the monitoring system.

In developing the framework, we have kept in mind several design principles, whereby the monitoring system will:

- Make maximum use of existing data, for efficiency
- Collect the minimum additional data necessary (i.e. only what is relevant, so as to minimise administrative burden)
- Automate as much as possible to shorten data collection and processing time
- Use common key performance indicator (KPI) definitions and reporting standards to ease sharing of data
- Be transparent towards the stakeholders and opt for making data publicly available, preferably as "open data" (c.f. principles of the eGovernment Action plan)

In addition to observing these design principles, our monitoring and indicator framework encompasses the regulatory system and lifecycle in terms of:

- Implementation and compliance
- Context
- Outputs and outcomes

## *9.2 Key performance indicators*

Table 6 presents an overview of a framework for monitoring the revisions to the EU pharmaceutical legislation, across its lifecycle. To minimise burden, we recommend using a relatively small number of KPIs relating to each lifecycle perspective (e.g. 2-3 indicators relating to critical aspects only). The exception to this principle would be the 'application' perspective, where we would recommend developing and computing 1-3 KPIs for each specific objective (c. 20 in total). Lastly, it would be helpful if several of these 'application' KPIs were carried over from the existing monitoring system, to provide a basis for longitudinal assessment.

**Table 6 A proposal for monitoring performance across the lifecycle of the revised regulation**

| M&E perspective / lifecycle | Description |
|---|---|
| Implementation | We assume the proposed revisions will be implemented through an update to the current EU regulation, which would be applicable immediately in its entirety across all member states. However, there are several examples of proposals for changes that will oblige member states to improve matters in some regard (e.g. prudent use of antimicrobials), but where the specific activities may need to be decided nationally.<br><br>So, there is no need to monitor transposition. However, it would be helpful therefore to put in place a series of monitoring procedures to determine when and how far member states have gone with the implementation of the common principles developed by for example the EMA or the regulatory network.<br><br>Data collection will need to be organised for these 'indirect' policy measures, such as that concerned with antimicrobial resistance where national hard and soft law governs issues such as the use of diagnostics, prescribing practice, and disposal. Member states do not routinely and consistently track / report on policies and practice for these particular dimensions, and the EC would need to set up a dedicated monitoring procedure possibly implemented through the HMA and via an annual (sample) survey. There are important contextual data available on consumption of antimicrobials (European Centre for Disease Prevention and Control-coordinated surveillance), but these are not sufficient to understand Member State support for the specific proposals of the revised regulation. |

| M&E perspective / lifecycle | Description |
|---|---|
| | Other implementation KPIs might be linked with member state reporting of medicines shortages or key implementation milestones, such as the timing of the implementation of proposed new digital solutions (e.g. electronic submission of applications) and underpinning agreements for work-sharing / open access to files, across national regulators. |
| Application | The monitoring system would need to collect data systematically on a series of key metrics relating to each of the specific objectives of the revisions, whether that is improved access to medicines for all patients and across all member states or an improvement in the environmental performance of the EU pharmaceuticals industry. |
| Compliance | The revisions to the regulation will apply to businesses primarily (healthcare systems and clinicians to a lesser extent), and it will be important to monitor the extent to which those organisations subject to the regulation are compliant with the legislation.<br>The compliance metrics will need to reflect the specific proposals included within the preferred policy option. However, they could for example include an annual report prepared by the EMA detailing the number and share of all holders of conditional marketing authorisations that have been granted a full authorisation in the year in review (based on the results of further studies) and the average time taken between the conditional and full authorisation. Given these data are already reported in part in the EMA statistical highlights, it may be reasonably straightforward to do a slightly more detailed analysis and present the data in an annualised form – and with a time series. |
| Context | Pharmaceuticals regulation operates within a broader context of political and economic developments, and it will be important for the monitoring system to maintain an overview of these key factors.<br>As a case in point, there are evident trends in global demand, international trade flows and competitiveness, which reflect many factors in addition to the regulatory attractiveness of the EU pharmaceuticals legislation.<br>A possible candidate KPI for pharma competitiveness would be the EU share of global exports to a select group of developed economies (using UN Comtrade data on exports). This metric could be compared with the US and possibly the UK and Switzerland, and possibly India and China in the medium term (as these two countries' industries are developing rapidly).<br>Likewise, there are important societal trends that will impact health in the EU, ranging from demographics (ageing populations) through to cultural and behavioural traits (e.g. the emergence of more lifestyle-related conditions). The EC / OECD periodical, Health at a Glance Europe (2020) includes several 'contextual' KPIs, including for example: Life expectancy and healthy life years at 65 by gender and country; the contribution of risk factors to inequalities in life expectancy; main causes of mortality. |

Table 7 presents a list of candidate KPIs for the core objectives with suggested data sources and proposed frequency of data collection, which will need to be developed further by the EC, in terms of the relevance and practicality for the detailed legislative design that derives from the overall IA process.

**Table 7 Proposed list of indicators to monitor progress towards the main objectives**

| Specific objective | Potential indicators | Data source/frequency |
|---|---|---|
| Promote innovation, in particular for UMN | EU share of global medicine pipeline overall and in selected key therapeutic areas<br>Number of authorised medicines with new active substance<br>Number of new authorised medicines that address an unmet medical need (UMN) e.g. number of novel antibiotics<br>EU share of the global pipeline for new antimicrobials, including non-traditional technologies, by pathogen and by phase | Informa or equivalent/ biennially or more frequently<br>EMA data/annual<br>EMA data/annual<br>WHO through its monitoring of the global pipeline /annual |

| Specific objective | Potential indicators | Data source/frequency |
|---|---|---|
| | Number of incentives granted for comparative trials | EMA data/annual |
| | Use of pre-marketing regulatory support (scientific advice, PRIME) | EMA data/annual |
| | | EMA data/annual |
| Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation | Market share of generic and biosimilar medicines | IQVIA data/biannual |
| | Development of prices of medicines | Euripid database, IQVIA data, OECD data/biannual |
| | Member States' pharmaceutical spending | Eurostat, OECD data/biannual |
| | Annual R&D expenditure (BERD) as share of sales, by EU pharma and indexed against trend in R&D intensity for EU manufacturing overall | Eurostat data/annually |
| | EU share of global, medicines-related patents | Patstat data/annually |
| Ensure access to innovative and established medicines for patients, with special attention to enhancing the security of supply across the EU | Time from authorisation to market launch | IQVIA sales data/biannual |
| | Average number of EU countries (%EU27, %EU13) where authorised medicines are approved for sale for selected therapeutic areas, indexed by volume of sales / million population | IQVIA sales data/1 to 5 years |
| | Number of critical medicines in shortage | EMA and NCA data/annual |
| | Number of withdrawals, by time of reporting and measures to limit impact of withdrawal | EMA and NCA data/annual |
| | Number of ongoing and resolved medicines shortages for the EU overall, by country, duration and by type / reason for the shortage. | EMA and NCA data/annual |
| Reduce the environmental footprint of the pharmaceutical product lifecycle | EU-based pharmaceutical manufacturers' GHG emissions (tCO2e in total and / €bn GVA) | EEA and Eurostat statistics/annually |
| | EU occurrences of pharmaceuticals in the environment | Unwelt Bundesamt database/ annually |
| | Consumption of antimicrobials | ECDC data/annually |
| Reduce the regulatory burden and provide a flexible regulatory framework | Number of applications | EMA data/annual |
| | Number of formal requests for scientific advice, early dialogues, etc. by type of stakeholder | EMA data/annual |
| | Average total elapsed time taken by EMA to make a recommendation on new medicines applications, overall and by regulatory pathway | EMA data/annual |
| | Average time for the EMA to complete its assessment and separately to conclude the decision process | EMA data/annual |
| | Average time for the company contributions / responses to queries (so called 'clock stop), for all firms / SMEs and for the main regulatory pathways. | EMA data/annual |
| | Average time taken by NCAs to assess medicines applications nationally | NCA data/annual |
| | Number of variations | EMA, CMDh and NCAs/ annually |

# 10 ANNEX II: METHODOLOGY AND MODELS

## *10.1 Data sources*

There have been multiple data sources and related analytical methods applied to provide evidence for the impact assessment of the policy elements and options in this study.

**Literature and document review**: we have carried out a targeted literature and document review of academic and grey literature, using specific topics of each policy option, such as access to medicines, to guide our searches. there is a growing body of published literature and analysis reports that studied specific phenomena relevant to aspects of the pharmaceutical legislation. These provide a direct source of facts and figures that we used in our assessments and referenced across the report. Wider literature relevant to newer challenges for the pharmaceutical industry were also reviewed in order to identify future proofing challenges, resilience of supply chains, new manufacturing methods, combination products, digitalisation, new evidence requirements by regulatory authorities and environmental protection.

Our search strategy followed a heuristic approach, using the objectives of the revision to focus our efforts, but building out from our existing view of matters, based on our and others' recent studies, but also the Commission's own recommendations. Our searches covered peer-reviewed and grey literature using keywords in English, Dutch, French, German and Spanish across Pubmed, Scopus, EU institutions, agencies and regulator websites, Google Scholar and international organisations such as WHO and OECD. We have also identified sources from stakeholders such as industry organisations and patient associations.

**Secondary data analysis:** quantitative data collected along the medicinal product lifecycle was analysed to derive a set of indicators and feed quantitative modelling of various policy scenarios. For problem analysis and baseline, we used data where available for the period of 2005-2020 from the IQVIA MIDAS dataset, Informa Datamonitor and Pharmaprojects, EMA's central Marketing Authorisation Application dataset (prepared by Utrecht University), MRI decentralized / mutual recognition procedures database, EudraGMP, and an EU shortages dataset collected from National Competent Authorities for a bespoke European Commission study by Technopolis Group. The results of this are available in a separate Analytical report.

**Stakeholder consultations:** a number of different approaches were used in gathering evidence and views of stakeholders, which are summarized in a separate Synopsis report. These included a feedback to roadmap and a public consultation (both through the 'Have Your Say' EC website), a targeted survey, semi-structured interviews and two dedicated stakeholder workshops with civil society organisations, academic researchers, public authorities, healthcare professionals and industry.

**Key challenges:** All methods applied to our research encountered a varying degree of difficulty in relation to lack of quantitative data available in the databases and sources examined. Despite a growing body of literature and evidence in several relevant areas (e.g. AMR), we did not find enough data to quantify all relevant impacts of every policy measure discussed in the policy options for the future of the legislation. Whenever possible, we have made reasonable assumptions to assess the impacts, but this lack of quantitative data is a key limitation to our analysis.

## *10.2 Identifying and selecting significant impact types*

We carried out an initial screening of the 35 impact types set out in the Better Regulation toolbox to identify the impacts the study will be reviewing more in depth for each policy block with each policy option. We used findings from the various analytical strands and data sources to identify all potentially important impacts, considering both positive/negative, direct/indirect, intended/unintended as well as short-/long-term effects. Specifically, our screening was based on the principle of proportionate analysis and considered the following factors.

- The relevance of the impact within the intervention logic
- The absolute magnitude of the expected impacts
- The relative size of the impacts for specific stakeholders
- The importance of the impacts for the EC's horizontal objectives and policies
- Any sensitivities or diverging views

This screening identified 10 of the 35 impact types as being of most significance for this impact assessment and therefore a deeper assessment was appropriate for the following key impact types (indicated with grey shading in Table 8):

- Conduct of business
- Administrative costs on businesses
- Position of SMEs
- Sectoral competitiveness and trade
- Functioning of the internal market and competition
- Innovation and research
- Public authorities
- Resilience and technological sovereignty
- Public health & safety and health systems
- Sustainable consumption and production

**Table 8 Overview of impacts screened with justifications**

| Impact type | Justification for inclusion / exclusion in the Impact Assessment |
|---|---|
| Climate | No stakeholder group has indicated that the legislation should be reframed to fight climate change.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and climate change. While pharmaceutical manufacturers do emit GHGs, their carbon improvement plans are being driven through other policy levers.<br><br>The legislation's oversight of manufacturing standards could be used conceivably to influence emissions; however, such a condition would be a major departure for pharma regulators and inspectors and would challenge their capacity and competence. Equally, it would likely duplicate efforts being pursued through various other policy initiatives and legislative actions occurring under the European Green Deal. |
| Quality of natural resources | Several regulators and environmental groups argued that the legislation should be revised in order to reduce releases to the environment of active substances (e.g. antimicrobials) to protect and improve the quality of the environment (e.g. water quality). |
| Biodiversity | No stakeholder group has indicated that the legislation should be reframed to improve biodiversity.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and biodiversity. |
| Animal welfare | No stakeholder group has indicated that the general legislation should be reframed to improve animal welfare.<br><br>Our desk research confirms there is an indirect link between new medicinal products and animal welfare, using animals in scientific research. However, this important issue is dealt with through the Lisbon treaty and other EU and national legislation, wherein there is a legal requirement for the pharmaceutical and scientific community not to use animals where there is an alternative. EUs Directive 2010/63/EU on the protection of animals used for scientific purposes addresses this issue and is based on the principal of an internationally recognised principle, the 3Rs (Replacement, Reduction, and Refinement). |

| Impact type | Justification for inclusion / exclusion in the Impact Assessment |
|---|---|
| Working conditions | No stakeholder group has indicated that the legislation should be reframed to improve working conditions.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and job standards / quality across the EU pharmaceutical economy broadly defined.<br><br>Moreover, so far as these types of issues may affect employees in the EU pharmaceuticals industry, regulatory bodies and healthcare services, these employers are regulated already by the more generic EU employment package that specifies citizens' rights to fair working conditions (e.g. the European Pillar of Social Rights and the EU Working Time Directive, 2003/88/EC). |
| Public health & safety and health systems | Both our primary and secondary research have confirmed the continuing primacy of public health & safety and health systems as a focus for the legislation. This impact dimension includes patients' interests. |
| Culture | No stakeholder group has indicated that the legislation should be reframed to improve European culture and cultural heritage.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and culture. There are aspects of culture that may be relevant indirectly, such as the culture of patient care or animal welfare. However, these indirect aspects are addressed by other existing legislation and codes of conduct, often national, such as the German Federal Code of Conduct of Healthcare Professionals, and as such there is no prima facie need to bring such principles and values into the general legislation. |
| Governance, participation and good administration | No stakeholder group has indicated that the legislation should be reframed to improve governance and administration. Our desk research found no evident direct association between the mandate of the general legislation and good governance.<br><br>There are aspects of good governance and administration that may be relevant indirectly to this specific legislation, such as the consistency, fairness and transparency of the scientific assessments that sit at the heart of the authorisation procedures.<br><br>However, while the legislation will be expected to enshrine these principles in its articles and implementation – reflecting the obligations set out in the Treaty of the Functioning of the EU and the EU Charter of fundamental rights – promoting good governance in general will not be an objective. |
| Education and training | No stakeholder group has indicated that the legislation should be reframed to improve education and training.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and education. |
| Conduct of business | While conduct of business is also impacted by national laws, stakeholders have indicated that the general legislation has a significant impact in the conduct of business, from medicine development to distribution.<br><br>Our desk research found that business have adapted to cope with increased regulatory requirements as well as to benefit from a more coherent and streamlined regulatory process (e.g. centralised authorisation procedure). |

| Impact type | Justification for inclusion / exclusion in the Impact Assessment |
|---|---|
| Position of SMEs | The evaluation revealed the 2004 revisions have been effective in supporting SMEs in developing novel medicines.<br><br>Our desk research and consultations confirm that micro and small businesses are an important sub-group driving innovation in medicines.<br><br>As is the case more generally, pharmaceutical and biotechnology SMEs face additional market barriers as compared with their larger counterparts.<br><br>While there is widespread policy support for SMEs in general, at EU, national and sub-national levels, biopharma SMEs are key drivers of innovation and they face bigger challenges than SMEs in general, given the very large cost, lengthy timelines and regulatory hurdles associated with the development of new medicines (c. 10 years from pre-clinical research through to regulatory approval, and with high attrition rates at each stage). |
| Administrative burdens on business | The legislation applies to pharmaceuticals businesses directly and as such places some additional administrative requirements on economic actors, beyond what they might need to carry out were there no general pharmaceuticals legislation.<br><br>Our consultations have found that the additional costs relate largely to companies' regulatory costs and that the evolving regulatory landscape is creating complexity and adding to their administrative burden.<br><br>Our consultations have further identified the ambition across industry to look at ways to streamline, simplify and automate aspects of the legislative process in order to reduce administrative burden (unnecessary costs). |
| Sectoral competitiveness, trade and investment flows | Our consultations suggest the legislation is a factor in industry competitiveness and our industry respondents in particular – public authorities too to a lesser extent – see competitiveness as an important focus for the general pharmaceutical legislation going forward.<br><br>Our desk research has confirmed that the legislation was designed to ensure the EU's regulatory attractiveness within a global industry and also to help secure the competitiveness of EU-based pharmaceutical industry internationally.<br><br>The EU Pharma Strategy notes the global strength of the EU pharma industry and that this strategically important industry is coming under increasing pressure from established and new regions (e.g. China and India), with risks in terms of direct economic benefits (e.g. EU jobs and investment being lost to other regions) and technological sovereignty (e.g. security of supply of medicines and key APIs). |
| Functioning of the internal market | This is an important focus of the legislation and one where it has had some but limited success, due to the interplay between EU laws on authorisations and national laws and practices on the approval and pricing of medicines.<br><br>Our consultations and desk research suggest this should continue to be a focus for the legislation going forwards. |
| Public authorities and budgets | Stakeholder feedback confirms the legislation impacts public authorities and their budgets, with national regulators flagging concerns about the increasing costs of supporting the work of the EMA and health systems / CSOs / academics raising concerns about potential new incentives and increasing pressure of national budgets for medicines and healthcare.<br><br>Our desk research confirms that changes to the legislation will have implications directly for the actions and budgets of both European institutions (the EMA) and |

| Impact type | Justification for inclusion / exclusion in the Impact Assessment |
|---|---|
| | national competent authorities and indirectly for national health technology assessment agencies and, critically, health payers. |
| Sustainable consumption and production | A minority of stakeholders – environmental groups – have signalled the need for the legislation to do more going forwards about the impact of any poor practice in pharmaceuticals disposal and other sources of environmental releases that can damage ecosystems, for example, manufacturing and use of pharmaceuticals.<br><br>Our desk research confirmed that there is a concern relating to the overuse of antibiotics and efforts to reduce use / misuse and thereby minimise the negative impact on the growing problem of antimicrobial resistance. There is also a concern about environmental degradation and downstream impacts on the public due to exposure to pharmaceuticals in the environment.<br><br>The EU pharmaceutical industry – and national healthcare systems that are prescribing medicines – do have obligations to support sustainable production and consumption. These actors are also subject to the various EU initiatives and regulations introduced as a result of the Sustainable Consumption and Production (SCP) Action Plan and Circular Economy Action Plan (and other aspects of the European Green Deal), from eco-design to green procurement. |
| Efficient use of resources | No stakeholder group has indicated that the legislation should be reframed to improve resource efficiency.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and resource efficiency.<br><br>As with sustainable consumption, the EU pharmaceutical industry is affected by the European Green Deal, however, there is no evident case for using this specific legislation to pursue this more general EU objective. |
| Land-use | No stakeholder group has indicated that the legislation should be reframed to improve land-user.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and land use.<br><br>The industry's production capacity, distribution and warehousing infrastructure is well established.<br><br>There is a conceivable risk, however, that EU-wide efforts to improve supply-chain resilience and reduce medicines shortages may lead to some reshoring of pharma production capacity and an expansion in warehousing and stockholding more generally. However, such changes are likely to be small in relative terms and offset by the continuing movement of at least some production capacity (e.g. generics) to regions outside Europe. Lastly, planning is not an EU competence. |
| Environmental risks | While there is a risk of release of pharmaceuticals in the environment, these risks arise from consumption and production of pharmaceuticals, and as such relevant impacts are covered under the dimension of sustainable consumption and production, which is more directly under the remit of the general pharmaceutical legislation.<br><br>Environmental risks also fall more directly under other EU legislations such as REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) and the EU Water Framework Directive. |
| Employment | No stakeholder group indicated that the legislation should be reframed specifically to expand EU employment. |

| Impact type | Justification for inclusion / exclusion in the Impact Assessment |
|---|---|
| | There is feedback from stakeholders that suggests changes to the legislation could affect the competitiveness of the EU pharma industry in future and – by implication – reduce the industry's total output and employment.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and employment. However, there is a large economy – in the public and private sector, involved in the development / production / supply of medicines. With more than 830,000 jobs (2020) across the EEA countries, many of which are high value jobs, it will be important to consider the implications of any proposed changes for employment in this strategy sector.<br><br>However, the legislation potential to impact EU employment in a more general sense is not material, and as such we propose to consider the issue of employment and economic output of the EU pharma industry under the competitiveness impact listed above. |
| Income distribution | No stakeholder group has indicated that the legislation should be reframed to improve income distribution.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and social inclusion.<br><br>There are however concerns about the legislation's impact on the price of medicines and a suggestion that the incentives are raising prices and creating issues of affordability that are experienced unevenly across member states and socio-economic groups, however, this is many points removed from the focus of the legislation. It will be considered through the impact on Fundamental Rights (medicines access and health inequality). |
| Technological development / digital economy | Stakeholder groups recognise the importance of scientific and technological advances to the development of novel medicines, however, it is really only industry that see it as a primary objective for the legislation.<br><br>The research-intensive pharma industry is the strongest advocate of the need for the legislation to continue to catalyse and reward technological development. Distributors and generics companies prioritise technological development in manufacturing and digitalisation more generally.<br><br>Public authorities, health systems and patients' groups are interested in unmet medical needs, which in many cases is likely to require.<br><br>Our desk research confirms the critical nature of technological development to new medicines, with pharma R&D investment levels far outstripping the research intensity of almost all other economic sectors, and with share prices / M&A activity being heavily influenced by the quality of medicines pipelines. |
| Consumers and households | No stakeholder group has indicated that the legislation should be reframed to improve the financial situation of the EU's consumers and households.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and consumer habits or household finances / savings.<br><br>There is a possible, but very indirect impact through the legislation's preferential support for novel – possibly higher-priced – medicines resulting in higher medicines bills for national health systems that may flow through to higher social costs or health insurance premiums for citizens.<br><br>The price of medicines and its impacts on national healthcare systems is included in impact dimension "Public authorities and budgets"; the underpinning drivers of the price of medicines are discussed under "Functioning of the internal market and |

| Impact type | Justification for inclusion / exclusion in the Impact Assessment |
|---|---|
| | competition" impact type. Patient interests are included in the 'public health and safety' impact dimension. |
| Capital movements, financial markets, stability of the Euro | No stakeholder group has indicated that the legislation should be reframed to improve the EU's macro-economic performance.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and the EU's macro-economic performance.<br><br>The pharmaceutical industry is a large global industry that will have some limited impact on capital movements in the EU, whether that is through major investments (e.g. share purchases) or Foreign Direct Investments (FDI) or infrastructure investments. These are too small to materially affect the stability of the EU financial markets / Euro, and are in any way covered by more general legislation (e.g. Article 63 of the Treaty on the Functioning of the EU). |
| Property rights, intellectual property rights | Stakeholders expressed support for the introduction of the Bolar provisions and various industrial and civil society groups would like to see the relationship between regulatory protection and IP rights looked at again to ensure the balance is right, between risk and reward for developers on the one hand and the cost to the health systems on the other.<br><br>Our desk research confirms that the legislation has been framed specifically to address market failures around IP in the medicines domain and that modifications to the term / nature of regulatory protection and IP can have important behavioural impacts (e.g. for industry).<br><br>However, the scope of the current study clearly states that the current legislation aims to be coherent with rather than impact on IP rights such as the patent system. |
| Territorial impacts | Stakeholders report the legislation as having had a positive impact geographically, inasmuch as the harmonisation of definitions and procedures has resulted in some small improvement in access. Many expressed concern that there is still too much unevenness in prices and access to medicines, particularly for smaller member states, and that the legislation should be reframed to improve matters<br><br>Our desk research underlined the commitment of the legislation to be geographically agnostic, while also confirming the territorial unevenness of access and prices. While these territorial impacts may be the result of wider factors, in large part, any future legislation may be able to improve matters indirectly.<br><br>We can address this question of access through considering the proposed revisions' impacts from the perspective of health inequality geographically and socially, through consideration of the EU's commitments to Fundamental Rights. |
| Innovation, research | Stakeholders confirm that the legislation positively reinforces industry's commitment to research and the development of innovative new medicines. The research-intensive industry has argued that the new legislation needs to be framed in a manner that ensures Europe's continuing regulatory attractiveness, to keep development in the EU and to ensure the EU market is one of the first recipients of innovative products. Other stakeholder groups (e.g. academics and clinical researchers) have expressed a desire for the legislation to give more targeted encouragement to research and innovation originating in the not-for-profit sector.<br><br>Our desk research confirms the legislation was framed with the express intention of incentivising greater investment in medicines research in the EU as a platform for the development of innovative new medicinal products. |

| Impact type | Justification for inclusion / exclusion in the Impact Assessment |
|---|---|
| Fraud, crime, terrorism, and security | No stakeholder group has indicated that the legislation should be reframed to improve the EU's crime and security.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and the EU's crime and security.<br><br>There is one area of fraudulent or criminal activity relating to licencing of medicines, which is the growing number of medicines being falsified. These include expensive medicines, such as anticancer medicines, and medicines in high demand, such as antivirals. In the EU, this phenomenon is regulated by the directive on falsified medicines, so that only licensed pharmacies and approved retailers are allowed to offer medicines for sale.<br><br>There is no suggestion that the general pharmaceutical legislation should be revised to strengthen the overall EU response to this problem. |
| Resilience, technological sovereignty, security of supply | Large numbers of stakeholders have suggested the legislation should consider ways in which it might give greater weight to resilience and security of supply, when granting authorisations. The pandemic has also raised concerns about the EU's strategic autonomy in for example antivirals.<br><br>Desk research confirms these aspects are not addressed directly by the current legislation, albeit there are evident opportunities for introducing such features as criteria used in the assessment process and as obligations to be reported on and monitored through refinements to the GMP / GDP procedures. |
| Transport and the use of energy | No stakeholder group has indicated that the legislation should be reframed to improve the EU's transport systems.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and the EU's transport systems. Studies do show that the industry's global supply chains and local distribution systems do contribute significantly to the sector's overall carbon footprint. That is to say, the industry's current modus operandi does make extensive use of transport systems, which results in higher energy use and emissions.<br><br>However, improvements in the carbon footprint of the pharma distribution industry will follow from the general implementation of the EU's Green Deal.<br><br>While stakeholders have suggested the general pharmaceutical legislation might consider including criteria relating to the resilience of supply chains (pre and post authorisation), and while this could lead to the reshoring of the manufacture of key ingredients and shorter supply chains in general, it seems unlikely to result in a significant change in energy use within the transport element. |
| Food safety, food security and nutrition | No stakeholder group has indicated that the legislation should be reframed to improve the EU's food safety or food security.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and the EU's food security. |
| Waste production, generation and recycling | No stakeholder group has indicated that the legislation should be reframed to improve the EU's waste management and recycling.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and the EU's waste management and recycling. Nevertheless, aspects may be included under the "Sustainable consumption and production" impact type. |

| Impact type | Justification for inclusion / exclusion in the Impact Assessment |
|---|---|
| | As with many of these important policy impacts, the pharma industry will be addressed through more general legislation and policy initiatives, such as the EU Circular Economy Action Plan and other elements of the Green Deal. |
| Third countries, developing countries and international relations | No stakeholder group has indicated that the legislation should be reframed to improve the EU's international relations.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and the EU's international relations.<br><br>There are important issues around medicines and developing countries, with an evident preference amongst developers for medicines for high income countries (90% of the global consumption of medicines is consumed by 15% of the world's population) and the consequent neglecting of tropical diseases affecting millions of the poorest and most marginalised people globally. There are also issues around the pricing and affordability of medicines, and the encouragement of earlier market entry by generics.<br><br>The general pharma legislation could conceivably be revised to reward the development of medicines for neglected diseases specifically or to change IP rules to allow the limited and exceptional right of developing countries to access and use IP for public health. These would be challenging developments, that have not been raised anywhere in respect to the general pharma legislation and moreover, there are other EU measures through which these issues are being tackled (e.g. through the operation of TRIPS; or the Horizon Europe support for research in neglected disease).<br><br>It is conceivable that changes to the legislation could have an impact on relationships with third countries like Switzerland, the UK and the US. However, this is unlikely to be a matter of concern for governments, and there are various institutional and professional fora and networks where the EU comes together with its regulatory counterparts from other countries. |
| Sustainable development | No stakeholder group has indicated that the legislation should be reframed specifically to improve the EU's sustainable development.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and the EU's sustainable development goals.<br><br>However, any major revisions to the legislation could have an impact on the EU's sustainable development, and so while this is not a general or specific objective for the EU general pharma legislation, any proposed revisions will need to be assessed in part against their potential impacts on sustainability.<br><br>Art. 37 of the EU Charter of Fundamental Rights states that a high level of protection and improvement of the quality of the environment must be integrated into the Unions' policies and ensured in accordance with the principle of sustainable development. |
| Fundamental rights | No stakeholder group has indicated that the legislation should be reframed specifically to improve the EU's fundamental rights. However, stakeholders do report issues with unequal access to medicines and affordability issues.<br><br>The European Charter of Fundamental Rights encompasses the ideals underpinning the EU: the universal values of human dignity, freedom, equality and solidarity, which have created an area of freedom, security and justice for people based on the principles of democracy and the rule of law.<br><br>Our desk research found no evident direct association between the mandate of the general legislation and the EU's sustainable fundamental rights. However, indirectly these could be linked to access issues and health inequality in general, covered partially under "public health and safety" impact type. |

### *10.3 Multi-criteria analysis*

Evidence from all data sources was structured along each impact type for each policy element within policy blocks in each of the policy options. This exercise involved a triangulation of qualitative and where available quantitative data explored in the study. Where data gaps were evident, these were clearly noted and best judgement was used by study team members in the following scoring process.

A 7-point scale was adopted to quantify the scale of the impact and likely balance of costs or benefits with a grading system between -3 (significant negative impact expected for the specific impact type) through 0 (no impact is expected from applying a specific policy elements) to +3 (significant positive impact expected for the specific impact type), as compared with the baseline. In most cases, the directionality of impacts for stakeholders was gathered via stakeholder consultation and the extent of impact (performance) was assessed by the study team. Initial scores were given for policy elements in a policy block by study team members responsible for data triangulation for a specific policy block. Scoring across all policy blocks was then reviewed by a panel of three senior members of the study team to ensure consistency.

Multiple policy elements may act in concert or partially against one another when looking through the lens of specific impact types and so internal synergies and tension within a block were considered when overall scores were given. Note that weightings for all impact types were assumed to be 1. Synergies across policy blocks were more challenging to adequately quantify as in any multi-body problem the effects are not additive. Therefore, we provide a qualitative assessment of identified synergies and trade-offs in case specific policy options are simultaneously implemented in a policy option.

This approach allows for a rapid overview and ranking of policy options, for policy elements in a policy block, and suggest which scenario is expected to meet the specific policy objective with the significant positive impact.

### *10.4 Modelling changes in regulatory data and market protection system*

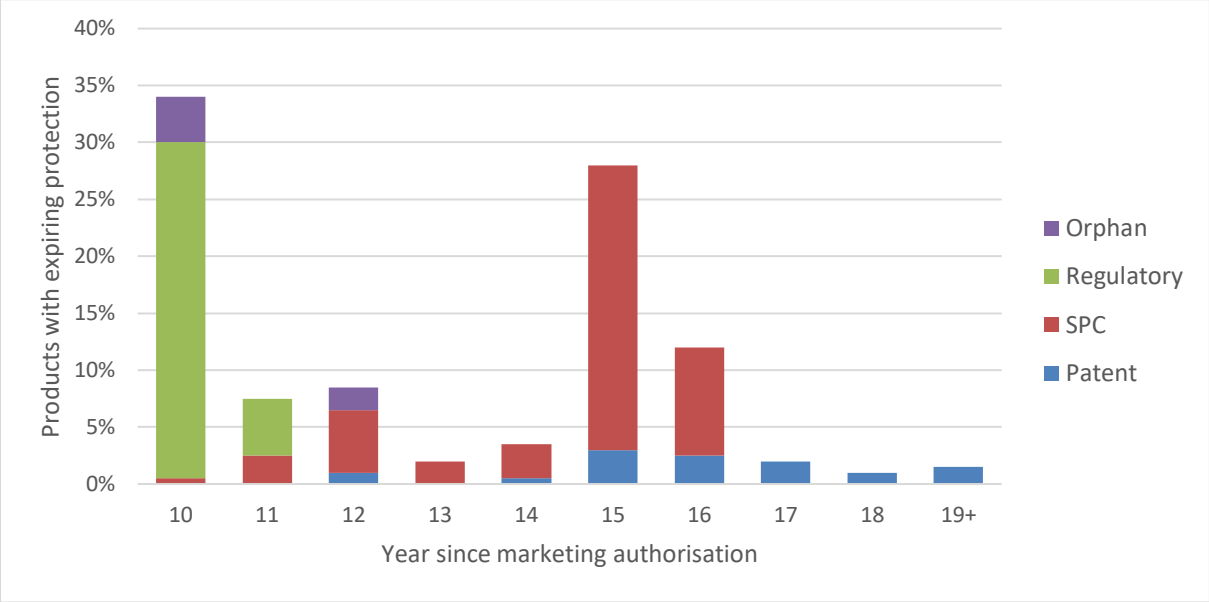
#### 10.4.1 Protection types and length in a sample of medicines

A basket of 217 products was selected based on IQVIA Ark Patent Intelligence data where the loss of protection (LOP) date was between 2016-2024 in four countries: France, Germany, Italy, and Spain. We chose this sample in earlier years and other countries the regulatory protection system was not fully harmonised due to the legacy of the pre-2005 system. This sample has an additional benefit of having a prospective feature, in that it shows, based on empirical data, the composition of the most recent and also the expected future protection expiries of medicinal products.

- Of the 200 products that are on the market (not withdrawn), 69 products had currently regulatory data and market protection (RDP) as last measure of protection. This means that 35% of the products in this sample would in principle experience reduced protection under a shortened standard regulatory protection system. Note however, that nine of these products had 24 months or less between RDP and patent/SPC expiry and consequently, these products will be affected to a smaller extent by a two-year reduction of the standard RDP period. We therefore estimate that 30% of all new medicines will be affected by a two-year reduction of the standard RDP period.

The figure below shows that after 10 years from marketing authorisation date, 30% of products have RDP expiry and 5% of products have RDP expiry in year 11 (due to the additional year of regulatory protection for a new therapeutic indication of significant benefit). Close to half of the products have an SPC expiring as the last measure of protection, predominantly 15 years after marketing authorisation (the maximum value for the combined patent and SPC protection period from marketing authorisation), with a smaller fraction having additional paediatric SPC extension.

**Figure 3 Distribution of protection expiry dates per type**




Note however that while RDP-protected products comprise about one third of the product basket, their share in total sales is only 23% of the total. The largest share of the total sales comes from SPC-protected product; when normalised per product, peak sales of SPC-protected products are 2.3 times higher than that of RDP-protected products.

**Table 9 Share and average peak sales of products under different protection types**

| Protection type | Share of total products | Average peak sales |
|---|---|---|
| Orphan | 6% | €42m |
| Regulatory | 34.5% | €158m |
| SPC | 48% | €358m |
| Patent | 11.5% | €257m |

### 10.4.2 Developing an 'analogue' representing an innovative medicinal product lifecycle

We generated an average sales revenue-volume graph that captures the lifecycle of innovative products over the non-contested RDP period and that contested by generic/biosimilar medicines in the post RP expiry period. Since this requires a minimum of 16 years of consistent longitudinal data for a product, we used a cohort of medicines approved between 2004 and 2011, where RDP is the last measure of protection. For practical reasons the cohort was split into two parts.

The first part included 20 products[123] (involving 2 biologic molecule) that have RDP expiry dates between 2016-2021 and for these annual sales were calculated over a 10-year period pre-expiry. The second part included 16 products[124] (involving 1 biologic molecule) that have RDP expiry dates between 2014-2016 and for these products annual sales were calculated over 5 years post expiry, along with annual sales data for their generic competitors. Note that 2 products were not contested

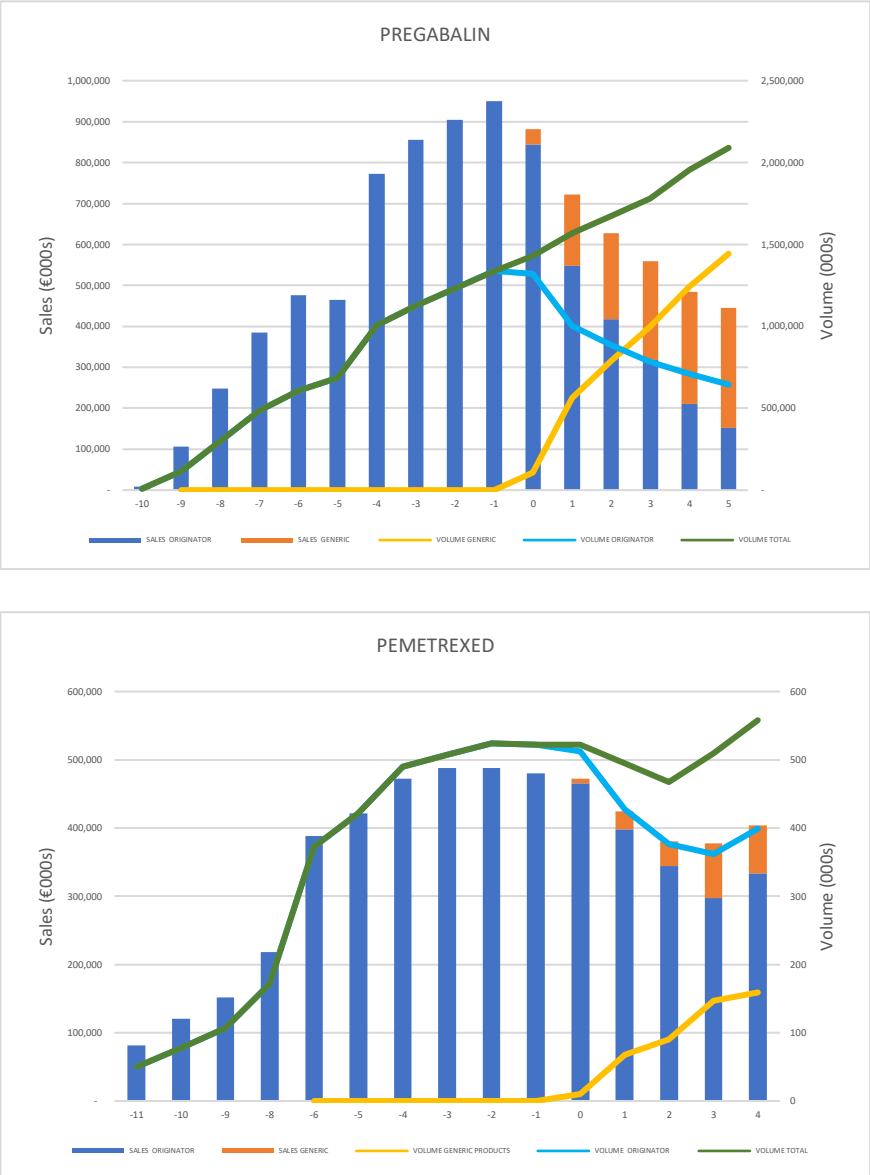
[123] Products included: AGOMELATINE, AMLODIPINE!HYDROCHLOROTHIAZIDE!OLMESARTAN MEDOXOMIL, AMLODIPINE!HYDROCHLOROTHIAZIDE!VALSARTAN, AMLODIPINE!OLMESARTAN MEDOXOMIL, ANAGRELIDE, AZACITIDINE, CABAZITAXEL, CLEVIDIPINE, CLOFARABINE, DRONEDARONE, FEBUXOSTAT, GEFITINIB, *MIFAMURTIDE*, NELARABINE, PALIPERIDONE, PRASUGREL, ROFLUMILAST, SILODOSIN, ULIPRISTAL ACETATE, *VELAGLUCERASE ALFA*

[124] Products included: ALENDRONIC ACID!COLECALCIFEROL, ANAGRELIDE, CEFDITOREN PIVOXIL, *CETUXIMAB*, CLOFARABINE, DULOXETINE, EPLERENONE, FULVESTRANT, HYDROCHLOROTHIAZIDE!OLMESARTAN MEDOXOMIL, METFORMIN!PIOGLITAZONE, PEMETREXED, PREGABALIN, RASAGILINE, TIMOLOL!TRAVOPROST, TREPROSTINIL, ZONISAMIDE

after RDP expiry but included in the cohort to allow for observing systemic effects. For example, the RDP period for the biologic Cetuximab expired in 2014 and no biosimilar entered the market to date.

There is significant variation of the sales revenue-volume graphs across individual products, in some cases rapid generics entry erode the market value of the originator product, in other cases the originator maintains their market share, dependent on the level of sales generated by the originator. For two examples, please see the figure below:

**Figure 4 Sales and volume data for two products from the 2014-16 cohort**




We noted that very few biologics were found to be in the cohort for our analysis, however the biologics pipeline is growing (especially antibody modality, see recent IQVIA report on biosimilar competition in Europe[125]) and expected to make a larger share of future product baskets. Biologics and biosimilars may have unique market dynamics because of differences in related development timeline and cost-profile. A comparative analysis of medicinal products launched between 1996-2014 shows that biologics are introduced faster and in more countries than non-biologic medicinal products[126] as it may be more profitable for developers compared to small-molecules. Switching from originator to biosimilars may also have different considerations, and recently launched

[125] The Impact of Biosimilar Competition in Europe (2021) IQVIA. Available at: https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/iqvia-impact-on-biosimilar-competition.pdf
[126] Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018) Copenhagen Economics. Available at: https://data.europa.eu/doi/10.2873/886648

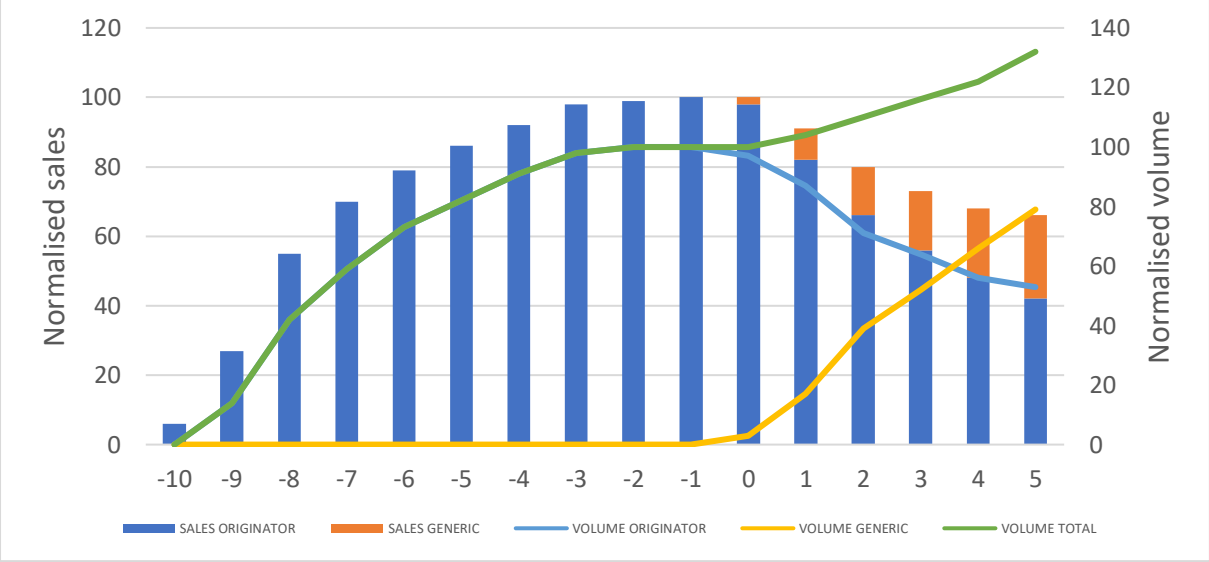
biosimilars achieved over 50% uptake in their market within two years.[4] Examples of blockbusters (e.g. Humira, Herceptin and Enbrel) show that biologics are often protected by SPCs beyond RDP expiry and biosimilars enter soon after expiry. In the RDP cohort, we noted however another blockbuster example Xolair (Omalizumab) where RDP as the last measure of protection expired in 2015 yet no biosimilar entry has taken place. While there is no current SPC on the product, there is a formulation patent until 2024 in force that may be constraining. In summary, it is not clear what share new biosimilars will have in future RDP product cohorts where reduced regulatory protection period would be of effect. If the share of biologics substantially increases, it is likely that the general product sales/volumes model employed here will be less predictive.

In order for sales revenues (euros) and volumes (standard units) across the pre-expiry and post-expiry cohorts and periods can be joined up and compared, aggregate absolute values were normalised so that the originator products' total sales and volume become equal to 100 at one year before protection expiry (Y-1). The resulting table and corresponding figure are shown below:

**Table 10 Normalised sales, volume and price for products with RDP as last measure of protection**

| Year from expiry | -10 | -9 | -8 | -7 | -6 | -5 | -4 | -3 | -2 | -1 | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Originator sales | 6 | 27 | 55 | 70 | 79 | 86 | 92 | 98 | 99 | 100 | 98 | 82 | 66 | 56 | 48 | 42 |
| Generic sales | | | | | | | | | | | 2 | 9 | 14 | 17 | 20 | 24 |
| **Total sales** | **6** | **27** | **55** | **70** | **79** | **86** | **92** | **98** | **99** | **100** | **100** | **91** | **80** | **73** | **68** | **66** |
| Originator volume | 0 | 14 | 42 | 59 | 73 | 82 | 91 | 98 | 100 | 100 | 97 | 87 | 71 | 64 | 56 | 53 |
| Generic volume | | | | | | | | | | | 3 | 17 | 39 | 52 | 66 | 79 |
| **Total volume** | **0** | **14** | **42** | **59** | **73** | **82** | **91** | **98** | **100** | **100** | **100** | **104** | **110** | **116** | **122** | **132** |
| Originator price | | 1.93 | 1.31 | 1.19 | 1.08 | 1.05 | 1.01 | 1.00 | 0.99 | 1.00 | 1.00 | 0.94 | 0.93 | 0.88 | 0.86 | 0.79 |
| Generic price | | | | | | | | | | | 0.67 | 0.53 | 0.36 | 0.33 | 0.30 | 0.30 |
| **Average price** | | 1.93 | 1.31 | 1.19 | 1.08 | 1.05 | 1.01 | 1.00 | 0.99 | 1.00 | 1.00 | 0.88 | 0.73 | 0.63 | 0.56 | 0.50 |

**Figure 5 Normalised sales and volume for products with 8+2 years of RDP period (baseline)**




It is evident from the graph that sales revenue and volume grow year-on-year over the 10-year RDP period as (i) the product is taken up by the health system and make it accessible to increasingly more patients; and (ii) product is launched in increasingly more member states. It should be noted that health systems may require a number of years before the product becomes accepted by health professionals and routinely prescribed. However, these effects are expected to reach a plateau within

a couple of years of introducing the product in a market, and indeed the figure shows that by Y-3 sales figures are close to peaking. The last year before expiry therefore accounts for 14% of total pre-expiry sales; while the final two years account for 28% of total pre-expiry sales.

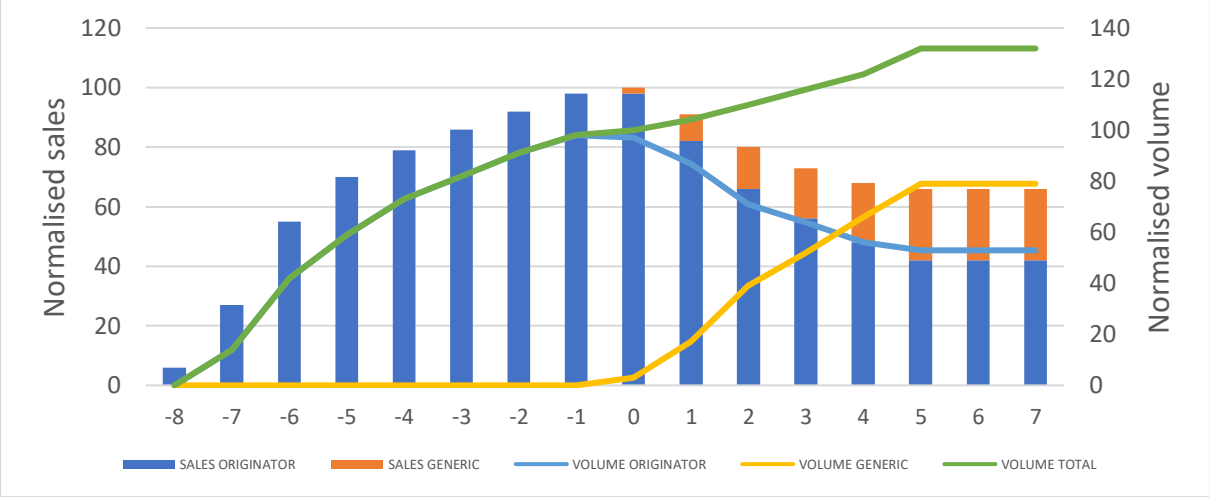
The baseline is the current standard regulatory protection (for all medicinal products) of 8 years of data exclusivity plus extra 2 years of market protection, and in cases of additional indication with significant benefit +1 year of market protection.

### 10.4.3 Modelling the economic impact of decreasing regulatory protection

We assume that after 5 full years of generic competition an equilibrium value of annual sales and volume of product sold are established and thus we can use Y5 data for originator and generic products as long-term level to calculate the value of RDP loss over the product lifetime. It should be noted again that this basket of products is dominated by small-molecule medicinal products; the lifecycle of biologics may be more extended given the absence of automatic substitution rules.

We also assume that the pre-expiry sales trajectory is not changed by company behaviour and thus the baseline Y-1 and Y-2 sales are lost under the new standard RDP regime. In the figure below thus the original Y-1 and Y-2 values are removed and Y6 and Y7 values are added at equilibrium level. In addition, we assume that the market dynamics of generic competition (between Y0 and Y5) in the new standard RP regime will not change compared with the RDP period of 8+2 years.

**Figure 6 Normalised sales and volume data for products with 6+2 years of RDP period**




Using the above model for the product lifetime, we can make the following observations at product level:

- Originator companies' pre-expiry sales loss of -199 (normalised units) over two years is partially compensated by the post-expiry gain of +84 (calculated at the equilibrium level) over two years, giving a net loss of -115 (normalised units) over the lifetime. In other words, originators lose 28 % of their pre-expiry sales when the RDP period is changed from 8+2 to 6+2 years. It should be noted that spreading this loss over the product lifetime, approximated as a 16-year period, and earning two years' sales in a competitive market by the end of this period, the originators' net loss is 22% of sales compared to baseline.

  We know that pharmaceutical industry is one of the most R&D intensive sectors and they reinvest a large share of their revenue into innovation for new products and technologies. This share is 20% on average globally[127] and we can assume that the revenue loss will translate to a loss of innovation budget and thus a loss of development of new innovative products and/or incremental (i.e. cheaper) product innovation (e.g. for combination products or new formulations).

[127] See https://www.drugdiscoverytrends.com/pharmas-top-20-rd-spenders-in-2021/

- Generic companies' start to benefit from sales two years earlier compared to baseline, and thus reach equilibrium level two years earlier. These two extra years of equilibrium generic sales of +48 (normalised units), equal to an additional 56% sales, compared to baseline situation.
- Healthcare payers pay less overall due to a decrease in the average price they need to pay for a standard unit of the product. If we look at the annualised average price healthcare payers pay (calculated by dividing total sales and total volume in each year of the final 8 years of the product lifetime) in the different RDP regimes, we note that, as expected, the average price drops faster to the equilibrium value in the case of the new standard RDP regime (see Figure 7 below). If we consider the 'peak' volume sold of the originator product pre-expiry under the baseline situation and use the average price in each year under the different RDP regimes to calculate post-expiry adjusted sales, we can assess the total savings healthcare payers would make in the RDP 6+2 regime given equal volumes purchased. In the baseline RDP 8+2 regime, the total adjusted lifetime sales would be 1141 (normalised units) and in the new RDP 6+2 regime it would be 1042 (normalised units). Thus in the RDP 6+2 regime healthcare payers would pay -99 (normalised units) less, which is -9% less when considering the lifetime sales of the product.

  In the real situation, however, healthcare payers may not realise this nominal saving but choose to purchase more units of the medicine at a lower price for the healthcare system and expand coverage of patients. This can be considered that payers 'reinvest' part of the savings in the same market and increase purchase of generic products at higher volumes for the benefit of the patient. We can thus calculate the total real sales of originator plus generics product volumes, which can be used to monetise patient benefit. Under the baseline situation, total sales value over the product lifetime is 1190 (normalised units), while under the RDP 6+2 regime it is 1123 (normalised units), equating to -67 (normalised units) or -6% saving to healthcare payers. Note, however, when considering total healthcare systems spending in the EU, pharmaceutical expenditure represents less than 20% of the total health spending so savings at the healthcare system level is marginal.
- Patients benefit due to the increased volume of the medicine sold after RDP expiry (2 years earlier) which then reach more patients creating higher level of health benefits. In the model, the total volume increases as soon as generic products enter the market and volume of generic products surpasses that of the originator product by year 4 after generic entry. In the new standard RDP 6+2 regime the total volume sold increases by +64 (normalised units) or 5% over the product lifetime above the baseline of 1343 (normalised units) under the RDP 8+2 regime. However, the extra volume of products available to patients manifest itself in the transition period between expiry and reaching the equilibrium value.

**Figure 7 Normalised price of medicines over the final 8 years of the product lifetime**


Monetising the systemic effects: Using the model in this study where only static effects are considered, we saw the normalised consequences for various stakeholders originating from a typical

product where the last measure of protection to expire is RDP. We can convert the normalised units to monetary value by equating the peak sales of 100 (normalised units) to the average peak sales calculated for the basket of RDP products of approximately €160m per year. Note that per product level change should be considered as nominal since the actual individual product sales have a wide range around this average. At a systemic level, for a basket of products over years, however, the calculated values are expected to have predictive power.

Therefore, we need to assume the number of products per year to be affected by this policy measure. In the coming 15 years, we estimate that on average 40-50 new active substances will be authorised by EMA in each year (see pipeline data in recent report[128]). From the current level of 30-40, we expect the baseline to evolve to 50-60 by the end of the period. As discussed, 30% of new authorised products are expected to be affected, however, products that address UMN or medicines with no return on investment (Option B) will not have reduced RDP period. Overall, we estimate 20-25% of new medicines or 8-13 products will be affected annually by the measure.

In the following we summarise the economic value calculated for each stakeholder group.

**Table 11 Changes calculated between baseline and RDP 6+2 per stakeholder group**

| Stakeholder | Product level change | % change | Annual systemic change (8-13 medicines) | Systemic change over 15 years |
|---|---|---|---|---|
| Originator non-contested sales | -€320m | -28% | -€2.5-4.1 billion<br>(lost innovation budget: -€0.5bn-0.8bn) | -€38-62 billion<br>(lost innovation budget: -€7.6bn-12.4bn) |
| Originator contested sales | +€134m | | | |
| Originator medicine's commercial value | | -22% | | |
| Generic sales | +€77m | +56% | +€0.6-1 billion | +€9-15 billion |
| Cost to public payer | -€107m | -6% | -€0.9-1.4 billion | -€0.9-1.4 billion |
| Patients served | | +5% | | |
| Patients + payer monetised gain/loss | +178m | +9% | +€1.4-2.3 billion | +€21-34.5 billion |

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

Caveats to the model used:

Data: IQVIA MIDAS data includes sales revenue data corresponding to list or ex-manufacturer price without accounting for rebates or discounts (especially in hospital sector) on the one hand and costs including wholesale, distribution, value-added tax and social security expenses on the other to healthcare payers.

Opportunity cost: We present data at current euro level without inflation or cost of capital / commercial risk accounted for. This latter is a factor for commercial actors where monetary gains and losses are normally discounted in business calculations and may change decisions related to product developments accordingly. In contrast, healthcare payers pay on an ongoing basis.

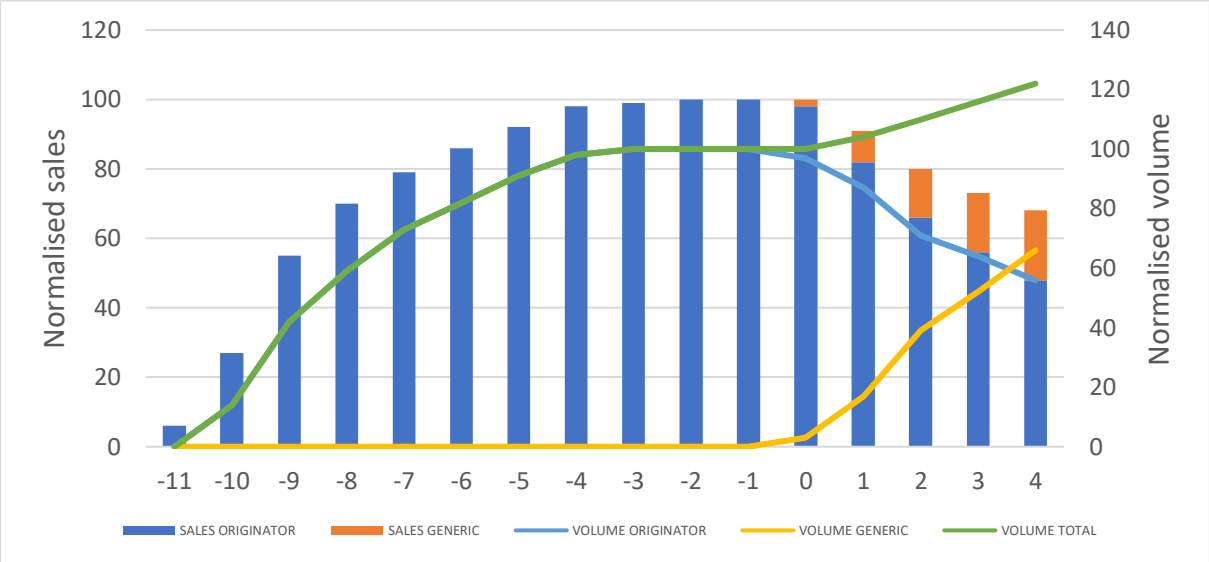
[128] Global Trends in R&D, IQVIA Institute for Human Data Science, 2022. Available at: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-trends-in-r-and-d-2022/iqvia-institute-global-trends-in-randd-to-2021.pdf

Business behaviour: There may be changes in the trajectory pre- or post-expiry compared to the current RDP 8+2 regime, because companies change behaviour and aim to earn similar level of total pre-expiry monopoly rent during the reduced RDP period. This may be achieved by entering more markets earlier leading to the same pre-expiry overall sales and volumes of product sold. There is however the risk that the shorter RDP period will lead to higher negotiated prices and relatively lower volumes of product sold in the pre-expiry period, or even a reduction in the number of products that enter EU markets.

### 10.4.4 Modelling the economic impact of special incentives through increasing regulatory protection

We use the same data as presented above and assume that after the Y-1 there will be an additional year of peak sales protected by a 1-year regulatory data protection period. We will use the result of this model to estimate the proportionate effect of incentives for 6 months (comparative trials) to 2 years (market launch, Option C). Again, we assume that pre-expiry sales trajectory is unchanged, the market dynamics of generic competition post expiry is unchanged. In the figure below thus data associated with a new Y-1 is added and the baseline Y5 is removed to maintain the overall product lifetime of 16 years. Note that the +1 year of protection added to the 6+2 RDP regime results in almost identical costs and benefits for stakeholders in our model.

**Figure 8 Normalised volume and sales data for products with 8+2+1 years of RDP period**




Using the above model for the product lifetime, we can make the following observations at product level:

- Originator companies increase pre-expiry sales due to additional year of monopoly sales by 58 (normalised units) or 5% of lifetime sales
- Generic companies' start to benefit from sales one year later, and thus generic sales are reduced by 24 (normalised units) which is equal to a reduction of 28% sales, compared to baseline
- Healthcare payers pay more overall due to an increase in the average price they need to pay for a standard unit of the product. We consider again the 'peak' volume sold of the originator product pre-expiry in baseline and use the average price in each year under the different RDP regimes to calculate sales. The total cost for healthcare payers is thus -50 (normalised units) over the product lifetime compared to baseline
- Patients lose -32 (normalised units) in decreased volumes of the medicine over the lifetime of the product compared to baseline

We summarise the change calculated for each stakeholder group below:

| Stakeholder | Change |
|---|---|
| Originator non-contested sales | +14% |
| Medicine's commercial value | +11% |
| Generic sales | -28% |
| Cost to public payer | +2.9% |
| Patients served | -2.4% |

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

### 10.4.5 Monetising the systemic effects for 1-year extension of RDP for medicines addressing UMN (Option A and C)

This measure affects RDP protected medicines and medicines with 10 years orphan market exclusivity as last protection, altogether 40% of all new medicines. Of these we expect 15-20% to address UMN. Applying these rates on the 40-50 annual new authorised medicines as per our dynamic baseline, 2-4 special UMN incentives per year is expected. It should be noted however that annual peak sales can deviate from the average value used in the model and for products with substantially larger expected annual revenue, the incentive may well worth the increased commercial cost/risk that is expected to be associated with developing a product that meet (at the early phases of development and up until authorisation) the UMN criteria.

**Table 12 Changes calculated for 1-year extension of RDP protection per stakeholder group**

| Stakeholder | Product level change | % change | Annual systemic change (2-4 medicines) | Systemic change over 15 years |
|---|---|---|---|---|
| Originator non-contested sales | +€160m | +14% | €320-640 million<br>(innovation budget gain: €64m-128m) | €4.8-9.6 billion<br>(innovation budget gain: €1bn-1.9bn) |
| Originator medicine's commercial value | | +11% | | |
| Generic sales | -€38m | -28% | -€77m-154 million | -€1.2-2.3 billion |
| Cost to public payer | +€107m | +2.9% | +€109-218 million | +€1.6-3.2 billion |
| Patients served | | -2.4% | | |
| Patients + payer monetised gain/loss | +178m | +9% | +€163-326 million | +€2.4-4.9 billion |

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

### 10.4.6 Monetising the systemic effects for 6-month extension of RDP for comparative clinical trials (Option A and C)

Similar to the previous incentive, this measure could benefit RDP-protected products and some orphan medicines. Around 40% of all new medicines would be eligible. Conducting comparative trials

should be feasible for many medicines, but not for some, especially UMN medicines[129]. Also, if the cost of the comparative trial is too high as opposed to the reward, companies will decide to decline the incentive. We expect that half of the RDP products could benefit from it, or 8-10 medicines annually. Of course, higher sales medicines would have a higher compensation, regardless the cost of the trial.

It should be noted that this data is expected to generate new knowledge for better decision making at an earlier time point and thus represent additional fixed cost compared to baseline. We assume the additional costs of conducting comparative trial with standard of care amount to €10m on average.[130] Therefore the incentive bonus could attract developers to factor in comparative trial design in their clinical study programme. There is no information on how stakeholders (including developers and regulators) would respond to statistically insignificant or negative outcome emerging from the comparative effectiveness arm of the study.

**Table 13 Changes calculated for 6-month extension of RDP protection per stakeholder group**

| Stakeholder | Product level change | % change | Annual systemic change (8-10 medicines) | Systemic change over 15 years |
|---|---|---|---|---|
| Originator non-contested sales | +€80m | +7% | €640 – 800 million<br>(innovation budget gain: €128m – 160m) | €9.6 – 12 billion<br>(innovation budget gain: 1.9bn – 2.4bn) |
| Originator medicine's commercial value | | +6% | | |
| Generic sales | -€19m | -14% | -€154m-192 million | -€2.3 – 2.9 billion |
| Cost to public payer | +€27m | +1.5% | +€218 – 272 million | +€3.2 – 4.1 billion |
| Patients served | | -1.2% | | |
| Patients + payer monetised gain/loss | +41m | +4.5% | +€326 – 408 million | +€4.9 – 6.1 billion |

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

### 10.4.7 Monetising the systemic effects of measures to improve market access

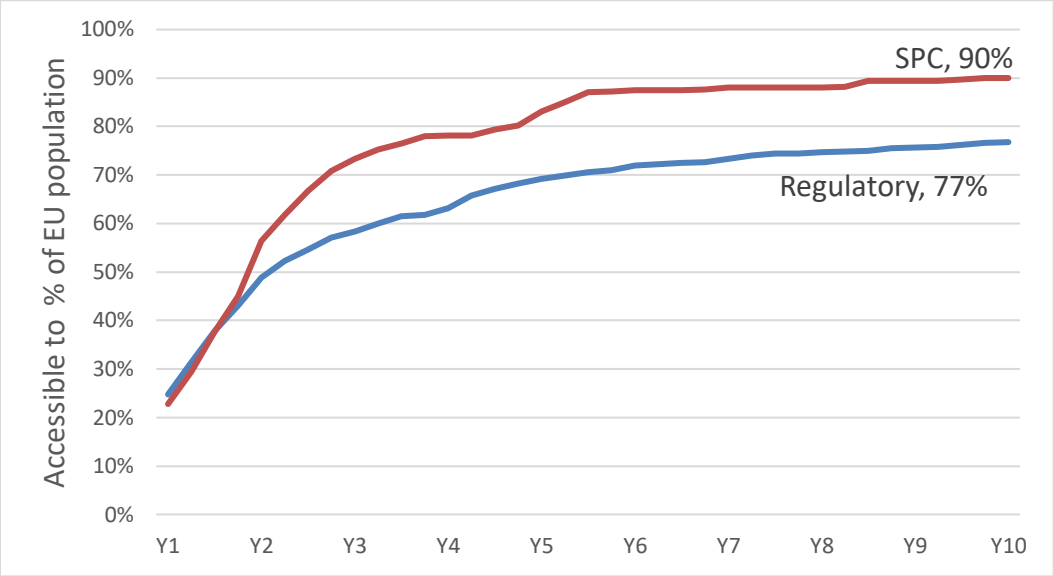
The baseline is that there is no obligation or incentive to launch a product in a particular member state. Indeed, products authorised only reach up to 15 Member States (MS) out of the maximum possible 27 (Kyle, 2019) and on average 49% EMA-approved medicines are reimbursed in an EU country (IQVIA, W.A.I.T. report 2021). Market launch incentives will not be a corrective measure for per capita utilisation rate of medicinal products but to increase the coverage across member states (breadth) and provide in some cases alternative medicinal products to existing therapies (depth) thereby creating positive spillover effects to better shortage management. Note that we had no access to IQVIA MIDAS sales data in three countries (Cyprus, Denmark and Malta) to ascertain market launch there.

We analysed products with protection expiry between 2016-2024 and recorded positive sales of originator products. For each molecule and each Member State, the first quarter in which meaningful

[129] As per the definition of UMN, there are no satisfactory therapeutic options. Consequently, a new therapy would have no comparator.
[130] Moore et al (2020) in a review of 101 new FDA medicines (225 individual clinical trials), found the median cost of an individual clinical trial was around $19m (range = $12m-$33m). They found the Phase 3 development costs almost doubled with second trial. (Albeit the single biggest cost driver is the number of patients). More et al identified 62 (27.5%) of the total set of 225 clinical trials had a comparison group rather than a placebo or uncontrolled trial.

non-zero sales occurred for at least two quarters. This is to eliminate cases where there may be one quarter of sales and then the product is not sold again in that Member State for several years. To follow the evolution of market access over 10 years, the sample was restricted to only those products that are authorised between Q1 2010 and Q4 2011. We have also created a larger sample of products between Q1 2010 and Q4 2014. The patterns for the first seven years in the two samples were very similar. We analysed access as a function of the number of Member States in which each product was available and the corresponding percentage of the EU population that was covered for each product. Taking a simple average across all products gives a representative time series for all RP products and a separate representative time series for all patent/SPC products. This analysis shows that those products that are SPC-protected are accessible to a higher share of the EU population than those that are RDP-protected.

**Figure 9 Product accessible to EU population over time per protection type**

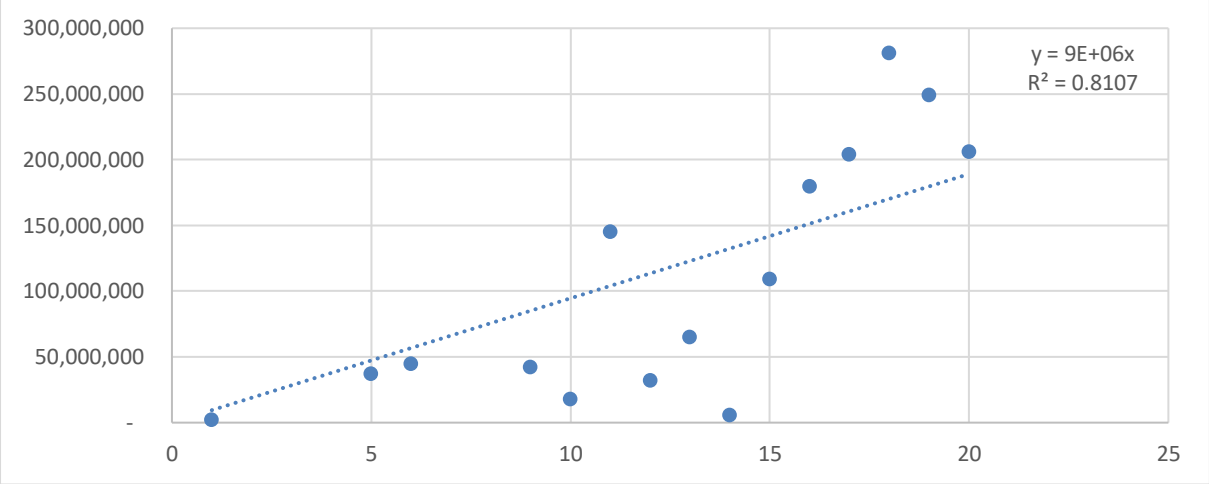



Deeper analysis point to higher coverage of products with higher sales and that larger member states with higher GDP tend to have a higher share of the products on their market. For example, there are 69 and 68 of the 78 products launched in Germany and Italy/Spain.

**Table 14 Distribution of 78 products with RDP expiry 2016-2024 launched in member states**

| Number of countries where product was launched | Number of molecules launched | Percent | Cumulative % |
|---|---|---|---|
| **1** | **3** | **3.9** | **3.9** |
| 2 | 1 | 1.3 | 5.1 |
| 3 | 2 | 2.6 | 7.7 |
| 4 | 2 | 2.6 | 10.3 |
| 5 | 2 | 2.6 | 12.8 |
| 6 | 3 | 3.9 | 16.7 |
| 7 | 1 | 1.3 | 18.0 |
| 9 | 2 | 2.6 | 20.5 |
| 10 | 2 | 2.6 | 23.1 |
| 11 | 5 | 6.4 | 29.5 |
| 12 | 3 | 3.9 | 33.3 |
| 13 | 6 | 7.7 | 41.0 |
| 14 | 2 | 2.6 | 43.6 |
| 15 | 5 | 6.4 | 50.0 |
| 16 | 5 | 6.4 | 56.4 |
| 17 | 5 | 6.4 | 62.8 |
| 18 | 7 | 9.0 | 71.8 |
| 19 | 12 | 15.4 | 87.2 |
| 20 | 10 | 12.8 | 100.0 |

**Figure 10 Average annual peak sales of products with RDP expiry 2016-2024 per country launch**



The different options use different policy measures to enhance access to patients. Option A provides an additional RDP period of +6 months in case centrally authorised product is placed on all EU market within 5 years of MA. Option B involves obligation to place a centrally authorised medicine on the market in the majority of MS. Finally, option C provides a milestone incentive of +2 year of RDP period if a medicinal product is supplied in all MS within a period of 2 years from MA.

Based on the size of the incentive/sanction we estimated the compliance as percentage of medicines. From this, we could calculate the costs or savings to the public (Table 15). For option A, we used the same model as for the special incentive for comparative trials, but expecting that only the higher sales medicines would comply, we used a higher average peak sales in the model. For option B and C, the model of the reduced regulatory protection was used (from option B), to calculate public savings stemming from non-complying medicines. Again, we adjusted the average peak-sales value, assuming that the low-sales medicines will be the ones not complying.

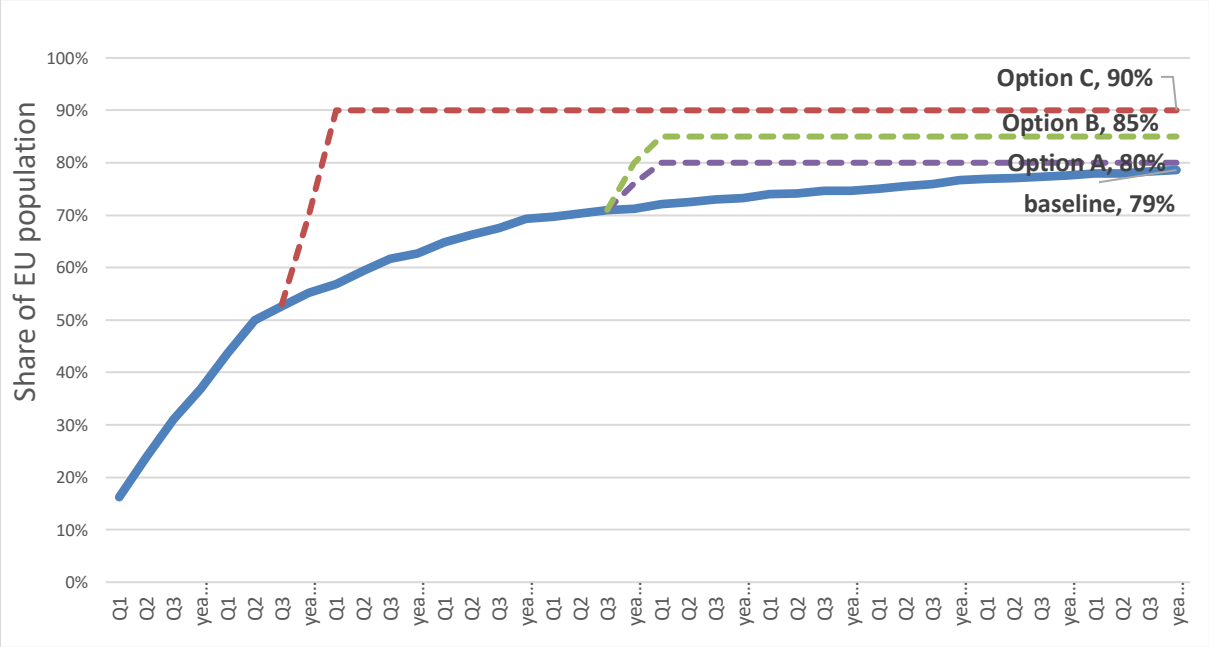
**Table 15 Compliance estimate for each option, commercial value and cost/benefit for public**

| Option | Expected compliance | Reward/sanction for firms | Cost/benefit for public |
|---|---|---|---|
| Option A<br>+6 months RDP, if product launched in all EU within 5 years of MA | 50% (6-8 medicines) | +5.5% commercial value | €389-522m public cost |
| Option B<br>Early generic competition if product not launched within 5 years of MA in majority of MS | 75% (11-13 medicines) but not in all markets | -20-60% commercial value | €200-250m gain from non-complying medicines |
| Option C<br>+2 years RDP, if product launched in all EU within 2 years of MA (re-establishes baseline) | 66% (10-12 medicines) | -22% commercial value | €210-270m gain from non-complying medicines |

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

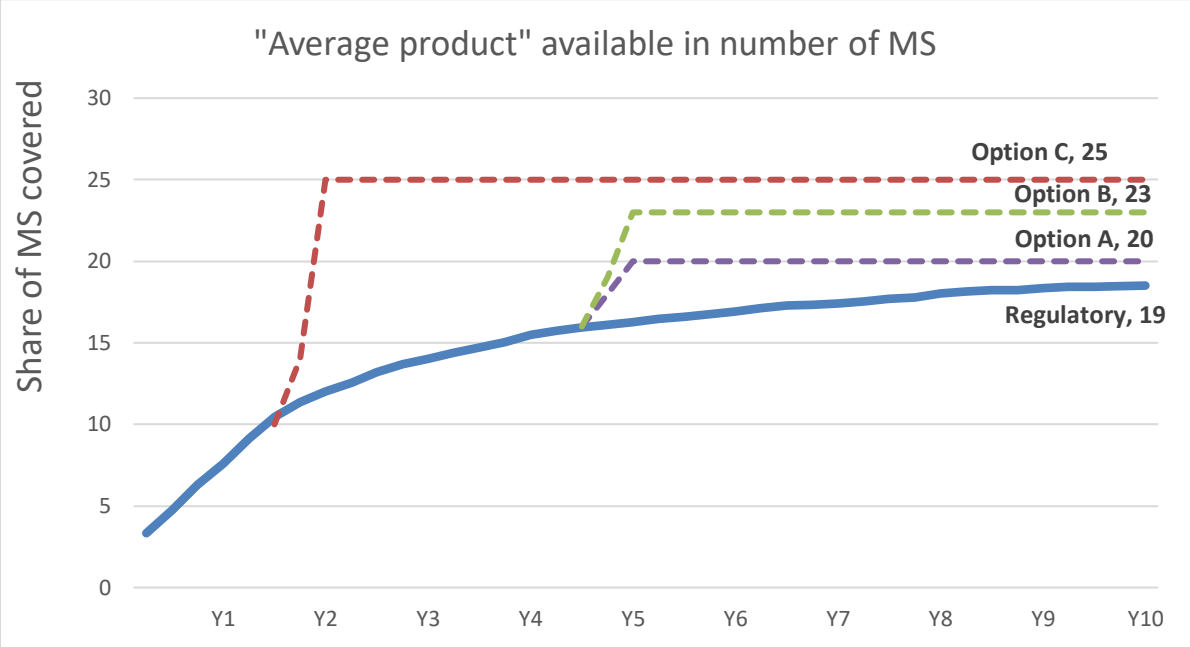
Again, launching products in all EU member states requires additional investments by companies compared to baseline, which will reduce the net gain experienced by companies.

**Figure 11 Share of EU population having access to RDP product across the EU**




| Option | Average coverage over 10 years<br>% population | Average coverage over 10 years<br>Number of member states |
|---|---|---|
| Baseline | 65.3% | 15 |
| Option A | 67.6% | 16 |
| Option B | 70.2% | 18 |
| Option C | 80.1% | 23 |

**Figure 12 Social impact of enhanced access to RDP product across the EU**




## 10.5 AMR transferable voucher

Antimicrobial resistance is a global challenge and the cost of inaction is very high when compared to expected societal benefits and cost savings in the mid/long term[131]. Antimicrobial products are not expected to be sold in large volumes on the market or generate large revenue stream and therefore the commercial incentive through the RDP system will have limited value. Developers of antimicrobials are often innovative SMEs without significant resources to take these products through the regulatory approval pathway and require alternative instruments for ensuring sustainable R&D of antimicrobials. A transferable regulatory protection voucher (or transferable exclusivity voucher) allows the developer of an antimicrobial product to benefit from an additional year of data exclusivity period on another product in their portfolio or sell the voucher to another company that would use the voucher for their own benefit. This mechanism could provide the developer a reward (or an incentive) for developing an antimicrobial product and meet (partially) the related investment needs of an estimated €1bn per product. [132] While the reward will directly be paid to developer by the buyer of the voucher, the cost of the voucher would eventually be met by healthcare payers of the product developed for other diseases (potentially also benefitting from lower level of AMR).

The transferable voucher is therefore only applicable to a subset of products where RDP is the last measure of protection rather than those with patent/SPC. As we noted above, products with high peak sales tend to have SPC as LOP, and thus on average, the cohort of products with RDP as LOP will have lower peak sales.

It should however be pointed out that when the voucher is sold on, only part of the value will be captured by the developer of the antimicrobial product (the seller) and the other part will go to the buyer of the voucher. The larger the share that goes to the seller, the more efficient the voucher is as an incentive or reward to develop antimicrobial products.

It has been observed, in the case of the priority review voucher introduced in the USA, that the more vouchers are available for the buyer, the lower price the buyer needs to pay and hence a larger share of the value is retained by the buyer.

### 10.5.1 Modelling the effect of transferable vouchers

[131] https://www.oecd.org/health/health-systems/Averting-the-AMR-crisis-Policy-Brief-32-March-2019.PDF
[132] New drugs to tackle antimicrobial resistance (2011) The Office of Health Economics

As a first approximation, the buyer of the voucher is assumed to be willing to pay up to the amount that the voucher would generate as additional revenue. However, with n vouchers available for sale, the sales price will reduce and we will calculate the final sales price as the average of the value (or the peak sales) of the $n^{th}$ and $n+1^{th}$ product. For example, if only one voucher is available for sale, the first buyer that aims to generate €545m during the additional year of data exclusivity period, will pay the seller (who is the developer of an antimicrobial) only €414m (the average of €545m and the value of the RDP of the second product, €283m) or 76% of the full value of the voucher. If two vouchers available for sale, it is sufficient for them to offer a price that is above the value of the RDP of the third product, and so on.

The assumption that the price to be paid for a voucher is given by the average of the $n^{th}$ and $n+1^{th}$ product's peak sales likely overestimates the value of the voucher for a number of reasons. The annual sales revenue includes the cost of goods and thus the buyer will likely use profitability rather than revenue in their calculations. The cost of goods may be considered as share of the revenue, however it is expected to be of lower share of the high revenue product than the low revenue product. The maximum value of the voucher for the buyer should also consider the opportunity cost of paying for the voucher for eventual exploitation years later (cost of capital). Finally, it is likely that negotiating power is not symmetrical between parties and the final negotiated price will be closer to the value for the $n+1^{th}$ product. While the precise details of a possible implementation of the transferable voucher system is not available, it is assumed that there will be a 'use it or lose it' system that will require the seller of the voucher to sell the voucher obtained for the antimicrobial developed, authorised and launched/supplied on the market, while the buyers need to apply for a product at least 2 years before product RDP expiry for predictability in the system. In the current model we do not foresee the buyer to resell the voucher to other buyers and hence 'trade' the voucher on the market. Therefore, for simplicity, since each product may only use one voucher, a year's supply of vouchers may be thought of as corresponding to a yearly cohort of products that vouchers will be transferred to. Thus, the impact of the voucher system may be analysed by considering the effect of a year of RDP on a cohort of products.

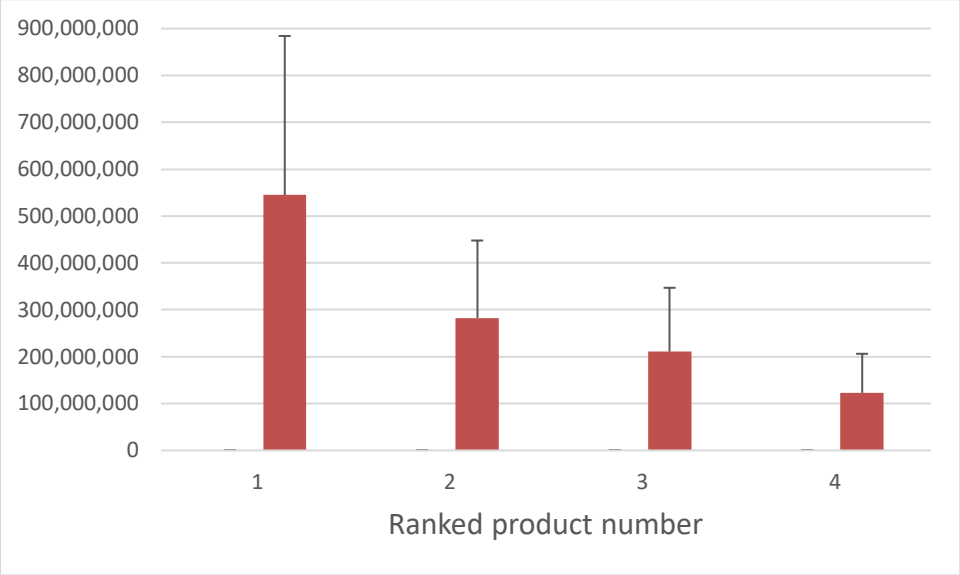
We will consider the possibilities to have (i) simultaneously three vouchers per year granted, (ii) one voucher per year granted, and (iii) one voucher granted every two years. In constructing these possibilities, we consider the global pipeline of antibiotics (see Analytical report Table AMR-2 and a recent independent analysis[133]). The number of vouchers may be controlled by eligibility criteria applied for innovativeness of antimicrobials such as the requirement that the product represent a new class and/or new mode of action addressing new target or absence of known cross-resistance (WHO innovation criteria) or candidates targeting priority pathogens (WHO list for antibiotics) or innovative platform technologies able to confer break-through clinical benefit. According to a recent study[134], possibly as few as 2 antibiotics may be eligible for a transferable exclusivity voucher within approximately the next 5 years.

We analysed the peak sales for a cohort of products where the RDP expiry was the last measure of protection between 2014-2024. We ranked the top four products and averaged the annual values for each category to obtain the level of revenue as cap for the value of the voucher.

[133] Global pipeline analysis of antibiotics by Pew Trusts (2021) suggests that 43 antibiotics are in development and would lead to approximately 15 new antibiotics considering attrition rate. Additionally, only in 4 candidates in the pipeline represent a novel drug class or mechanism of action. Available at: https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/tracking-the-global-pipeline-of-antibiotics-in-development

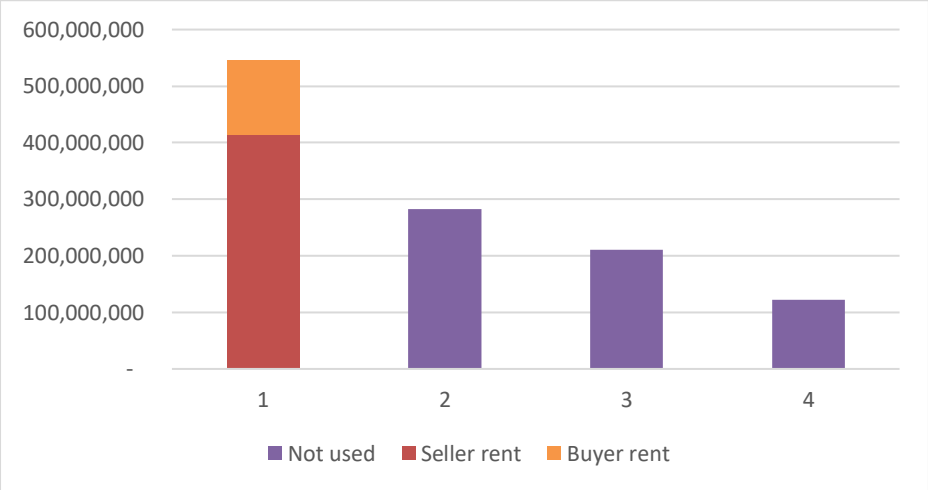
[134] Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe (2020) Årdal, Lacotte, Ploy, and EU-JAMRAI

**Figure 13 Average peak annual sales of products with RDP expiry 2014-2024**




The 'erosion' of the value of the voucher will increase with increasingly more vouchers concurrently available on the market. Similarly, the seller's share is changing dependent on the number of vouchers simultaneously competing for products to transfer the voucher to. In the figures below, we see that share that goes to the seller of the voucher (i.e. developer) will decrease and the total incentive in the system reach a plateau. Thus the system designed to support the developer becomes less efficient. Note that the total incentive plateau is at about €500m that is half of the expected development cost of an antimicrobial product. It is therefore clear that the transferable voucher in this model will not cover the total development cost of the developer.

**Figure 14 Share of the seller and buyer in the value of the voucher for (top) n=1 voucher per year and (bottom) n=3 vouchers per year**



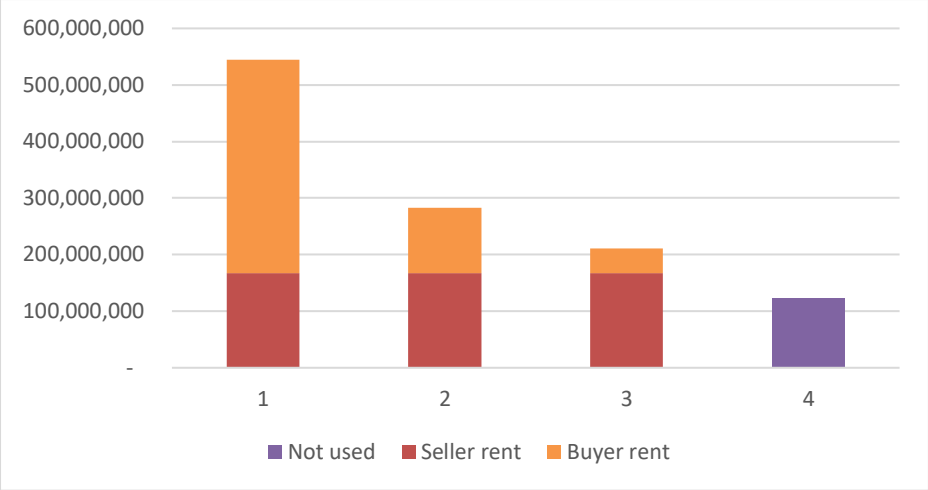
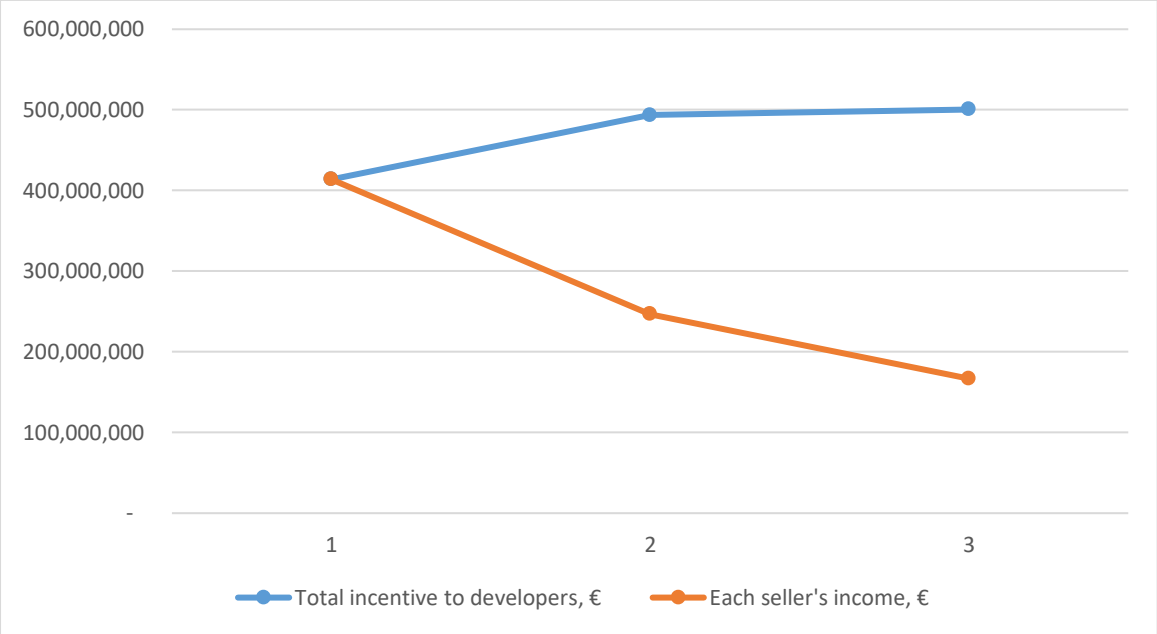
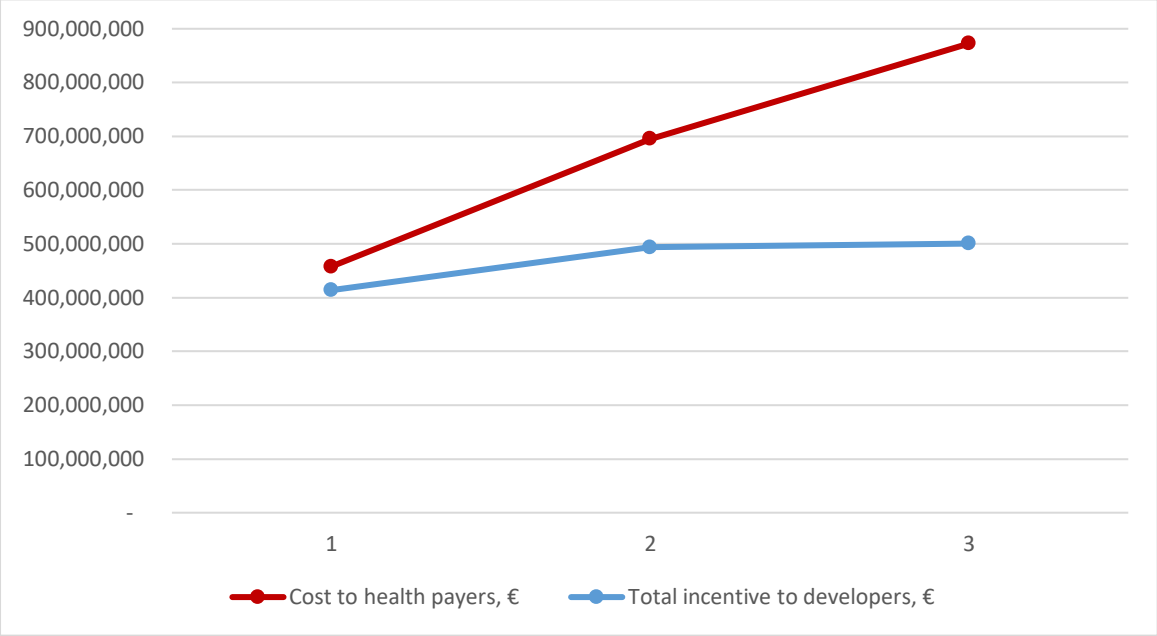



**Figure 15 Impact of a voucher scheme on developers, by number of vouchers**




The cost to healthcare payers (i.e. difference of peak sales and equilibrium sales for a given product) will also increase from a value initially close to the value of the voucher (1.1 times the total incentive) to a higher multiple of 1.75. Note however this analysis compares only the cost rather than the benefit of developing antimicrobials. OECD estimates that AMR already costs about €1.1bn every year to the EU Member States healthcare systems.

**Figure 16 Comparison of total incentive to developers and total cost to health payers, by number of vouchers**




The distribution of the average peak sales of products that have RDP expiry as LOP and the number of vouchers will therefore determine the cost and benefit to the various stakeholders. In our cohort we focussed on high-revenue products and therefore we used a normalised product sales and volumes curve that is expected to represent this cohort of products more closely (i.e. higher rate of generic entry and originator price erosion, see Figure 4). We use the model introduced earlier and apply to the three scenarios that link to the number of simultaneous vouchers in issue. The corresponding costs and benefits are detailed below:

Scenario 1. Three transferable vouchers are granted per year

**For originators:** The top three products in each year will benefit from an extra year of RDP extension; using the average values for these (€545m, €283m, and €211m) we obtain €872m per year net gain in revenue compared to baseline, which accumulates to €13.1bn over 15 years for originators at current euro values. The corresponding share of innovation budget generated for industry (20%) is €174m annually or €2.6bn over the 15 years.

**For developers:** The figures earned by originators may be compared to the amount they had paid as buyers of the transferable vouchers to antimicrobial developers as sellers of the vouchers. Developers obtain €500m for their three vouchers annually or €7.5bn over the 15 years. While no discount is considered for cost of goods and cost of capital for originators, these companies can afford the cost of the voucher as the annual net gain from the extended RDP is greater than the annual cost of the vouchers. Nevertheless, it is worth noting that the annual €174m innovation budget generated through the RDP extension does not cover the cost of buying the transferable vouchers from sellers. Finally, the total AMR development incentive of €500m shared across three developers provides a fraction of the development cost of three antimicrobial products (about 17%) they had invested in.

**For generic companies**: The cost of delayed market entry for generics of the three products per year was calculated as €322m or €4.8bn over 15 years.

**For healthcare payers:** The nominal cost calculated at constant peak volume of the originator product sold, national healthcare systems pay an additional €561m compared to baseline per year or €8.4bn over 15 years.

**For patients:** Patients have costs and benefits associated with the voucher: Developing antimicrobials has a significant patient benefit that is hard to monetise but as pointed out before, any reduction of the current high cost of AMR (€1.1bn per year) in the national healthcare systems is the ultimate aim of the voucher system. As before, we may attribute the share of the revenue for innovation (€174m per year, or €2.6bn over 15 years) or better the amount originators pay developers for the vouchers (€500m per year that is €7.5bn over 15 years) as patient benefit.

However, patient will not be served from lower coverage of the other products that are protected by an extended RDP period compared to baseline, with reduced volume distributed to patients -55 (normalised units) or a reduction of -4%.

Scenario 2. One transferable voucher is granted per year

**For originators:** Only the top selling product in each year will benefit from an extra year of RDP extension; using the average value for this (€545m) we obtain €458m per year net gain in revenue compared to baseline, which accumulates to €6.9bn over 15 years for originators at current euro values. The corresponding share of innovation budget generated for industry (20%) is €92m annually or €1.4bn over the 15 years.

**For developers:** The developer that obtained the voucher will obtain €413m (as the average price of the top and top+1 product) in each year or €6.2bn over the 15 years. It appears that the annual net gain from the extended RDP companies earn is sufficient to pay the price of the voucher. The AMR development incentive of €413m for one developer in each year provides a larger fraction of the development cost of an antimicrobial product than the previous scenario where three developers shared the total incentive.

**For generic companies**: The cost of delayed market entry for generics of the product with extended protection was calculated as €169m per year or €2.5bn over 15 years.

**For healthcare payers:** The nominal cost calculated at constant peak volume of the originator product sold, national healthcare systems pay an additional €294m compared to baseline per year or €4.4bn over 15 years.

**For patients:** Again, we can attribute the share of the revenue for innovation (€92m per year; €1.4bn over 15 years) or better the amount originators pay developers for the vouchers (€413m per year; €6.2bn over 15 years) as patient benefit.

However, patient will lose coverage of the product that is protected by an extended RDP period compared to baseline, which through a reduced volume distributed to patients can be equated to €305m per year or €4.6bn over 15 years.

Scenario 3. Transferable voucher is granted every two years

Here we assume that only the top selling product will benefit from an extra year of RDP extension every other year. There is however the potential for higher selling products on the market. The Table below It does not appear to provide any further efficiency gain in the system compared to the previous scenario and selecting this makes no policy sense as a large share of the originator's gain will already have been paid to developers, long before originators can reap the benefits of their investment. Of course, if there is no qualifying antimicrobial for a transferable voucher each year (which may well be the case if no sufficient incentive/profit margin exist in the system) pipelines will dry up, and the system will have reduced direct costs and benefits for all stakeholders. Nevertheless, there remains a distinct risk that a resulting lack of preparedness for a future pandemic of antimicrobial resistance will be counted in trillions of euros lost globally.

**Table 16 Average peak annual sales of top products with RDP expiry 2014-2024 segmented bi-annually**

| Year (RDP expiry) | Top 1 (sales, €) | Top 2 (sales, €) |
|---|---|---|
| 2014-2015 | 978,000,000 | 493,000,000 |
| 2016-2017 | 473,000,000 | 120,000,000 |
| 2018-2019 | 469,000,000 | 386,000,000 |
| 2020-2021 | 703,000,000 | 408,000,000 |
| 2022-2023 | 1,270,000,000 | 174,000,000 |
| **AVERAGE** | **778,600,000** | **316,200,000** |
| STD | 345,033,766 | 160,680,428 |

# 11 ANNEX III: WHO IS AFFECTED AND HOW?

## *11.1 Practical implications of the initiative*

The proposed revisions have substantial positive implications for EU patients, national health systems. There are improvements foreseen in all areas of importance to citizens, whether that is improving the flow of cutting-edge treatments available for conditions for which there are no effective treatment options currently (UMNs), reversing the decline in investment in antimicrobial research and encircling the issues driving antimicrobial resistance (AMR), through to the improved access to medicines through measures to broaden market reach. The proposed revisions have also sought to strike a balance between ensuring a strongly positive environment for research-intensive pharma to continue to develop its cutting-edge products within the EU and the need to ensure all EU member states and citizens have access to a broader array of treatment options.

## *11.2 Summary of costs and benefits*

Taken together, we estimate the benefits should be in the order of **€2.19bn a year** and €32.86bn over 15 years. We estimate the total costs to be in the order of **€1.91bn a year** of recurring costs which equates to €28.64bn over 15 years. It should be noted that these aggregate figures represent the benefits and costs across all stakeholder types where data allowed quantification. Hence, these numbers should be interpreted with caution in light of the benefits and costs that could not be quantified/monetised as well as differences in benefits and costs across stakeholder types. We present the disaggregated figures in the tables below.

The principal direct benefits relate to the income for originators associated with additional flow of protected sales that will result from the various incentives foreseen (e.g. a year one extension to the overall period of regulatory data protection for medicines addressing an unmet medical need). The main indirect benefits relate to the lower prices for health payers associated with those medicinal products where MA holders elect to sell in fewer markets and where generic competition will emerge two years earlier. There are also savings expected from the various horizontal measures, which will better coordinate, simplify and accelerate regulatory processes to the benefit of industry and launch new digitalisation programmes to improve the integration and efficiency of the regulatory system overall (as well as its interfaces with other regulatory systems). This estimate of total benefits is an underestimate as there will be many indirect benefits for health systems and patients from improved access to new medicines for UMNs, new classes of antimicrobials and extended market access. However, while we expect many tens of thousands of individual citizens to benefit in some degree from these revisions, it has not been possible to establish quantify and monetise these many and various social impacts.

Administrative cost savings for businesses and regulators are estimated to be in the tune of €45m and €153m respectively annually and €675m and €2.3bn respectively across 15 years.

**Table 17 Overview of the benefits for the pivotal measures under the preferred option**

| *Description* | *Amount* | *Comments* |
|---|---|---|
| | ***Direct benefits*** | |
| Medicines for unmet medical needs (UMNs) | An additional **2-3 new medicines annually** relevant to UMNs (c. 40 new medicines over 15 years).<br>This would result in originators securing an additional **€320m-€640m** protected sales annually (15 years: €4.8bn - €9.6bn).<br>Overall additional income of on average **€480m annually** (€7.2bn over 15 years). | +12 months extension of RDP for innovation, particularly around unmet medical needs (UMNs) would result in a higher proportion of UMNs within all newly authorised medicines. |
| Novel antimicrobials | An additional **1 novel antimicrobial annually** (c. 15 over 15 years). This would result in originators securing an additional **€545m** protected sales annually (15 years: €8.2bn). | The transferable voucher would provide strong support for innovation in novel antimicrobials. The additional income may be secured by the developer of the novel antimicrobial where they use a voucher with another high value medicine in their portfolio or split between the developer of the |

| *Description* | *Amount* | *Comments* |
|---|---|---|
| | | antimicrobial and another originator that has purchased the (transferable) voucher. We have estimated the purchase value at €360m (assuming one voucher a year), with more breakthroughs and more vouchers the average sale price would fall. |
| Comparative trials | A significant minority of EMA medicine applications will be able to implement more robust trials and take advantage of the incentive (**8-10 a year**).<br><br>This would result in originators securing an additional **€640m-€800m** protected sales annually (15 years: €9.6bn - €12bn).<br><br>Overall additional income of on average **€720m annually** (€10.8bn over 15 years). | +6 months extension of RDP for medicines applications that include the findings of comparative trials. |
| Market access | The great majority of new medicines will be able to comply with the market access conditions.<br><br>**10-12 medicines annually** (150-180 over 15 years) may fail to meet the conditions, and in these cases the RDP will lapse at 6+2 years (not 6+2+2).<br><br>For this sub-set of products where the RDP is the last line of defence, there will be a **€210m-€270m** gain each year (€3.1bn-€4.1bn over 15 years) to the EU health system, because of lower prices from earlier competition by generics.<br><br>Overall additional income of on average **€240m annually** (€3.6bn over 15 years). | +2 years' protection conditional on launch in all EU markets in 2 years. |
| ***Indirect benefits*** | | |
| Patients benefit from effective medicines (UMNs) | Thousands of EU citizens will have access to treatments that help them recover from or manage their debilitating conditions, improving their quality of life and life expectancy.<br><br>There may also be indirect benefits / savings for health systems from more effective treatment and reduced hospitalisations.<br><br>There would be benefits for families and carers too, in terms of both quality of life / independence and earning potential. | It is not possible to quantify / monetise (indirect) patient benefits given the diversity of UMNs (certain neurological conditions, cancers, muscular dystrophy, etc.). These conditions may affect hundreds of citizens or millions in the case of Alzheimer's. |
| Patients have access to new classes of antimicrobials that help to contain AMR | It is estimated that each year about 670,000 infections occur, and that 33,000 Europeans die as a consequence of antibiotic-resistant bacteria with the burden being highest in the elderly and infants.<br><br>It is also estimated that AMR costs the EU €1.5bn per year in healthcare costs and productivity losses.<br><br>Even a 1% improvement in our management of AMR could save several hundred lives annually and save health systems hundreds of millions too. | It was not possible to quantify / monetise the (indirect) patient benefits that might result from new classes of antimicrobials. |
| Improved decision making for HTAs / Reimbursement bodies | More robust evidence from comparative trials should facilitate HTA decision making, leading to improved reimbursement decisions and faster decisions / access where medicines are approved for reimbursement. | It was not possible to quantify / monetise the (indirect) HTA and patient benefits that might result from the greater use of more robust trials. |
| All EU member states (incl. smaller countries) have improved access to new medicines | On average, new medicines will be available to patients in 22-25 markets compared with the current situation | It was not possible to quantify / monetise the (indirect) patient benefits that might result from the |

| *Description* | *Amount* | *Comments* |
|---|---|---|
| | (12-15), reaching 80% of the population compared with the current situation (c. 65%).<br>The availability of all new medicines in 5-10 additional markets will mean that hundreds of thousands of EU citizens will have better treatment options, with accompanying improvements in health equality and possibly public health. | systematic extension of market access. |
| Improved management of shortages | Most EU countries report increasing numbers of medicine shortages, with the great majority having recorded shortages for 200 or more medicines in the year.<br>Fewer shortages may benefit tens of thousands of patients, with access to the more appropriate medicines.<br>According to the pharmaceutical Group of the EU, eliminating shortages might save healthcare systems 5-10% of their pharmacy-related staff costs as well as time wasted by frontline staff. | Fewer shortages would mean more patients have access to the medicines they need.<br>Healthcare systems would see cost savings from avoiding time wasted deciding / finding appropriate alternative medicines. |
| Improved environmental performance of pharma industry | This may make a positive difference to 40-50 New medicines a year (600-750 in 15 years).<br>This should result in a reduction in the intrinsic environmental risks of a proportion of medicines, a lowering of the levels of active ingredients getting into the environment through excretion and a lowering of the level and number of accidental releases to the environment by manufacturers (mostly non-EU). | New medicines would be subject to a more rigorous assessment, which should feed forward to more informed selection of APIs, encourage green pharma and select for higher standards across global supply chains. |
| ***Administrative cost savings related to the 'one in, one out' approach**** | | |
| Streamlining, acceleration and coordination of network | Businesses should realise savings in the range **€15m-€30m annually** (€225m-€450m over 15 years)<br>European and national regulators should see savings in the range **€33.5m-€67m annually** (€502.5m-€1005m over 15 years)<br>Overall savings of on average **€72.75m annually** (€1.09bn over 15 years) | Businesses will benefit from various simplification and governance enhancements producing administrative cost savings.<br>European and national regulators should see a reduction in duplication of effort across committees and among regulators, producing savings in regulatory costs. |
| Digitalisation | Digitalisation savings for businesses in the range **€7.5m-€15m annually** (€112.5m-€225m over 15 years).<br>Digitalisation savings for regulators in the range **€67m-€134m annually** (€1,005m-€2,010m over 15 years).<br>Overall savings of on average **€112m annually** (€1.68bn over 15 years). | The various digital initiatives proposed will save time and administrative costs for businesses and deliver substantial efficiencies / reductions in costs for regulators. |
| Enhanced support for SMEs | Enhancement savings for businesses in the range **€7.5m-€15m annually** (€112.5m-€225m over 15 years).<br>Enhancement indirect benefits for businesses in the range **€5m-€10m annually** (€75m-€150m over 15 years).<br>Enhancement savings for regulators in the range **€1.75m-€3.5m annually** (€26.25m-€52.5m over 15 years).<br>Overall savings of on average **€21m annually** (€321mn over 15 years). | Industry - and SMEs in particular - should benefit from better and more dynamic advice avoiding queries on applications (delay) and rework to the same (cost); regulators should benefit from more mature applications that can be assessed more easily and quickly.<br>There may be some limited indirect benefits, whereby faster assessments, on average, may facilitate at least some new medicines being approved for sale earlier and some generics entering the market earlier. |

*(1) Estimates are gross values relative to the baseline for the preferred option as a whole (i.e. the impact of individual actions/obligations of the preferred option are aggregated together); (2) We indicate which stakeholder group is the main recipient of the benefit in the comment section;(3) For reductions in regulatory costs, we describe how the saving arises (e.g. reductions in administrative costs, regulatory charges, enforcement costs, etc.;)*

The principal costs for industry comprise costs associated with the implementation of market access conditions and more stringent assessment and reporting on shortages and environmental risks. The principal costs for health payers relate to the additional period in which they will need to pay a premium price for medicines benefiting from any extensions to the period of regulatory data protection. For regulators, the principal costs relate to the design and implementation of the wide-ranging proposals for streamlining and digitalisation. For patients, the principal costs (indirect) will relate to reduced access to treatments associated with the additional delays in generic entry for new medicines that have benefitted from extensions.

We were unable to quantify or monetise adjustment costs for stakeholders owing to unavailability of relevant data or information.

**Table 18 Overview of the main costs associated with pivotal measures under the preferred option**

| | | **Citizens/Consumers** | | **Businesses** | | **Administrations** | |
|---|---|---|---|---|---|---|---|
| | | **One-off** | **Recurrent** | **One-off** | **Recurrent** | **One-off** | **Recurrent** |
| UMNs | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | |
| | Indirect costs | | | | Lost income for generics industry €77m-€154m a year (ave €115.5m)<br><br>€1.15bn-€2.3bn over 15 years (ave €1.7bn) | | Additional costs for payers €163m-€326m a year (ave €245m)<br><br>€2.45bn-€4.9bn over 15 years (ave €3.67bn) |
| AMR | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | |
| | Indirect costs | | Costs for 'unserved' patients €158m a year<br><br>€2.37bn over 15 years | | | | Additional costs for payers €283m a year<br><br>€4.2bn over 15 years |

| | | Citizens/Consumers | | Businesses | | Administrations | |
|---|---|---|---|---|---|---|---|
| | | **One-off** | **Recurrent** | **One-off** | **Recurrent** | **One-off** | **Recurrent** |
| Comparative trials | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | |
| | Indirect costs | | | | Lost income for generics industry €154m-€192m a year (ave €173m)<br><br>€2.3bn-€2.9bn over 15 years (ave €2.6bn) | | Additional costs for payers €326m-€408m a year (ave €367m)<br><br>€4.9bn-€6.1bn over 15 years (ave €5.5bn) |
| Market access | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | |
| | Indirect costs | | | | Lost income for originators €352m-€422m a year (ave €387m)<br><br>€5.3bn-€6.3bn over 15 years (ave €5.8bn) | | |
| Shortages | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | Additional costs for originators €10m-€20m a year (ave €15m)<br><br>€150m-€300m over 15 years (ave €225m) | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | Additional costs for regulators €10m-€20m a year (ave €15m) |

| | | Citizens/Consumers | | Businesses | | Administrations | |
|---|---|---|---|---|---|---|---|
| | | **One-off** | **Recurrent** | **One-off** | **Recurrent** | **One-off** | **Recurrent** |
| | | | | | | | €150m-€300m over 15 years (ave €225m) |
| | Indirect costs | | | | | | |
| Environment | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | Additional costs for industry €20m-€25m a year (ave €22.5m)<br><br>€300m-€375m over 15 years (ave €337.5m) | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | Additional costs for regulators €20m-€25m a year (ave €22.5m)<br><br>€300m-€375m over 15 years (ave €337.5m) |
| | Indirect costs | | | | | | |
| Streamlining | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | Additional one-off costs for regulators €16.8m-€33.6m (ave €25.2m) | Additional costs for regulators €33.5m-€67.5m a year (ave €50.5m)<br><br>€502.5m-€1.01bn over 15 years (ave €757.5m) |
| | Indirect costs | | | | | | |
| Digitalisation | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | | | |
| | Direct regulatory fees and charges | | | | | | |

| | | Citizens/Consumers | | Businesses | | Administrations | |
|---|---|---|---|---|---|---|---|
| | | **One-off** | **Recurrent** | **One-off** | **Recurrent** | **One-off** | **Recurrent** |
| | Direct enforcement costs | | | | | Additional one-off costs for regulators €120m-€350m (ave €235m) | Additional costs for regulators €24m-€70m a year (ave €47m)<br><br>€360m-€1.05bn over 15 years (ave €705m) |
| | Indirect costs | | | | | | |
| Enhanced support | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | Additional costs for regulators €4.8m-€7.2m a year (ave €6m)<br><br>€72m-€108m over 15 years (ave €90m) |
| | Indirect costs | | | | Additional costs for industry for engaging with regulators €1.6m-€2.4m a year (ave €2m)<br><br>€24m-€36m over 15 years (ave €30m) | | |
| ***Costs related to the 'one in, one out' approach*** | | | | | | | |
| **Total** | Direct adjustment costs | | | | | | |
| | Indirect costs | | Costs for 'unserved' patients €158m a year<br><br>€2.37bn over 15 years | | Lost income for businesses and additional costs of enhanced support €677.5m / yr €10.16bn / 15 yrs | | |
| | Administrative costs (for offsetting) | | | | Administrative costs to businesses<br><br>€37.5m / yr €562.5m / 15 yrs | | |

### *11.3 Relevant sustainable development goals*

Six of the 17 SDGs are likely to be addressed through the proposed changes to the EU general pharmaceutical legislation, with SDG3 and SDG9 being the most directly relevant, while four other SDGs may be affected positively but to a lesser degree. Table III presents our qualitative assessment of the proposed revisions' potential relevance and likely contribution to progress against each of the six SDGs.

Given the 'macro' nature of the SDGs, we have provided a qualitative and directional statement as regards expected progress, and have not sought to include any quantification of those possible contributions. This is because the legislative actions in scope are many points removed from the SDG goals: there is a long chain of cause-and-effect even for the most relevant SDGs.

As a case in point, the proposals to strengthen the legislation's support for critical areas of innovation (e.g. UMNs) are likely to bring forward new medicines that may be made available to patients at some point in time, ultimately delivering health gains to thousands of Europeans that had previously had few or no treatment options. However, that is a long way from arguing that the revisions will shift the dial as regards the state of the health of 450 million EU citizens.[135]

**Table 19 Overview of relevant Sustainable Development Goals – Preferred Option(s)**

| Relevant SDG | Expected progress towards the Goal | Comments |
|---|---|---|
| SDG 3: Good Health and Well-Being for people | Highly relevant<br><br>The revisions will help futureproof the legislation, continuing to safeguard public health.<br>The revisions will increase the proportion of new medicines that address unmet medical needs, thereby creating the potential for millions of people across the EU and internationally to access effective treatments for their debilitating conditions.<br>The revisions will introduce new incentives for innovative antimicrobials with the potential to tackle disease resistant pathogens and contribute to managing AMR. | Future-proofing<br>Innovation<br>Repurposing<br>Market access |
| SDG 5: Gender Equality | Slightly relevant<br><br>The revisions may have a small positive impact on gender equality because of the commitment to reduce unmet medical needs and improve access, both of which can have a gender dimension, albeit this is most pronounced around access to and use of healthcare services rather than medicinal products more narrowly. | UMNs |
| SDG 8: Decent work and economic growth | Somewhat relevant<br><br>The revisions may have some small positive impact on the quality of work and economy since new and improved access to effective medicines may improve citizens' abilities to manage chronic conditions and sustain more demanding / rewarding jobs. Moreover, the legislative revisions have the capacity to further strengthen Europe's pipeline of major innovative medicines and help to sustain growth rates of the innovative pharma and biotech industries if production occurs in Europe. The legislative measures designed to support earlier access to markets by the producers of generics and biosimilars may also help to sustain or even expand the EU's generics industry. | UMNs<br>Market access<br>Streamlining |
| SDG 9: Industry, Innovation, and Infrastructure. | Highly relevant<br><br>The revisions have sought to balance support for the EU pharma industry and patients, with substantial additional incentives for major medicines innovations in the areas of UMN, AMR and other therapeutic areas where there is an evident social need and a demonstrable market failure (e.g. difficult / costly science and small, volatile markets). | Innovation<br>Streamlining<br>Digitalisation<br>Enhanced support |

[135] We have noted elsewhere that to quantify patient benefits would require making a series of unsupported assumptions about a typical unmet medical need, the patient population and health burden of that typical UMN, a typical value of a Quality Adjusted Life Year for that typical product, the total number of UMNs, and so on.

| Relevant SDG | Expected progress towards the Goal | Comments |
|---|---|---|
| | The revisions should strengthen the EU industry's global competitiveness in those areas most directly related to UMNs.<br><br>The revisions may lead to a refocusing of industrial R&D and possibly even a loss of R&D investment / capacity linked with less novel therapeutic work (may follow other industries in relocating to other regions with more attractive regulatory environments, strong clusters and lower prices).<br><br>The revisions should strengthen the EU generic industry's competitiveness and help to retain more of its manufacturing capacity within the EU.<br><br>The revisions should help to maintain the EU's attractiveness as a place for carrying out medicines research globally (new incentives for innovation, new definitions, various streamlining and digitalisation measures).<br><br>The revisions are largely agnostic as regards the differential costs or benefits for Europe's SMEs, however, the transferable vouchers may provide a good opportunity for small biotech firms working on novel antimicrobials to secure substantial additional funding for research through the sale of vouchers or through the raising of new finance or acquisition. The proposals to make the regulatory advice and scientific support more dynamic / interactive is likely to be especially valuable to SMEs. | |
| SDG 10: Reduced Inequalities | Somewhat relevant<br><br>The revisions will support improvements in health equality through improved market access, increasing the number and speed at which new medicines are launched on the great majority of EU markets (12-15 markets will become 22-25 markets).<br>The revisions will also support improvements in the management of medicines shortages across the EU, helping to contain the upward trend in shortages and increasing the likelihood patients receive the most suitable medicines.<br>The increase in the proportion of medicines addressing unmet medical needs will provide those patients with treatment options where that is not the case currently. | Innovation focused on UMNs<br>Market access conditions |
| Goal 12 Responsible Consumption and Production | Slightly relevant<br><br>The revisions to the legislation will help to improve the pharmaceutical industry's environmental performance in some limited degree, through more stringent environmental risk assessments and the expansion of the scope of the assessment to include manufacturing risks. This may encourage the use of less risky APIs and higher quality global supply chains, helping to reduce manufacturing-related releases to the environment of the most problematic substance.<br>The revisions will also look to encourage member states to redouble their efforts in respect to the prudent use of antibiotics, through the greater use of diagnostics, more cautious prescribing practice and more appropriate disposal regimes and infrastructure. These signals should help to reinforce trends towards less widespread use of antimicrobials as well as more informed disposal, both of which would help to reduce releases to the environment through excretion or poor waste management. | More stringent environmental assessments<br>Prudent use of antimicrobials |

# 12 ANNEX IV: IMPACT ANALYSIS OF ALL POLICY MEASURES

## 12.1 Introduction

This appendix provides an assessment of the likely impacts of each of the 77 policy measures considered as part of the impact assessment study.

The presentation also includes the 10 pivotal policy measures that were identified from within the 77 measures, based on the initial assessment of the long list, as being of critical importance for the revisions to the legislation, and which have therefore been looked at in more depth. The pivotal measures are also presented in the main report of the study supporting the IA and the accompanying Staff Working Document. The assessment of the remaining policy measures is only presented here in the appendices.

For ease of reference, Table 1 presents the titles and reference number for each of the long list of 77 measures that have been assessed by the study team, the results of which are presented in some detail over the subsequent pages.

The measures are organised by policy block (e.g. antimicrobial resistance [AMR]), with the different combinations of policy elements set out under each of the three policy options. The tabular presentation allows the reader to more readily understand the different combinations of policy elements that have been brought together for each policy block, and with the common elements being tagged as such. For example, under the 'incentives for innovation' Policy Block, policy element C.1.1. is the same as policy element B.1.1. and C.1.8. is the same as B.1.8 and so on.

Option C is the most comprehensive of the three policy options and is expected to become the preferred option, having been able to strike the best balance between encouraging further innovation, supporting a strategic industry, while promoting improvements in access, affordability and environmental impact. The 77 measures are considered from the perspective of the current baseline and the specific policy option. The pivotal measures are listed in **bold**, to distinguish them visually from the other policy measures.

Following these policy measures for each of the options, we present a similar overview of the 30+ horizontal measures that have been identified as a possible means by which to streamline the regulatory system in order to speed up assessments and otherwise reduce administrative burden. These measures would apply in principle to any of the three policy options, and have therefore been presented once only. The initial assessment of the long list of horizontal measures has been used as the basis for selecting a series of 10 pivotal horizontal measures, which are looked at in more depth and have been the subject of our cost-benefit analysis.

*Table 1 Principal policy elements considered under each of the three policy options*

| Option A | Option B | Option C |
|---|---|---|
| **Incentives for innovation, in particular to address unmet medical needs (UMNs)** | | |
| A.1.1. PRIME remains under the current scheme (i.e. not included in the legislation).<br>A.1.2. Establish a non-binding system for scientific assessment of evidence for repurposing<br>A.1.3 Add a special incentive bonus (+1 year): of regulatory (data) protection for products with a demonstrated ability to address an UMN | B.1.1. Codification of PRIME in the legislation<br>B.1.2. Establish a binding system for scientific assessment for repurposing<br>B.1.3. Obligation for MAHs to include a new indication when supported by scientific evidence | C.1.1. As B.1.1 Codification of PRIME in the legislation<br>C.1.2. As B.1.2 Establish a binding system for scientific assessment for repurposing |

| Option A | Option B | Option C |
|---|---|---|
| A.1.4. Special incentive bonus: if data package includes comparative trial with standard of care (+6 months) | B.1.4. Reduce duration of incentives for originators from 8+2 to 6+2 years<br>B.1.5. Medicines with demonstrated ability to address UMN get +2 years data protection.<br>B.1.6. Breaking market protection in case of urgency<br>B.1.7. Require transparency on any relevant public contribution or funding<br>B.1.8. Give regulators the possibility to impose a post authorisation obligation for additional studies | C.1.3. Additional data protection period for the new evidence generated to support repurposing<br>**C.1.4. Reduce duration of incentives for originators from 8+2 to 6+2 years (but with +2 years for launch in all markets [C.4.3.])**<br>**C.1.5 As B.1.5 Medicines with demonstrated ability to address UMN get +1-year data protection.**<br>**C.1.6. Same as A.1.4. Incentive bonus: if data package includes comparative trial (+6 months)**<br>**C.1.7 Transparency on public contribution to clinical trials.**<br>C.1.8 As B.1.8. Allow regulators to impose a post authorisation obligation for additional studies<br>C.1.9. Breaking market protection in case of urgency |
| **AMR specific** | | |
| A.2.1. Harmonisation of summary of product characteristics for nationally authorised antimicrobials to support prescription practices.<br>A.2.2 Transferable voucher independent and in addition to data/market protection for antimicrobial products<br>A.2.3. Consider adapted system for authorisation of phage therapies and other alternative products | B.2.1 Make central procedure mandatory for new antimicrobials.<br>B.2.2. PRIME like support scheme, including rolling review<br>B.2.3. Optimise package size<br>B.2.4. Stricter rules on disposal<br>B.2.5. Tighten prescription requirements<br>B.2.6. Mandatory use of diagnostics<br>B.2.7. Pay or play model<br>B.2.8. Establish a monitoring system for consumption and use and the environment<br>B.2.9. same as A.2.3 | C.2.1. Novel antimicrobials fall in the CAP mandatory scope<br>C.2.2. PRIME like support scheme, including rolling review<br>C.2.3 Require companies to develop AMR lifecycle management plan<br>C.2.4. same as B.2.3: Optimise package size<br>C.2.5. same as B.2.5: Tighten prescription requirements for antimicrobials<br>**C.2.6. Transferable voucher independent and in addition to data/market protection for antimicrobial products.**<br>C.2.7. Consider adapted system for authorisation of phage therapies and other alternative products |

| Option A | Option B | Option C |
|---|---|---|
| **Future proofing** | | |
| A.3.1. Maintain current exemptions from the scope of the legislation – add some clarifications/conditions<br>*GMO OPTIONS*<br>A.3.2. Clinical trials: a risk-based approach is applied to determine when a specific GMO assessment is required.<br>A.3.3. An environmental risk assessment continues to be performed (by EMA) in the context of the marketing authorisation procedure. | B.3.1. Adapted regulatory framework for certain categories of novel products/technologies<br>*GMO OPTIONS*<br>B.3.2. same as A.3.2 but for clinical trials: Where required, the assessment of the GMO aspects of investigational medicinal products is performed at Member State level<br>B.3.3. Adapt certain definitions, including that of medicinal product and *delink scope from industrial process*.<br>B.3.4. Create a central *classification mechanism* for advice on whether products are medicines or not | C.3.1. Adapted regulatory framework for certain categories of novel products/technologies<br>C.3.2. Clinical trials: a risk-based approach is applied to determine when a specific GMO assessment is required.<br>C.3.3. Same as B.3.3. Adapt certain definitions, including that of medicinal product and *delink scope from industrial process.*<br>For specific cell-based (ATMP) medicinal products [*-link with revision of BTC legislation*]:<br>C.3.4. adapted regulatory requirements to facilitate production in the hospital setting<br>C.3.5. less complex cell-based medicinal products to be defined on the basis of clear risk-based approach<br>C.3.6. Introduction of a regulatory sandbox environment, in the context of complex/cutting-edge 'medicinal product'<br>C.3.7. Same as B.3.4. Create a central [i]*classification mechanism* for advice on whether products are medicines or not. |
| **Access** | | |
| A.4.1. Facilitate 'multi country packs' with labelling to allow their placing on the market in several Member States.<br>A.4.2. Milestone incentive – +6 months data protection if product marketed in all MS within 6 years.<br>A.4.3. (non-regulatory option) Voluntary reporting of market launches within 2 years of centralised authorisation.<br>A.4.4. Promote placing on the market in all Member States within 5 years | B.4.1. Conditional marketing authorisation: more powers to regulators to enforce obligations for post-market evidence generation.<br>B.4.2. Require MAHs to notify regulators of their market launch intentions.<br>B.4.3. Obligation to place a centrally authorised medicine on the market in the majority of Member States within 5 years<br>B.4.4. Requirement to MAH applying for MRP/DCP to include small markets | C.4.1. Conditional marketing authorisation: UMN incentives are only granted upon switching to standard MA.<br>C.4.2. same as A.4.1. Facilitate 'multi country packs' with labelling to allow their placing on the market in several Member States.<br>**C.4.3. 2 years of protection conditional to launch of all EU markets within 2 years**<br>C.4.4. same as B.4.4.: Requirement to MAH applying for MRP/DCP to include small markets |
| **Competition: generic, biosimilar entry** | | |
| A.5.1. New simpler regulatory pathway for generics<br>A.5.2 No change to current situation and no restriction on duplicate marketing authorisations. | B.5.1. same as A.5.1. New simpler regulatory pathway for generics<br>B.5.2. Interchangeability of biosimilars with their reference product will be generally recognised | C.5.1. same as A.5.1. New simpler regulatory pathway for generics<br>C.5.2. same as B.5.2. Interchangeability of biosimilars with their reference product will be generally recognised |

| Option A | Option B | Option C |
|---|---|---|
| | B.5.3. Broaden Bolar exemption<br>B.5.4. Extend Bolar exemption beyond generics<br>B.5.5. Specific (regulatory) incentive for a limited number of first biosimilars<br>B.5.6.a. Reforming the duplicates regime: No auto-biologicals.<br>B.5.6.b. Duplicates restricted to cases of IP protection or co-marketing | C.5.3. same as B.5.3. Broaden Bolar exemption<br>C.5.4. same as B.5.4. Extend Bolar exemption beyond generics<br>C.5.5. same as B.5.6.b Duplicates restricted to cases of intellectual property protection or co-marketing |
| **Security of supply** | | |
| A.6.1. Encourage use of HMA/EMA guidance definitions<br>A.6.2. Notifications two months in advance<br>A.6.3. Marketing authorisation offered to another MAH before a permanent withdrawal<br>A.6.4. Use of the Falsified Medicines Directive (FMD) system to monitor shortages<br>A.6.5. EU coordination to exchange information on supply and supply chains | B.6.1. Introduce an EU definition of a shortage<br>B.6.2. Increase notification period to 6 months in advance<br>B.6.3. Shortage prevention and mitigation plans added to GMP for all medicines<br>B.6.4. Stockpiling requirements for MAHs and wholesalers for critical medicines<br>B.6.5. Introduce an EU shortage monitoring system<br>B.6.6. Require specific penalties for breaking supply obligations.<br>B.6.7. Expanded requirements for key suppliers and back-ups to diversify supply chain<br>B.6.8. Increase transparency of the supply chain, including active supply sites. | **C.6.1. Introduce an EU definition of a shortage**<br>**C.6.2.a. Withdrawals: Increase notification period to 12 months**<br>**C.6.2.b and at least 6 months in advance for all shortages (non-withdrawal).**<br>**C.6.2.c Introduce a common template for reporting withdrawals and shortages.**<br>**C.6.3. Stockpiling requirements for MAHs for unfinished critical medicines, as appropriate**<br>**C.6.4. same as A.6.3 Marketing authorisation offered for transfer to another MAH before a permanent withdrawal**<br>**C.6.5. MAHs to have shortage prevention and mitigation plans for all medicines**<br>**C.6.6. Monitoring remains at MS level, with information exchange based on national monitoring, using a common format**<br>**C.6.7. Same as B.6.7. Expand requirements to diversify supply chains.**<br>**C.6.8. Establish a mechanism of information exchange to identify bottlenecks / vulnerabilities**<br>**C.6.9. same as B.6.8. B.6.8. Increase transparency of supply chains** |

| Option A | Option B | Option C |
|---|---|---|
| **Quality and manufacturing** | | |
| A.7.1. Strengthen enforcement by introducing harmonised system of sanctions.<br>A.7.2. Inclusion of the information on the sustainability performance of supply chains actors by using international standards in the application dossiers.<br>A.7.3. Adaptation of legislation/inclusion of specific provisions covering new manufacturing methods | B.7.1. Improve oversight of supply chains *by modifying the provisions on inspections*<br>B.7.2. Reinforcing Member States GMP and GDP inspections capacity by setting up a mandatory joint audit scheme.<br>B.7.3. Stronger overall responsibilities of MAH over the entire supply chain.<br>B.7.4. same as A.7.3. Adaptation of legislation/inclusion of specific provisions covering new manufacturing methods | C.7.1. Strengthen the oversight of the sites within a supply chain *by extending the scope of mandatory inspections and modifying provisions on inspections*<br>C.7.2. Stronger EMA role in oversight of coordination of inspections, including in setting up multinational inspection teams.<br>C.7.3. same as B.7.2. Reinforcing Member States GMP and GDP inspections capacity by setting up a mandatory joint audit scheme.<br>C.7.4. same as A.7.3. Adaptation of legislation/inclusion of specific provisions covering new manufacturing methods |
| **Address environmental challenges[ii]** | | |
| A.8.1. No change<br>A.8.2. Obligation to include information on sustainability performance of supply chain using international standards | B.8.1. Include assessment of the environmental risk of manufacturing into ERA, including main supply chain actors (API, raw materials).<br>B.8.2. Strengthen the ERA requirements and conditions of use for medicines<br>B.8.3. Include the AMR aspects in GMP to address environmental challenges. | **C.8.1. Include assessment of the environmental risk of manufacturing into ERA, including main supply chain actors (API, raw materials).**<br>**C.8.2. same as B.8.2. Strengthen the ERA requirements and conditions of use for medicines**<br>**C.8.3. Advisory role of EMA on ERA and green manufacturing aspects and quality (e.g. with relation to generics)**<br>**B.8.4. Include the AMR aspects in GMP to address environmental challenges.** |
| **COVID-19 lessons learnt to be applied during and beyond crises** | | |
| A.9.1. No further changes apart from the extension of the EMA mandate | B.9.1. Refusal of immature applications<br>B9.2. Codification of rolling reviews for UMNs | C.9.1. same as B.9.1. Refusal of immature applications |

## 12.2 The baseline situation

### *12.2.1 Policy Block A (Baseline): support for innovation, including unmet medical needs*

Table 2 presents a qualitative assessment of the likely future impacts of the current regulatory arrangements on innovation. It acknowledges that the current system – the baseline – has been a catalyst for innovation over the past 15 years and would be likely to continue to encourage innovation going forwards, were it to continue unchanged from its present arrangements. In simple terms, the table presents a dynamic view of the baseline situation.

*Table 2 Baseline situation: assessment of future impacts of current incentives for innovation*

| **Assessments of innovation related sub-themes** |
|---|
| 1. Incentives |
| The current system provides incentives for innovation in terms of data (8 years) and market protection (2 years) to give time to developers to recoup their investment by delaying the entry of generics or biosimilars. These are without prejudice to intellectual property (IP) protection and specific rewards and market exclusivity for orphan and paediatric indications.<br>The evaluation found the expanded scope and harmonised incentives of the current regulatory system had contributed to the growing numbers of applications for new medicines received by the EMA. Feedback from originators underlines support for the status quo and the relevance of current incentives, while other stakeholder groups and especially the representatives of generic companies and patients' groups see the current arrangements as favouring one particular model of innovation, and to a degree that is not optimal over other important objectives are considered (e.g. patients' access to affordable medicines).<br>We identified several factors that present challenges for the current arrangements' ability to continue to encourage innovation to the extent that it has done in the past. These issues largely revolve around the exciting advances in science and technology and the increasing numbers of more complex medicinal products and a greater diversity of manufacturing methodologies. These trends are largely to the cost and time of making and assessing applications, rather than acting as a brake on innovation, however, it is conceivable that the current system is feeding forward into developers' planning and causing originators to look at less ambitious candidates or even to look to other regulatory systems in the first instance.<br>Another external factor includes the increasing cost of medicines research, with statistics showing a long-run decline in research productivity overall (based on average success rates across phases of development), albeit these data point to an improvement in regulatory submission success rates. This trend is possibly driven in part by regulators' encouragement of and reward for increasingly risky or aspirational research.[1]<br>Given the long-run nature of medicines development cycles, we assume historical growth rates – in the numbers of innovative medicines – will continue to hold in the medium term but may start to slow slightly in the longer term. In 2021, the EMA approved 92 new medicines and 53 new active substances[2]. As such, EU health care systems and patients would continue to see an expanding pool of novel medicines and treatment options in the next five years with some fall off in the rates |
| 2. Expedited regulatory schemes |
| The current legislation successfully introduced several new schemes such as conditional marketing authorisation (CMA) and accelerated assessment (AE) to allow earlier authorisation of innovative products of major interest for public health. These regulatory pathways have supported the authorisation of more innovative medicines, and these expedited schemes have been given a further boost by the EMA's introduction of the Priority Medicines Scheme (PRIME), which is outside the legislation currently, but is nonetheless attracting a growing number of applications for promising medicines that address unmet medical needs.<br>Our consultations confirmed the added value of these expedited regulatory schemes from an innovation perspective, with originators expressing strong support for the retention or enhancement of these existing pathways. By contrast, while national competent authorities and health payers acknowledge the potential boost to innovation, there was a concern that these expedited pathways were being used more for the convenience of industry and less for public health. Health payers and HTAs argued that the CMA had encouraged early submission of immature applications, and that the resulting conditional authorisations were difficult to assess in terms of cost-effectiveness – against standard treatments – and that there was a hardening of attitudes towards these regulatory pathways, with approvals for reimbursement become less likely in the absence of supporting evidence. |

[1] For a trend analysis, see exhibit 27 of 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022.

[2] https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2021_en.pdf

| **Assessments of innovation related sub-themes** |
|---|
| Analysis of EMA statistics show increasing numbers of applications and authorisations running through these expedited schemes, especially CMAs and PRIME, many of which relate to major innovations relating to unmet medical needs.<br>We would expect this expansion in interest and activity to continue over the next 5-10 years – and possibly intensify – even within the current regulatory system.<br>There is a good pipeline of novel medicines in development, driven in part by more specific regulatory actions in the EU and the US, and relating to rare diseases and paediatric medicines in particular.[3] There is a substantial and growing interest across all stakeholder groups in addressing a number of key aspects around unmet medical needs, whether that is coming from patients groups and health systems or regulators and payers wanting to frame a coherent definition / set of criteria or major public private research initiatives seeking to develop breakthroughs around specific UMNs, such as the €2.4bn Innovative Health Initiative (IHI) supported by Horizon Europe. Perhaps most critical, there is evident growth in investment in cell and gene therapies, and the EMA and other regulators are handling a growing number of CGT / ATMP applications. This next wave of pharma technology has the potential to improved research productivity, accelerate innovation, expand treatment options and address UMNs and all within the existing regulatory arrangements.[4] |
| 3. Repurposing |
| There is an extended length of (market) protection available for new indications/repurposed medicinal products, whereby the 8+2+(1) major development would be maintained<br>The current legislative arrangements include a special incentive that encourages and rewards originators for identifying opportunities to extend the use of existing medicines to include new indications. This is used largely with newer medicines and is used less often with off-patent or off-label products, which is the main focus of concerns to promote repurposing.<br>While repurposing was one aspect where all stakeholder groups judged the current arrangements to have been less effective in driving a significant change in behaviour, the EMA annual reports and statistical highlights show the number of extensions of indications recommended is increasing over time: 51 recommendations in 2017, 65 in 2018, 60 in 2019, 83 in 2020 and 80 in 2021.[5]<br>From this perspective, the current arrangements are likely to see a growing number of extensions, however, the commercial uncertainty around repurposing suggest the current level of incentives are unlikely to result in a substantive change in the underlying level of repurposing of medicines. This may be the case for older medicines in particular, where there is a weaker business case for extensions, as products near the end of the patent or regulatory protection periods, and paradoxically where there is a greater likelihood that wider health benefits have been identified through off-label uses of existing medicines.<br>Originators are motivated to apply for extensions to new indications in the early years following the original marketing authorisation, taking advantage of the 8+2+1 incentive, however the incentive is not always strong enough to offset the costs / risks associated with repurposing medicines as they approach the end of the period of IP or regulatory protection.<br>For novel medicines, a continuation in the expansion in the numbers of new medicines being submitted to the EMA for assessment – and the growing number of positive opinions – is likely to continue to drive, indirectly, an expansion in the numbers of new indications / variations extensions applied for.<br>The current regulatory arrangements are therefore likely to accommodate an increase in demand for extensions of existing medicines to new conditions, which will continue to expand treatment options for patients. Support for repurposing will remain quite limited. |

Table 3 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories. For most impact types, we have concluded that the baseline policy option would be likely to have a largely neutral effect. That is, there would be no substantive change, positive or negative, in impacts over time. We foresee several areas of positive impact that reflect the current regulatory arrangements past successes, relating primarily to the realms of research and innovation, treatment options for patients and support to Europe's research-intensive pharmaceutical industry. There are many exciting new developments already in progress, around advanced therapies, novel products, next generation manufacturing, real-world evidence, and more. The current regulatory system

3 https://invivo.pharmaintelligence.informa.com/-/media/supporting-documents/in-vivo-issue-pdfs/iv2003_lrs.pdf

4 https://www.marketwatch.com/press-release/europe-cell-and-gene-therapy-market---size-by-type-by-distribution-channel-and-forecast-till-2022-2031-2022-03-22

5 https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines/medicine-evaluation-figures#annual-medicines-highlights-(2015-2021)-section

has not impeded these global developments, and as such, one could expect the current regulation to continue to accommodate this progress and the benefits that will follow from it.

The current arrangements have not been particularly influential in changing behaviour around repurposing, albeit we would expect the gradual increase in the number of extensions to continue. In terms of the downside, the current system's expedited pathways are causing difficulties for health technology agencies nationally, which struggle to determine the cost-effectiveness of new medicines with only limited data, and where there is less likelihood that these innovative treatments will be approved for reimbursement and where they are there may be less good treatment outcomes for patients as a higher proportion of expedited medicines prove to be less effective than had been anticipated.

*Table 3 Baseline – Summary assessment of incentives for innovation*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Incentives | +++ | +/- | +/- | +/- | +/- | +++ | +/- | ++ | +/- |
| Expedited pathways | ++ | +/- | +/- | +/- | +/- | + | - | - | +/- |
| Repurposing | +/- | +/- | +/- | +/- | +/- | +/- | +/- | + | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### *12.2.2 Policy Block B (Baseline): Antimicrobial Resistance (AMR)*

As noted in the problem analysis, the EC has several flagship projects underway that aim to restrict and optimise the use of antimicrobials, which are encompassed by the EU One Health Action Plan against AMR (June 2017)[6] built on 3 main pillars:

- Making the EU a best practice region
- Boosting research, development and innovation
- Shaping the global agenda

The Commission has also adopted the first deliverables of the plan, for example the EU Guidelines on the prudent use of antimicrobials in human health.

These commitments are underlined by the EC 2020 Pharmaceutical Strategy, which highlights the importance of AMR in the context of unmet medical needs, and presents two flagship initiatives in the field of AMR: (i) a public procurement mechanism to generate pull incentives; (ii) a role for the new Health Emergency Response Authority (HERA) in the process of promoting investment and coordinating research, development, manufacturing, deployment and use of novel antibiotics; and it furthermore commits to (iii) Review the pharmaceutical legislation with the aim of restricting and optimising the use of antimicrobial medicines.

From the perspective of the EU general pharmaceutical legislation, the baseline is clear: the current legislation includes no special incentives or obligations for the development of or prudent use of antimicrobials. As such, we see no change in impact (across the different impact dimensions) if the current scenario were to continue.

While the current legislation is silent on AMR, statistics show that the problem is wide ranging and expected to worsen without further interventions by governments and health systems around the world.

[6] https://ec.europa.eu/health/antimicrobial-resistance/eu-action-antimicrobial-resistance_en

- The social costs of AMR are high and increasing
  - It is estimated that each year about 670,000 infections occur, and that 33,000 Europeans die as a consequence of antibiotic-resistant bacteria. With the burden being highest in the elderly and infants[7]. It is also estimated that AMR costs the EU €1.5bn per year in healthcare costs and productivity losses.
- The use of antimicrobials in Europe is reducing overall but with substantial unevenness across the EU
  - Stewardship measures are expected to continue to restrict and optimise the use of antimicrobials overall, however, there is considerable variability in stewardship policies and practices across the EU.
- The global AM pipeline is much weaker than other therapeutic areas

The development challenge is widely documented, with a weak global pipeline that is not expected to be rebuilt without substantive public support, as there are evident and growing market failures, with an evident gap between the typical cost and scale of the scientific challenge involved in developing new antimicrobials and the typical income and profit that can be derived from sales of these products. Global efforts to reduce use is increasing this gap between costs and benefits.

  - The WHO Global Observatory on Health Research and Development monitors antibacterial products in development, and its April 2021 dashboard[8] shows that as of September 2020, there was a total of 41 antibiotics and 27 non-traditional antibacterial agents in clinical development globally. Those 68 products are distributed across the three phases of clinical trials. Overall, the WHO concludes that the clinical pipeline and recently approved antibiotics are insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance.
  - We would expect to see increasing support for innovation and novel antimicrobials, through major public research programmes, such as Horizon Europe, and other regulators' actions (FDA), which should help to sustain and possibly improve the global pipeline, from its admittedly weak status currently.

### *12.2.3 Policy Block C (Baseline): Future Proofing*

To regulatory system needs to be adaptive to adequately protect public health[9]. Exclusions exist to limit the scope of what medicinal products fall within the pharmaceutical legislation (currently there are seven product categories excluded from the scope). However, novel medicines, approaches and processes which do not naturally meet the scope or definitions or which the legislation does not fully fit can therefore find themselves unregulated or subject to unintended barriers.

Our consultations and desk research suggest that advances in science and technology have led to several regulatory challenges:

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[7] Cassini, A., Högberg, L. D., Plachouras, D., Quattrocchi, A., Hoxha, A., Simonsen, G. S., Colomb-Cotinat, M., Kretzschmar, M. E., Devleesschauwer, B., Cecchini, M., Ouakrim, D. A., Oliveira, T. C., Struelens, M. J., Suetens, C., Monnet, D. L., Strauss, R., Mertens, K., Struyf, T., Catry, B., … Hopkins, S. (2019). Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *The Lancet Infectious Diseases*, *19*(1), 56–66. https://doi.org/10.1016/S1473-3099(18)30605-4

[8] https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antibacterial-products-in-clinical-development-for-priority-pathogens

[9] Klein, K., Stolk, P., de Bruin, M. L., & Leufkens, H. (2021). Regulatory density as a means to refine current regulatory approaches for increasingly complex medicines. *Drug Discovery Today*, *26*(10), 2221–2225. https://doi.org/10.1016/J.DRUDIS.2021.04.005

- Delays and inefficiencies due to uncertainty around the most appropriate regulatory pathway(s) resulting in applications being assessed in several committees rather than one, additional external advice being sought, and applicants being asked to clarify evidence or resubmit applications. The problem is exacerbated by the fact that each committee's mandate is narrow, fitting to the scope of the framework under which is set up, and there is a lack of coordination/consultation between the committees.
- Legislative barriers within regulatory pathways and processes due to definitions and guidance that do not apply to changing technology and heterogenous interpretation of such guidance by member states.
- Several new technologies, product combinations and innovative processes are causing uncertainty regarding their inclusion within the scope of the legislation in part as a result of the narrowness of current definitions and uncertainty on which legislative framework is most appropriate. For instance, certain technologies can also be subject to other EU legal frameworks that provide for safety, quality and efficacy requirements such as those for medical devices, substances of human origin, etc.

Challenges are particularly evident around these key areas:

1. Gene Therapy medicinal products:
   - Advanced therapy medicinal products (ATMPs): ATMPS are highly innovative and complex medicines based on genes, tissue or cells. Classification of these complex products can be complicated due to difficulties to distinguish between different biological subcategories.[10] These classification challenges are further complicated by the blood, cells, tissue (BTC) legislation where there are difficulties distinguishing between BTC and medicines because of (a) different criteria set in the general pharmaceutical legislation (industrial process, intention to put on market, hospital exclusion) and in the ATMP regulation (substantial manipulation, non-homologous use) as well as (b) lack of coordination between authorities/advisory bodies in relevant sectors on interpretation of these borderline criteria.[11]
   - Hospital exemption: Target markets for ATMPs are often small and not appealing for larger pharmaceutical organisations to invest in their development. The hospital exemption (HE) was implemented to encourage ATMP production in the hospital setting for non-commercial purposes to facilitate patient access to affordable novel therapies. For example, the price of a CAR-T developed under the HE-ATMPs pathway is one-third of the cost of commercial CAR-Ts available.[12] However, the HE has been interpreted and implemented differently across Member States, which risks undermining patient safety[13]. This is because there is no requirement to collect data on safety of efficacy of HE products. Furthermore, HE products do not fall under the centralised procedure (CP) limiting patient access. However, the HE has enabled the manufacture of a 'modest' number (~12) of ATMPs within EU between 2009 and 2017[14]. There are also concerns the HE is creating a competitive

[10] Iglesias-López, C., Agustí, A., Obach, M., & Vallano, A. (2019). Regulatory framework for advanced therapy medicinal products in Europe and United States. *Frontiers in Pharmacology*, *10*(JULY), 921. https://doi.org/10.3389/FPHAR.2019.00921/BIBTEX

[11] BTC impact assessment

[12] Trias, E., Juan, M., Urbano-Ispizua, A. et al. The hospital exemption pathway for the approval of advanced therapy medicinal products: an underused opportunity? The case of the CAR-T ARI-0001. Bone Marrow Transplant 57, 156–159 (2022). https://doi.org/10.1038/s41409-021-01463-y

[13] EuropaBio (2020) *EU ATMP Hospital Exemption*.

[14] Coppens, D. G. M., Hoekman, J., de Bruin, M. L., Slaper-Cortenbach, I. C. M., Leufkens, H. G. M., Meij, P., & Gardarsdottir, H. (2020). Advanced therapy medicinal product manufacturing under the hospital exemption and

disadvantage to commercial ATMP developers that incur higher development costs through the CP.

2. Combinational products: Medicines are increasingly being used in combination with a medical device, usually to enable the delivery of the medicine. Medical products are regulated through the pharmaceutical legislation, whereas devices are regulated through the medical device legislation. However, these combinational products have brought regulatory difficulties for NCAs in terms of uncertainty whether they should be classified as a medical product or medical device and what regulatory framework applies.
3. Industrial process/manufacture: Technological and scientific advances have raised issues regarding the definition of 'industrial process' or 'industrial manufacture'; these terms were to limit the scope of what products fall within pharmaceutical legislation. Differences in the interpretation of the definition has caused challenges for Member States in determining what legislation is appropriate or created legislative gaps where products are not regulated, meaning some products are not regulated under pharmaceutical legislation when they should be, thus potentially compromising the safety of patients. This has been particularly problematic for bedside production, personalised medicines, industrially prepared radionucleotides and medical products derived from blood in the hospital setting.
4. Novel technologies and approaches: There is an increasing number of novel technologies and approaches emerging that are transforming the development and production of medicines[15]. Notable examples include the application of novel manufacturing approaches to a range of areas from developing personalised medicines to addressing medicine shortages. Other areas of notable advancement include the application of artificial intelligence to medicines in a range of areas from improving medicine development, clinical trials, and medicine manufacturing[16]. These rapidly advancing technologies are bringing new regulatory challenges in terms of how best to accommodate them under the current legislation.

Medicinal products that contain or consist of GMOs, such as gene based and cell-based therapies, will increasing become more important as they have great potential to treat a range of diseases, including areas of unmet medical needs. There are specific requirement for products contain or consist of GMOs. During marketing authorisation: the evaluation of the environmental impacts of medicinal products for human use that contain or consist of GMOs is done, in accordance with the principles set out in Directive 2001/18/EC, by EMA or the national competent authority, as applicable, in the context of the assessment of the marketing authorisation application pursuant to the medicinal product legislation. Investigational medicinal products for human use (those in clinical trials) that contain or consist of GMOs are subject to the GMO legislation. Some Member States apply Directive 2001/18/EC, other Member States apply Directive 2009/41/EC and others decide on a case-by-case basis or apply both. This creates complexities for developers as different MSs have different requirements and stakeholders involved, ultimately causing regulatory burdens and delays in

other exemption pathways in seven European Union countries. *Cytotherapy*, *22*(10), 592–600. https://doi.org/10.1016/J.JCYT.2020.04.092

[15] Anklam, E., Bahl, M. I., Ball, R., Beger, R. D., Cohen, J., Fitzpatrick, S., Girard, P., Halamoda-Kenzaoui, B., Hinton, D., Hirose, A., Hoeveler, A., Honma, M., Hugas, M., Ishida, S., Kass, G. E. N., Kojima, H., Krefting, I., Liachenko, S., Liu, Y., … Slikker, W. (2022). Emerging technologies and their impact on regulatory science. *Experimental Biology and Medicine*, *247*(1), 1–75. https://doi.org/10.1177/15353702211052280

[16] Paul, D., Sanap, G., Shenoy, S., Kalyane, D., Kalia, K., & Tekade, R. K. (2021). Artificial intelligence in drug discovery and development. *Drug Discovery Today*, *26*(1), 80–93. https://doi.org/10.1016/J.DRUDIS.2020.10.010

market authorisations. To overcome these challenges, NCAs and the EC have updated and published good practice documents and common application forms concerning the conduct of clinical trials with GMOs to harmonise approaches across Member States. Specific ERA for GMO-containing medicinal products has been introduced for certain categories of investigational medicinal products containing GMOs that are highly unlikely to pose a risk to the environment or to public health to simplify requirements for developers.

According to our stakeholder consultation the current approach is still not ideal, and these main challenges were highlighted:

- Delayed authorisations of GMO-containing therapies and ultimately slower access to medicines[17]: GMO assessments are complex and vary across the EU leading to delays in clinical trials and authorisation of GMO-containing medicinal products[18]. Further harmonisation is needed for Contained Use versus Deliberate Release classification, risk classifications for the same GMOs (within Contained Use), and data requirements (content and format). GMO assessments are not always necessary as exemplified by the temporary derogation from some provisions of the GMO requirements for potential COVID-19 treatments and vaccines.
- Increased cost and burden of clinical trials in EU leading to reduced attractiveness to conduct trials in EU[19]: The EU is considered less attractive than other regions for conducting clinical trials. The number of new gene therapy clinical trials is proportionally lower in EU (55% of all new clinical trials) than in North America (71% of all new clinical trials)[20].
- Reduced investment and consequently development of GMO containing therapies[21]: In the US, a "categorical exclusion" exists for gene therapies, vectored vaccines, and related recombinant viral or microbial products[22]. However, in the EU, these types of GMO-containing products require a GMO assessment. This is seen to be delaying and restricting access to GMO-containing medicinal products in the EU[23]. Furthermore,

[17] Technopolis. (2022). *Stakeholder Consultation Narrative Data: KIIs, OPC, Targeted Survey*.

[18] Beattie, S. (2021). Call for More Effective Regulation of Clinical Trials with Advanced Therapy Medicinal Products Consisting of or Containing Genetically Modified Organisms in the European Union. *Human Gene Therapy*, *32*(19–20), 997–1003. https://doi.org/10.1089/hum.2021.058;

Lambot, N., Awigena-Cook, J., Reimer, T., Persson, A., Romanetto, J., Friedeberg, B., Acha, V., Dandapat, S., Ruppert, T., Correas, C., Wonnacott, K., Fleischmann, T., Holzhauser, C., Galaup, A., Montes, F., Garcia, S., Tellner, P., & Beattie, S. G. (2021). Clinical trials with investigational medicinal products consisting of or containing genetically modified organisms: implementation of Clinical Trials Regulation EU 536/2014. *Cell and Gene Therapy Insights*, *7*(9), 1093–1106. https://doi.org/10.18609/CGTI.2021.143

[19] Technopolis. (2022). *Stakeholder Consultation Narrative Data: KIIs, OPC, Targeted Survey*.

[20] Alliance for Regenerative Medicine. (2019). *CLINICAL TRIALS IN EUROPE: RECENT TRENDS IN ATMP DEVELOPMENT*. www.alliancerm.org

[21] Technopolis. (2022). *Stakeholder Consultation Narrative Data: KIIs, OPC, Targeted Survey*.

[22] U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research. (2015). *Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products; Guidance for Industry*. https://www.fda.gov/media/91425/download

[23] Iglesias-Lopez, C., Obach, M., Vallano, A., & Agustí, A. (2021). Comparison of regulatory pathways for the approval of advanced therapies in the European Union and the United States. *Cytotherapy*, *23*(3), 261–274. https://doi.org/10.1016/J.JCYT.2020.11.008

globally companies invested €20.1B in cell- and gene- based therapies in 2021; EU only raised €2.9B funding which was down 8% compared to 2020[24].

- EU patients are at risk of not having access to novel life-saving therapies[25]: Developers plan to submit ten market authorisation applications (MAAs) for gene therapies in the United States (USA) next year (2022), whereas they only plan to submit two of these MAAs in the EU[26]. However, a retrospective analysis until 2020 reported the EU authorised fifteen ATMPs, compared to nine in the USA[27].

This suggests EU regulatory framework is not well aligned with other regions, and a proportion of new medicines are being developed and launched in other markets (US) rather than the EU. Thus, further streamlining and harmonisation of the GMO assessment process would be desirable to avoid unnecessary delays in authorisation of GMO-containing medicines and for EU to be competitive concerning innovation of GMO medicines. Otherwise, EU patients may be at risk of not having timely access to novel life-saving therapies.

Table 4 presents an assessment of the likely future scenario if the existing scope, definitions GMO requirements for market authorisation and clinical trials continue without amendment. For most impact types, we have concluded that the effect of the baseline policy option would be largely negative. This reflects the continuing and rapid pace of technological change which will increasingly challenge the legislation in this baseline situation leading to decreasing efficiency, predictability and gaps in the regulatory framework.

*Table 4 Baseline Policy Option: summary assessment of future proofing*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Scope and definitions | - | - | +/- | - | - | - | +/- | - | +/- |
| GMOs | +/- | +/- | +/- | - | - | - | +/- | +/- | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### *12.2.4 Policy Block D (Baseline): Access*

To promote timely access to innovative medicines, particularly those that meet a previously unmet medical need or would be used in a public health emergency, the EMA may fast-track approval by granting a conditional marketing authorisation (CMA). This allows for medicines to enter the market on less comprehensive clinical data than normally required. It does,

[24] Alliance for Regenerative Medicine. (2022). *Cell & Gene State of the Industry Briefing*. https://alliancerm.org/arm-event/sotibriefing/;

Lambot, N., Awigena-Cook, J., Reimer, T., Persson, A., Romanetto, J., Friedeberg, B., Acha, V., Dandapat, S., Ruppert, T., Correas, C., Wonnacott, K., Fleischmann, T., Holzhauser, C., Galaup, A., Montes, F., Garcia, S., Tellner, P., & Beattie, S. G. (2021). Clinical trials with investigational medicinal products consisting of or containing genetically modified organisms: implementation of Clinical Trials Regulation EU 536/2014. *Cell and Gene Therapy Insights*, *7*(9), 1093–1106. https://doi.org/10.18609/CGTI.2021.143

[25] Technopolis. (2022). *Stakeholder Consultation Narrative Data: KIIs, OPC, Targeted Survey*.

[26] Alliance for Regenerative Medicine. (2022). *Cell & Gene State of the Industry Briefing*. https://alliancerm.org/arm-event/sotibriefing/

[27] Iglesias-Lopez, C., Obach, M., Vallano, A., & Agustí, A. (2021). Comparison of regulatory pathways for the approval of advanced therapies in the European Union and the United States. *Cytotherapy*, *23*(3), 261–274. https://doi.org/10.1016/J.JCYT.2020.11.008

however, require the MAH to fulfil specific obligations including the generation of additional post-authorisation evidence.

At present, there is no obligation on MAHs of centrally authorised medicines to enter a specific number or a particular set of EU markets. The only legal provision, known as the 'sunset clause', that applies is that the MA will cease to be valid if a medicine is not placed on any EU market within three years of the authorisation being granted or if the medicine is removed from the market for three consecutive years. This provision, however, is satisfied by placement on a single EU market. The EU pharmaceutical legislation currently also does not provide any incentives for MAHs to place their products on markets that, on their own, do not offer a sufficient business case for doing so.

*Table 5 Baseline situation: Access*

| **Continuation of baseline situation: effect on access** |
|---|
| *1. Accelerated assessment* |
| Accelerated procedures, conditional marketing authorisations (CMA) exist. |
| *2. Obligations and incentives for placement on the market* |
| For centrally authorised medicines companies market the product as they see fit in one or more Member States. Placing on the market in a single Member State satisfies the obligation to place on the EU market. There is a sunset clause - a marketing authorisation can be withdrawn if the product is not placed on the market within 3 years. |

Technopolis Group, based on information provided by client

A 2019 longitudinal analysis of the CMA instrument has suggested it has primarily been used as a path for regulators and companies to take when available evidence was not (yet) strong enough to support a regular authorisation[28]. This study furthermore suggested the pathway is plagued by substantial ambiguity about the need to balance patient's need for swift access to potentially life-saving medicines on the one hand with generation of sufficient evidence on effectiveness and risk on the other. These concerns have been echoed by interviewed representatives of NCAs and public health organisations who fear that increased use of accelerate access pathways places a heavy burden on health systems charged with deciding whether to allow these fast-tracked medicines into packages of reimbursed care based on limited evidence. It stands to reason that without changes to the procedure or to the ability of regulators to enforce post-authorisation evidence generation obligations, this trend will continue to put pressure on health systems.

In the market access and pricing environment the current trend is towards increasing use of 'gatekeeping' measures and price controls[29]. Such measures may have the effect of further limiting the number of markets in which products are launched or causing longer delays between authorisation and availability. Although a 2018 study by Ferrario found that, for medicines launched between 2010 and 2014, the time between authorisation and first use of

[28] Hoekman, J., & Boon, W. (2019). Changing standards for drug approval: A longitudinal analysis of conditional marketing authorisation in the European Union. *Social Science & Medicine (1982)*, *222*, 76–83. https://doi.org/10.1016/J.SOCSCIMED.2018.12.025

[29] Deloitte Centre for Health Solutions. (2019). *Patient access to innovative medicines in Europe A collaborative and value based approach*.

cancer medicines had shortened[30], analysis by IQVIA has suggested that between 2014 and 2018 in several countries the average delay had increased.

Thus, there is an assumption that, without EU intervention, the problems of selective market entry and delayed patient access to innovative medicines could remain or even worsen.

*Table 6 Baseline – Summary assessment of incentives for innovation*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Accelerated assessment | +/- | +/- | +/- | +/- | +/- | ++ | - | - | +/- |
| Obligations and incentives for placement on the market | +/- | +/- | +/- | +/- | +/- | +/- | - | - | +/- |
| OVERALL | +/- | +/- | +/- | +/- | +/- | ++ | -- | -- | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### *12.2.5 Policy Block E (Baseline): Competition*

Table 7 presents an assessment of the likely future scenario if the current arrangements on competition are continued with no changes. The current system has resulted in more generics and biosimilars entering EU markets and led to improved access to medicines and lowered healthcare costs.

Evidence from 2005 to 2015 for 7 chronic conditions shows that patient access to treatment has doubled while overall spending has remained flat.[31] In Germany, the waiting time for patients with rheumatoid arthritis to be treated with a biologic has been reduced from 7.4 years to 0.3 years after the introduction of biosimilars.[32] Currently, generics offer 80%[33] savings on average and biosimilars 20%[34] compared to originator products.

*Table 7 Baseline situation: assessment of competition-related themes*

| **Continuation of baseline situation: effect on competition-related subthemes** |
|---|
| *1. Regulatory measures* |
| There are specific, abridged pathways that are applicable for generics and biosimilars.<br>Development and submission times for generics under Art. 10 (1) i.e. standard generic (abridged) application and Art. 10(3) i.e. hybrid (abridged) application are 2-5 and 3-7 years respectively, and are 5-8 years for biosimilars under Art. 10 (4).[35] |

[30] Ferrario, A. (2018). Time to Entry for New Cancer Medicines: From European Union-Wide Marketing Authorization to Patient Access in Belgium, Estonia, Scotland, and Sweden. *Value in Health : The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, *21*(7), 809–821. https://doi.org/10.1016/J.JVAL.2018.01.003

[31] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

[32] https://www.pharmatimes.com/magazine/2021/may_2021/15_years_of_biosimilar_access_in_europe

[33] Mestre-Ferrandiz, J., Towse, A. & Berdud, M. Biosimilars: How Can Payers Get Long-Term Savings?. *PharmacoEconomics* **34**, 609–616 (2016).

[34] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilarsv

[35] Mohammed, Y.M. (2019) Regulatory pathways for development and submission activities. *Medical Writing*, 28(2), 8–19.

| **Continuation of baseline situation: effect on competition-related subthemes** |
|---|
| Generics account for the majority of DCP/MRP applications.[36] Of these, the assessment usually takes 210 days with the national phase of DCP/MRP taking between 4 weeks and 2 years.[35] |
| *2. Faster market access of generics and biosimilars* |
| The Bolar exemption makes it possible to conduct the testing required to obtain regulatory approval for the generic/biosimilar to take place during the patent/supplementary-protection-certificate (SPC) protection period of the reference medicine. According to NCAs, payers and industry representatives (including generic industry representatives) interviewed for this study, this has been beneficial for entry of generics/biosimilars but the provision is applied differently in different member states.[37]<br>There is currently no additional regulatory protection for new biosimilar products. |
| *3. Duplicates* |
| Ordinarily only one market authorisation is granted to an applicant for a specific medicinal product, however the applicant/holder can obtain a duplicate authorisation at reduced cost for the same medicinal product where "*there are objective verifiable reasons relating to public health regarding the availability of medicinal products to healthcare professionals and/or patients, or co-marketing reasons*". MAHs have been making use of this exception to obtain a duplicate authorisation for the first generic product on the basis that its inaugural launch into the market can improve availability.<br>No changes to the duplicate regime will have implications for the biosimilar market (including anti-competitive effects) and could also undermine the availability of treatment options for patients despite the intention behind the existence of the duplicate MA provision. |

The EMA has recommended approval of 5 biosimilars on average each year (based on 84 biosimilars authorised between 2006 and 2021[38]). It is however foreseen that the number of biosimilars approved will increase over time with regulatory protection running out on many biologics esp. in oncology. About 139 biologics are due to lose regulatory protection between 2021 and 2030.[39] EMA has recommended approval of 19 generics on average each year (296 generics authorised between 2006 and 2021[40]) with around 1015 MA applications submitted via the MRP/DCP procedures per year (based on 8120 applications under Art. 10.1 between 2006 and 2013[41]). If current compound annual growth rates for generics and biosimilars (7.1%[42] and 10.5%[43] respectively) are maintained to 2035, the European markets for these product types would reach around €175 billion and €36 billion respectively from values of €67 billion and €8.8 billion in 2021.

Table 8 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories. For most impact types, we have concluded that the effect of the baseline policy option would be largely neutral. Considering the current

[36] Ebbers, H. C., Langedijk, J., Bouvy, J. C., Hoekman, J., Boon, W. P., de Jong, J. P., & De Bruin, M. L. (2015). An analysis of marketing authorisation applications via the mutual recognition and decentralised procedures in Europe. *European journal of clinical pharmacology*, *71*(10), 1237–1244.

[37] https://cms.law/en/content/download/77965/2989749/version/1/file/BolarProvisioninEU.pdf

[38] GaBI Online - Generics and Biosimilars Initiative. Biosimilars approved in Europe. Mol, Belgium: Pro Pharma Communications International. Available from: www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe

[39] https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf?_=1640100592119

[40] EMA website

[41] Ebbers, H. C., Langedijk, J., Bouvy, J. C., Hoekman, J., Boon, W. P., de Jong, J. P., & De Bruin, M. L. (2015). An analysis of marketing authorisation applications via the mutual recognition and decentralised procedures in Europe. *European journal of clinical pharmacology*, *71*(10), 1237–1244.

[42] https://www.marketdataforecast.com/market-reports/europe-generic-drugs-market

[43] https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf?_=1640100592119

regulatory regime, we expect the positive impacts relating to increased competition, savings for health systems and access to patients to continue.

*Table 8 Baseline Policy Option - Summary assessment of competition*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Regulatory measures | +/- | +/- | +/- | +/- | + | +/- | + | + | +/- |
| Faster market access of generics and biosimilars | +/- | +/- | +/- | +/- | + | + | + | + | +/- |
| Duplicates | +/- | +/- | +/- | +/- | - | +/- | - | - | +/- |
| OVERALL | +/- | +/- | +/- | +/- | + | +/- | + | + | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### *12.2.6 Policy Block F (Baseline): Supply Chain Security*

The EU pharmaceutical legislation currently has two provisions that directly connect to security of supply. The first (Article 23a) places an obligation on MAHs to notify NCAs in the relevant Member States if they expect a temporary or permanent withdrawal of an authorised medicine from an EU market. The second (Article 81) obliged MAHs and wholesalers to ensure appropriate and continued supplies of authorised medicines. Both articles need to be transposed into national legislation by the Member States, who may opt to add more specific requirements.

In December 2016, the EMA and Heads of Medicines Agencies (HMA) set up a 'Task Force on the Availability of Authorised Medicines for Human and Veterinary Use'. To improve the collection and standardisation of information on shortages across the EU, in 2019 this task force published a 'Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)'[44]. The guidance includes a template detailing what information should be included. However, many elements are not mandatory and, thus far, are not required by NCAs.

*Table 9 Baseline situation: Security of supply*

| **Market withdrawal notification system** |
|---|
| • *Obligation to notify a withdrawal two months before the interruption in the placing on the market of the product (Article 23a)*<br>• *Obligation to ensure appropriate and continued supplies by MAHs and distributors (Article 81).* |
| **Detecting and reporting shortages** |
| *The EMA/HMA guidance on detecting and reporting medicine shortages.* |

Despite several methodological challenges posed by lack of standardised comprehensive data, available evidence suggests that across the EU the frequency of shortages and their impact on patients and healthcare providers is increasing. The expectation thus is that, without further action, supply chain disruptions and shortages will continue to happen. At the same

[44] European Medicines Agency. (2019). *Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)*.

time, MS have already introduced a variety of actions at the national level to help protect their security of supply[45]. The impact of these measures on preventing and mitigating the impact of shortages is not yet sufficiently understood but it is likely that, at least at the MS level, they can be effective in protecting the national availability of medicines.

Many MS have invested in recent years in setting up and/or improving shortage notification systems. This has resulted in increased notification of shortages and better insight into key issues such as the extent of the problem, products affected and causes. Nonetheless, substantial space remains to further improve and standardise the collection of information. Given the increasing emphasis on data collection, it may be expected that the costs associated with notifying shortages (to MAHs and wholesalers) and administratively processing notifications (by NCAs) will continue to rise. Introduction of more automated systems for detection of supply problems and sharing of information between parties, however, could reduce these costs.

*Table 10 Baseline Policy Option - Summary assessment of competition*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Market withdrawal notification | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| Detecting and reporting shortages | +/- | - | +/- | +/- | +/- | +/- | - | +/- | +/- |
| OVERALL | +/- | - | +/- | +/- | +/- | +/- | - | +/- | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### *12.2.7 Policy Block G (Baseline): Quality and Manufacturing*

Table 11 presents an assessment of the likely future scenario if the current arrangements on quality and manufacturing are continued with no changes.

*Table 11 Baseline situation: assessment of quality and manufacturing-related themes*

| **Continuation of baseline situation: effect on quality and manufacturing** |
|---|
| *1. Inspections and sanctions* |
| GMP inspections are carried out by national competent authorities (NCAs). The HMA (Joint Human and Veterinary) established an audit programme among the GMP inspectorates of all EEA GMP human and veterinary medicines agencies known as the Joint Audit Programme (JAP) in 2002.[46] Mutual recognition agreements are in place between 44 inspectorates to optimise the use of inspection resources; grant mutual recognition of reports, certificates, authorisations issued by national authorities; reduce technical barriers to trade and avoid duplication of audit work.<br>Under Article 84(1) of Regulation (EC) No 726/2004 and Article 111(8) of Directive 2001/83/EC, Member States are asked to penalise marketing authorisation holders (MAHs) who fail their obligations. The penalties must be dissuasive, proportionate and effective. Such penalties however vary from country to country. Moreover, Regulation 2019/5 has changed the scope of financial penalties by including Article 84a on Regulation 726/2004. This article ensures that financial penalties imposed by the Commission are applicable to the correct legal entities, for example legal entities that are part of the same economic entity as the MAH, legal entities that have decisive influence over the MAH or that could address a non-compliance issue. |

[45] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages* (Issue December).

[46] https://www.hma.eu/about-hma/working-groups/hma/ema-joint-audit-programme-jap/hma/ema-joint-audit-programme-jap.html

| **Continuation of baseline situation: effect on quality and manufacturing** |
|---|
| *2. Sustainability performance of supply chain actors* |
| Sustainability performance of supply chain actors is currently not included. Environmental risk of the API is covered under the ERA (as discussed in the next section). |
| *3. New manufacturing methods* |
| Non-industrial manufacturing methods such as decentralised, continuous manufacturing, etc are not accommodated adequately by the current legislation. |

Table 12 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories. For most impact types, our assessment is that the effect would be largely neutral. We expect that inspections and sanctions will continue to involve administrative burden on the part of MAHs and NCAs.

*Table 12 Baseline Policy Option - Summary assessment of quality and manufacturing-related measures*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Inspections and sanctions | +/- | - | +/- | +/- | +/- | +/- | - | +/- | +/- |
| Sustainability performance | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| New manufacturing methods | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### *12.2.8 Policy Block H (Baseline): Addressing environmental challenges*

Table 13 presents an assessment of the likely future scenario if the current arrangements for addressing environmental challenges are retained.

The ERA is the main mechanism within the current legislation for ensuring environmental sustainability of pharmaceuticals. It is required for all new MA applications whether through a centralised, mutual recognition, decentralised or national procedure and ensures the potential environmental risks of pharmaceuticals are adequately assessed. While the outcome of the ERA does not affect the decision to award an MA, it serves as the basis for minimising the amount of pharmaceuticals released into the environment (using appropriate measures), identification of specific risk-minimisation activities to be undertaken by the user of the medicine and appropriate labelling to ensure correct disposal.[47]

*Table 13 Baseline situation: assessment of themes addressing environmental challenges*

| **Continuation of baseline situation: effect on addressing environmental challenges** |
|---|
| *1. Environmental risk assessment (ERA)* |
| If no changes are made to current requirements, the ERA would continue to be performed by companies when applying for an MA. A 0.01 µg/L threshold value for predicted environmental concentration in surface water |

[47] EMA. (n.d.). *Environmental risk-assessment of medicines*.

| **Continuation of baseline situation: effect on addressing environmental challenges** |
|---|
| ($PEC_{SW}$)[48] would continue to be used and any active substance with $PEC_{SW}$ greater than this threshold would undergo further assessment as to its fate in the environment and potential effects on representative organisms. Thereafter precautionary measures or recommendations to minimise risk would be provided if necessary. |

Table 14 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories. For most impact types, we have concluded that the effect of the baseline policy option would be largely neutral. Continued review of potential risks to environment from medicinal products and increased awareness of and promotion of prudent use of pharmaceuticals (outside the legislation e.g. based on the European Union Strategic Approach to Pharmaceuticals in the Environment[49]) could help drive down emissions of pharmaceuticals in the environment and improve waste management to some extent, at least for medicines requiring new MAs.

The impact of these measures on patient and public health is however unknown. There is not enough evidence to show the direct effect of pharmaceutical residues found in the environment e.g. drinking water on human health. The potential effect of long-term exposure on vulnerable populations is also as yet unknown. Potential impacts of AMR have already been covered above.

*Table 14 Baseline – Summary assessment of measures to address environmental challenges*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| ERA | +/- | +/- | +/- | +/- | +/- | +/- | +/- | unknown | + |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### *12.2.9 Policy Block I (Baseline): Lessons from COVID-19*

The pandemic has underlined the added value of an EU-level response to a global pandemic and has resulted in Member States agreeing to extend the role of the EMA in respect to future crises, with the publication of the Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices.

The EMA is now responsible for monitoring medicine shortages that might lead to a crisis, as well as reporting shortages of critical medicines during a crisis. It is also updating the role of the EU Single Point of Contact (SPOC) network, to improve the flow / exchange information on shortages among member states and provide recommendations on management of shortages. The EMA is also updating its plan for Emerging Health Threats; and establishing a list of the main therapeutic groups of medicines necessary for emergency care, surgeries and intensive care, to help prepare the lists of critical medicines to respond to public health emergencies or major events. The EMA will also invest in real-world evidence efforts through the establishment of DARWIN EU[50], a pan-European network of real-world data.

[48] Whomsley, R., Brendler-Schwaab, S., Griffin, E. *et al.* Commentary on the draft revised guideline on the environmental risk assessment of medicinal products for human use. *Environ Sci Eur* **31**, 17 (2019).

[49] European Commission, 2019. European Union Strategic Approach to Pharmaceuticals in the Environment

[50] https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu

The pandemic focused attention on the EU's ability to forecast demand during crises, secure supplies and manage shortages of critical medicines going forwards.[51] There is an assumption that public health crises are highly likely to occur in future and that against the backdrop of a growing problem with medicines shortages more generally, there is a case for more concerted action at the EU level.

Moreover, learning from this exceptional experience, the EU has sought to improve the regulatory framework in two main areas: a) reducing the number of immature marketing authorisation applications, which can waste public authority resources and create uncertainty over decisions; b) providing a rolling review regulatory pathway for medicinal products addressing UMN, which will allow earlier engagement with developers around potentially critical new medicines.

*Table 15 Baseline situation: assessment of lessons learned from the pandemic*

| **Continuation of baseline situation: effect on shortages, resourcing and speed of assessment** |
|---|
| *Monitoring and mitigating shortages of medicines and devices* |
| The EMA's extended mandate and the main actions agreed in respect to improving the management of shortages of critical medicines should produce improvements in the situation more generally, with greater coordination, data transparency and reallocation of medicines (cross-border) being expected to strengthen a Member State's ability to respond to any important shortages. The proposed European Shortages Monitoring Platform (ESMP) is planned to be implemented by early 2025 and should help to overcome some of the residual technical challenges relating to the fragmented and sometimes inconsistent implementation of reporting systems nationally. The question of interoperability will need to be tackled also through agreements on common data records, architectures, process definitions, etc. |
| Reducing numbers of immature marketing authorisation applications |
| Assessment procedures for CMAs usually involve resolving differences of opinions among regulators regarding the evaluability or suitability of a marketing authorisation application for processing through the CMA pathway. This can be time consuming and slow down the approval process. Between 2006 and 2016, the median number of days spent on assessment procedures for CMAs was 421 (329-491), in comparison to 337 (281-400) for standard applications in the same period. There were 30 CMA granted and 22 unsuccessful CMA applications in the same period. From these 52 applications, 24 did not include a proposal for CMA in the initial application, despite not qualifying for standard marketing authorisation. |
| Rolling reviews of innovative medicines addressing an unmet medical need |
| Unmet medical needs (UMN) are usually conditions that are complex and/or affect small patient populations, which creates uncertainty for medicinal product developers and results in a market failure. Creating better regulator/developer interaction and reducing the approval time for medicinal products addressing UMN can bring very important benefits for patients. The median approval time for medicinal products that address UMN (accelerated assessment) between 2016 and 2020 was 251 days, with an average reduction in the approval time of 1.5 days per year. Rolling reviews for medicinal products that address UMN could help to reduce the total approval time. |

Table 16 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories.

*Table 16 Baseline – Summary assessment of lessons learned from the pandemic*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Managing shortages | +/- | - | +/- | +/- | + | +/- | + | ++ | +/- |

[51] https://www.ema.europa.eu/en/documents/other/reflection-paper-forecasting-demand-medicinal-products-eu/eea_en.pdf https://www.ema.europa.eu/en/documents/other/reflection-paper-forecasting-demand-medicinal-products-eu/eea_en.pdf

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Immature marketing authorisation applications | +/- | +/- | +/- | +/- | +/- | +/- | - | +/- | +/- |
| Rolling Reviews for UMN | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

## 12.3 Policy Option A

### *12.3.1 Policy Block A (A.A): support for innovation, including unmet medical needs*

#### Assessment of the key impacts for the policy elements

Table 17 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

*Table 17 Option A - Assessment of the proposed Incentives for Innovation*

| **Assessment** |
|---|
| 1. Expedited regulatory schemes |
| A.1.1. PRIME – remains under the current scheme |
| This is business as usual (BAU) and as such there would be no additional impacts in comparison with the baseline policy option discussed earlier. |
| 2. Repurposing |
| A.1.2. Establish a non-binding system for scientific assessment |
| The ability to include academic and other scientific evidence within applications for extensions might encourage MAHs to seek approvals for repurposing medicines that are being used off-label, albeit these tend to be older medicines where there is less opportunity to secure sufficient additional income to offset the costs of repurposing. Research suggests that where new indications are added, this tends to happen earlier in the period of regulatory protection.[52]<br>Moreover, due to the non-binding nature of this policy element, companies are expected to keep deciding not to go on-label for certain extensions if this could affect their more lucrative on-label indications[53] or for liability reasons.<br>Given these competing pressures on MA holders, the initiative seems unlikely to have a significant impact on the level of repurposing overall.<br>Where it is implemented, the initiative would not impose significant additional costs for developers, as the use of this broader evidence base would be voluntary. Moreover, updating the SmPC and printing an indication on the product's label does not involve substantial extra costs. Small administrative costs are expected related to pharmacovigilance (smaller relative to a binding system).<br>EMA statistics show an upward trend in the annual number of extensions of indications it is recommending (87 in 2021, up from 83 in 2020 and 60 in 2019), with an annual growth rate of 5-10%.<br>We assume a non-binding system would at best increase that growth rate only marginally, by one or two percentage points, perhaps reaching an annual growth rate of 6-12%. In the longer term, even such a small |

[52] Sahragardjoonegani, B., Beall, R.F., Kesselheim, A.S. *et al.* Repurposing existing drugs for new uses: a cohort study of the frequency of FDA-granted new indication exclusivities since 1997. *Journal of Pharmaceutical Policy and Practice* **14,** 3 (2021). https://doi.org/10.1186/s40545-020-00282-8

[53] https://www.fiercepharma.com/sales-and-marketing/sanofi-pulls-campath-to-clear-way-for-higher-priced-lemtrada

| Assessment |
|---|
| boost to repurposing, would result in perhaps tens of additional treatment options for patients and expanded geographical access to those now on-label medicines. |
| 3. Incentives: Adaptation of the period of regulatory protection |
| **A.1.3 A special incentive bonus for products with a demonstrated ability to address an UMN.** |
| An additional year of regulatory protection would increase the numbers of medicines being developed for UMNs<br>The baseline of c. 15 UMNs a year might be increased by 2-4 products a year<br>This would result in additional income for originators of perhaps €320m-€640m, associated with those products (based on €160m average peak sales in the EU)<br>The bonus would result in a delay in the market entry for generics for these additional products, which might amount to a loss of income of around €77m-€154m a year for the generics industry<br>A small additional administrative burden for originators, assuming the burden of proof for demonstrating that a product meets the UMN criterion falls on the MAH applicant<br>There would be some additional costs for health payers, which result from the delay in the market entry of generic competition. This may amount to €163m-€326m a year<br>A small additional cost for regulators involved in the development of the UMN criteria and the implementation of the UMN 'test'<br>There would be an improvement in patient benefits from the expansion in the flow of medicines addressing UMNs |
| |
| **A.1.4. Special incentive bonus: if data package includes comparative trial with standard of care (+6 months)** |
| We assume a 6-month extension might increase the use of comparative trials for 8-10 products a year.<br>We assume the additional costs of a comparative trial design might amount to €10m.<br>With average additional peak income (EU) of €160m, a 6-month extension might secure an additional €80m in income, or €640m-€800m a year in additional protected sales for originators<br>The bonus would result in a delay in the market entry for generics for these additional products, which might amount to a loss of income of around €154m-€192m a year for the generics industry<br>There would be some additional costs for health payers, which result from the delay in the market entry of generic competition. This may amount to €326m-€408m a year<br>This should deliver faster access to markets and costs savings thanks to improved reimbursement decisions<br>Moore et al (2020) in a review of 101 new FDA medicines (225 individual clinical trials), found the median cost of an individual clinical trial was around $19m (range = $12m-$33m).[54] They found the Phase 3 development costs almost doubled with second trial (albeit the single biggest cost driver is the number of patients).<br>Moore et al identified 62 (27.5%) of the total set of 225 clinical trials had a comparison group rather than a placebo or uncontrolled trial. |

## Assessment of the principal costs and benefits by impact type

Table 18 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block A under Policy Option A and for each impact type.

*Table 18 Option A - Summary assessment Incentives for innovation*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| A.1.1. | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| A.1.2. | +/- | +/- | +/- | +/- | +/- | +/- | - | +/- | +/- |
| A.1.3 | + | - | +/- | + | +/- | + | - | + | +/- |

[54] Moore, T. J., Heyward, J., Anderson, G., & Alexander, G. C. (2020). Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval of new therapeutic agents, 2015–2017: a cross-sectional study. *BMJ open*, *10*(6), e038863.

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| A.1.1. | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| A.1.4. | + | - | +/- | +/- | +/- | + | + | + | +/- |
| Overall impact | + | - | +/- | + | +/- | + | - | + | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

In summary, the introduction of:

- A special incentive bonus for UMNs should have a positive impact overall. It would bring additional costs for developers offset by an additional period of premium pricing, which should support an increase in R&D investment and expand the numbers of products in the pipeline. This should flow through to an increase in treatment options and benefit more patients. There may be substantial deadweight costs associated with the additional rewards granted to products that would have been developed without the bonus
- A special incentive bonus for comparative trials should have a positive impact overall. It would bring limited additional costs for developers that should be more than offset by the additional protected income and a more straightforward and robust assessment by regulators, with any positive recommendations being accompanied by a better evidence base for HTAs, which should lead to a greater proportion of authorised medicines being approved for reimbursement and thereby improving treatment options and benefiting more patients
- A non-binding system for the scientific assessment of new evidence would be unlikely to have any significant impact on the underlying situation regarding the numbers of extensions to new indications or the repurposing of older medicines more generally, given the commercial uncertainty around repurposing and potential additional liabilities of third-party evidence

### Assessment of synergies and tensions

Within the Policy Block, the three policy elements proposed under Policy Option A are complementary, comprising additional special bonus incentives for both novel innovations (new medicines relevant to UMNs; and for the use of comparative trials) and incremental innovations (e.g. the inclusion of additional types of scientific evidence to encourage MA holders to consider extending their existing medicines for use with new indications).

### *12.3.2 Policy Block B (A.B): Antimicrobial Resistance*

### Assessment of the proposed incentives for antimicrobial resistance

Policy Option A proposes measures to stimulate the development of novel antimicrobials and comprises three policy elements. Table 19 presents an overview of these three proposals, noting the key design assumptions and likely strengths and weaknesses.

*Table 19 Option A - Assessment of the proposed incentives for antimicrobial resistance*

| Assessment |
|---|
| A.2.1 Harmonisation of summary of product characteristics for nationally authorised antimicrobials to support prescription practices |
| The harmonisation process will affect market authorisation holders, in as much as any referral for reassessment will result in the company being invited to carry out a wide-ranging review of evidence on efficacy, indications, |

| Assessment |
| --- |
| posology, etc. to prepare an up-to-date technical dossier for consideration by the EMA and a resulting new SmPC and Product Leaflet for sharing with member states. The Opsalka et al study suggests the majority of updated SmPCs would result in a narrower set of more specific indications and more stringent dosage guidelines, resulting in a reduction in the numbers of prescriptions and the associated volume / sale of those antimicrobials. In simple terms, updated SmPCs supports more prudent use and would result in lower sales volumes for the 3-5 MA holders subject to a reassessment each year.[55] |
| The reassessment process will bring additional regulatory compliance costs that could amount to many tens of thousands of Euros, and the proposed policy element might be expected to increase the numbers of MAHs affected from 1-2 a year to 3-5. |
| This policy element would not have a significant impact on SMEs. Nationally authorised antimicrobials tend to be the older, broad-spectrum antimicrobials manufactured by larger (generics) companies. |
| The policy element could have a small negative impact on the competitiveness of the EU generics industry, since it would create additional costs for small numbers of generics companies while also reducing their income from the assessed medicines (more prudent use). Given the focus on the most widely used, older antimicrobials, it would disadvantage some MA holders rather than all. Given the relatively narrow geographical markets of these medicines, the policy element may also have a relatively greater (negative) impact on those companies based in or focused on addressing the biggest current users of antimicrobials in the EU (e.g. Greece, Italy, Spain). Indirectly, it should reduce consumption overall, but may increase the diversity of use and in limiting some medicines, it may boost demand for other antimicrobials. |
| The policy element could have a small positive impact on the functioning of the single market, inasmuch as the harmonised SmPCs should result in more consistent prescription practice across the EU and broader / more consistent demand for these generic medicines across EU member states. |
| The reassessment process might entail some limited additional research by the MA holders and could trigger a small increase in the demand for work by technology consultancies or academic researchers. However, the number of harmonisation exercises is likely to be limited. We have estimated 3-5 reviews a year initially, perhaps increasing to 5-10 a year, if the process proves to be useful and the resources can be found to coordinate the reviews and manage the resulting assessments. From this perspective, the total additional investment in research might be €1m-€3m a year. The policy element is unlikely to have a direct impact on innovation, albeit indirectly, it may make a small contribution to increasing demand for newer and more novel antimicrobials. |
| There would be an additional cost for the EMA in overseeing the increase in the number of reviews / assessments from the current baseline. There would be additional costs too for member state regulators in providing at least some of the staff and scientist that will be involved in the assessments. There would also be some limited costs in the implementation of the resulting SmPCs nationally. |
| Patients should benefit from improved prescription with medicines being prescribed only where they are likely to be effective and at more prudent levels. There would be a one-off cost to national health systems when implementing the new SmPCs, and the need to update relevant guidance and otherwise communicate about the required changes in prescription. There should be a reduction in the usage of the affected medicines, which could save money, albeit this may be offset by healthcare practitioners prescribing different antimicrobials (some more expensive, and a greater diversity of consumption may also reduce discounts and increase prices). Indirectly and in the longer term, the reductions in overuse and misuse should have a positive impact on the number of instances of AMR in the EU and the negative health impacts associated with that. This is the most critical social benefit, however, an increase in harmonisation may have only modest impacts here. |
| The more prudent prescription of antimicrobials should result in fewer and smaller prescriptions. Indirectly and over the longer term, this should reduce usage overall in the EU. |
| These improvements should result in fewer antibiotics entering the environment (whether through lower levels of manufacturing activity, better stewardship, or improved disposal practices). If the harmonised SmPCs do affect prescribing behaviour (and there are some major cultural factors that could frustrate ambitions here), then the policy element's targeting of the oldest and most widely used antimicrobials could result in quite significant reductions in usage (especially in those countries with the highest per capita usage), so the volume of releases to the environment may be equally positive affected. |
| **A.2.2. Transferable voucher (TV) independent to data/market protection for antimicrobial products** |
| The right to be transferred relates to the transfer of the right to extend the data protection by a length to be determined. The assumption/calculation is based on an extension of data protection by 1 year. |
| The antimicrobials that would be applicable to generate this right are all antimicrobials or a subgroup e.g. antibiotics only or their alternatives which either (i) represent a new class and/or new mode of action, addressing new target or absence of known cross-resistance (WHO innovation criteria) or candidates targeting priority pathogens (WHO list for antibiotics) or innovative platform technologies able to confer break-through clinical benefit, (ii) ground-breaking innovation within an existing class. |
| The average number of TVs we expect per year is 1. EU JAMRAI predicts fewer. |

[55] Opalska, A., Kwa, M., Leufkens, H., & Gardarsdottir, H. (2020). Enabling appropriate use of antibiotics: review of European Union procedures of harmonising product information, 2007 to 2020. *Eurosurveillance*, *25*(45), 2000035.

| Assessment |
|---|
| Companies may use a TV on existing successful medicines that are still covered by data protection, and which are still at least 2 years (EFPIA proposal) away from the expiry of their data protection period.[56,57]<br>The TV would be most relevant to products where the last defence before generic entry is the regulatory protection. For those where there is a 10+ years patent or SPC protection, the extended data protection does not give any benefit. Hence, only a part of all products could benefit from a TV.<br>In principle the extension would need to be sufficient to provide a substantial incentive to compensate for the development of a new antibiotic, which is estimated to be on the order of €1.2bn. However, the EU market is some 20% of the total pharmaceutical market globally, and so a proportionate contribution to the development cost with the EU voucher may be a sufficient incentive. It would be possible for companies to receive the right to a TV for antimicrobial products that were already in the pipeline ahead of the implementation of the new regulation, to generate additional income / profits within 2-3 years of implementation, and thereby underpin an early expansion in investments in novel antimicrobials.<br>Based on the application of a voucher to an average top-10 product, we estimate an originator would secure an additional €543m in non-contested sales because of the 1-year extension.<br>There would be a cost to the generics industry of a year's delay on the order of €164m.<br>There would a cost to the health system too, which we estimate at €283m. We further estimate the patient + payer monetised loss would be on the order of €441m<br>Some vouchers may be sold rather than used directly by the developer of the antimicrobial and we have estimated the average sale value of a voucher at €360m.<br>Each year, about 33,000 Europeans die as a consequence of antibiotic-resistant bacteria.[58] On average, a hospitalised patient with antibiotic-resistant infections costs an additional 10,000 to 40,000 USD.[59] The expansion in the development and authorisation of novel anti-microbials should help to manage and even reduce AMR, with fewer hospitalisations and deaths, although it has so far not been possible to estimate the scale of these potential benefits, in order to compare with the social costs of the incentives for taxpayers and health payers. |
| A.2.3. Adapted system for authorisation of phages therapies and other alternative products |
| This policy element would support the development of phage therapies potentially increasing the number of companies willing to invest and develop these therapies which will in turn increase competition, reducing prices of these therapies. The use of phage therapies may also reduce healthcare costs/budgets since phages are an inexpensive natural resource present in the environment, and offer immense potential as an alternative when antibiotics are rendered ineffective due to bacterial resistance[60]. Finally, by reducing the use of antibiotics it would help reduce the presence of antibiotics in the environment. |

## Summary assessment by impact type

*Table 20 Option A - Summary assessment of prudent use of antimicrobials*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| A.2.1 | - | -- | -/+ | -/+ | + | -/+ | -/+ | ++ | + |
| A.2.2. | +++ | -/+ | +++ | ++ | -/+ | +++ | --- | + | +/- |
| A.2.3. | + | -/+ | -/+ | + | + | + | - | + | + |

[56] There is also the TEE: https://www.ifpma.org/wp-content/uploads/2018/09/IFPMA_AMR_Position_Incentives_Pull_2018.pdf

[57] Recent paper: https://healthpolicy.duke.edu/sites/default/files/2022-01/Transferable%20Exclusivity%20Voucher%20Program.pdf

[58] Cassini, A., Högberg, L. D., Plachouras, D., Quattrocchi, A., Hoxha, A., Simonsen, G. S., Colomb-Cotinat, M., Kretzschmar, M. E., Devleesschauwer, B., Cecchini, M., Ouakrim, D. A., Oliveira, T. C., Struelens, M. J., Suetens, C., Monnet, D. L., Strauss, R., Mertens, K., Struyf, T., Catry, B., … Hopkins, S. (2019). Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *The Lancet Infectious Diseases*, *19*(1), 56–66. https://doi.org/10.1016/S1473-3099(18)30605-4

[59] https://www.oecd.org/els/health-systems/Antimicrobial-Resistance-in-G7-Countries-and-Beyond.pdf

[60] https://www.nesta.org.uk/blog/when-the-drugs-dont-work-could-bacteriophages/?gclid=Cj0KCQjw_4-SBhCgARIsAAlegrUn5LXTOVza5VKzwfA4XcfpeUXcHW8jiSFfDhOBM2_MUMNcQ0GrXVQaAtQVEALw_wcB

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Overall impact | +++ | -- | +++ | ++ | + | +++ | --- | ++ | + |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

### Assessment of any synergies and tensions within the Policy Block

Within the AMR Policy Block, the policy elements proposed under Policy Option A are largely complementary to each other, whereby the proposal to accelerate the rate at which SmPCs are harmonised and updated would address one of the key sources of differences in prescribing practices across the EU in respect to older, lower cost, broad spectrum antibiotics and should restrict and support more prudent use in general. The Transferrable Voucher addresses one of the other key challenges around AMR, which is the inadequacy of the global pipeline for antimicrobials and the substantial gap that exists between the cost to develop innovative antimicrobials and their likely market performance. Lastly, the proposal to adapt the legislation to allow authorisation of phage therapy is an important step to allow this promising alternative to conventional antibiotics to be further developed for safe use in humans. These proposals also fit well with the EC's AMR Action Plan and its objectives to increase innovation and reinforce prudent use.

Assuming novel antimicrobials might be considered to address an unmet medical need (UMN), there would be an additional synergy between the Transferrable Voucher proposed here and the proposal to extend the period of regulatory protection for medicinal products addressing an UMN, under the Innovation Policy Block. An additional period of regulatory protection for the novel antimicrobial would generate a period of additional revenue at premium prices (before generic entry) and thereby deliver an additional profit stream to support investment in antimicrobial R&D.

### *12.3.3 Policy Block C (A.C): Future Proofing*

Policy Option A is a refinement of the current arrangements, with three principal interventions around scope and definitions and GMOs. Table 21 presents our schematic overview of these three proposals, noting the key design assumptions and likely strengths and weaknesses.

*Table 21 Option A - Assessment of the proposed incentives for Future Proofing*

| **Assessment** |
|---|
| 1. Scope and Definitions |
| A.3.1 Maintain **current** exemptions from the **scope** of the legislation –add some **clarifications**/conditions |
| Technological advances are providing innovative medicines that test the limits of the pharmaceutical legislative framework in terms of scope and definitions. Products can end up in a legislative gap (such as novel manufacturing processes) or there is risk of duplication or misalignment between frameworks (BTC, clinical trials, hospital exemption).<br>A.3.1 has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. It would also address the issues of accommodating technological advancements in the legislation. For instance, by promoting coordination with concerned authorities in particular in the framework of medical devices and substances of human origin. However, these impacts may be short term and not sustained as technological change is ongoing and increasing in pace the changes could soon be outdated and may lack flexibility to keep pace. |
| 2. GMO |
| A.3.2 Clinical trials: a **risk-based** approach is applied to determine when a specific GMO assessment is required. Where required, the assessment of the GMO aspects of investigational medicinal products is performed by **EMA**, within the maximum timelines defined in the Clinical Trial Regulation (centralised assessment). |

| Assessment |
|---|
| Clinical trials for investigational medicinal products (IMPs) for human use that contain or consist of GMOs are subject to both clinical trials and GMO legislations under national competences. This causes delays in clinical trials as the directives are not uniformly interpreted or applied between MSs and is especially problematic for clinical trials that are conducted over multiple MSs. These differences in interpretations also impact on the authorisation of GMO-containing medicinal products that fall under the mandatory scope of the centralised procedure creating complexities for developers as different MSs have different requirements and stakeholders involved, ultimately causing regulatory burdens and delays in market authorisations.<br>A3.2 has potential to improve the efficiency of GMO assessment and thus accelerate authorisation of GMO-containing medicinal products by focussing regulatory efforts on GMO containing medicines that pose the greatest threat to the environment. A centralised approach to GMO assessment has already been adopted by the United States where the review of medicinal products containing GMOs has been centralised within the FDA to improve efficiency and regulatory agility[61]. |
| A.3.3. An environmental risk assessment continues to be performed (by EMA) in the context of the marketing authorisation procedure |
| This is the same as business as usual for this element. |

Table 22 contains a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under Option A.

*Table 22 Option A - Summary assessment of future proofing*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| A.3.1 | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| A.3.2 | + | + | + | + | + | + | - | + | +/- |
| A.3.3. | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| Overall impact | +/- | +/- | +/- | +/- | +/- | +/- | - | + | +/- |

## Assessment of any synergies and tensions within the Policy Block

Policy option A is most like the baseline policy option and least impactful in terms of future proofing as it risks not keeping pace with new products and technologies. It is the least 'friendly' towards innovation due to relying on 'hard law' changes that would suffer the same issues in a short time and are not flexible enough to consistently adapt moving forwards. Ultimately this creates a tension with the overarching policy option goal to: "use additional incentives to address unmet medical needs and to support public health objectives."

Future proofing elements in this policy option related to risk-based approach for GMO assessments (A3.2) have synergies with innovation in UMN (Block A) in creating incentives and removing barriers for innovation. The element related to reduction of regulatory burden - definitions and scope (A3.1) has synergies with horizontal streamlining measures. There are also complementary measures in Block E (Creating new simpler regulatory pathway for generics (A.5.1), Block F (Encourage use of HMA/EMA guidance definitions A.6.1.) and Block G (Adaptation of legislation to cover new manufacturing methods (A.7.3.))

[61] U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research. (2015). *Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products; Guidance for Industry*. https://www.fda.gov/media/91425/download

### *12.3.4 Policy Block D (A.D): Access*

#### Assessment of the key impacts for the policy elements

Table 23 presents our broad assessment of the likely costs and benefits of each of the proposed legislative actions. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

*Table 23 Option A - Assessment of the proposed elements to improve access*

| **Assessment** |
|---|
| *A.4.1 Facilitate 'multi-country packs' with labelling to allow their placing on the market in several Member States with the same packaging and pack sizes* |
| Currently, information on the pack (outside and inside) must be in the official language(s) of the MS where a product will be placed on the market, bar a few exceptions for certain products that are not intended to go directly to a patient. This language requirement, along with other potentially country-specific requirements, means that MAHs must produce packs specifically designed for each market. This increases production costs and may make smaller markets, where these costs cannot sufficiently be offset by revenues, commercially unattractive. Additionally, country-specific requirements can hinder the movement of medicines between different EU markets when products need to be repacked and relabelled, to meet all requirements of the importing country.<br>Facilitating 'multi-country packs' may result in more products being placed on a greater number of markets, in particular smaller or less economically attractive markets. In addition, medicines can be moved between EU countries more easily to mitigate or resolve shortages. This would improve security of supply and mitigate some of the risks resulting from product unavailability (e.g. treatment interruption, suboptimal treatment with alternatives). It will, however, be important to ensure that use of multi-country packs does not limit the ability of patients and healthcare providers to access information regarding, for instance, the correct use and safety profile of medicines. No studies were identified that detail experiences with multi-country packs as a way to overcome access challenges and that thus could inform an estimation of impact.<br>In economic terms, it is expected that multi-country packs would result in a cost saving to MAHs by reducing the number of different presentations they need to produce and streamlining production lines. The magnitude of these savings will depend primarily on the number of countries and languages included, whilst the size of the markets reached by multi-country packs will further influence the profit potential for the MAH.<br>In theory, multi-country packs may have the added benefit of facilitating joint procurement between countries. Several initiatives already exist whereby smaller countries engage in joint procurement to increase their purchasing power. Such initiatives have the potential to negotiate lower prices. A 2020 study for WHO shows that whilst these initiatives hold promise, they often take months or years of cooperation before tangible results are achieved[62]. The study did not specifically look at the role of multi-country packs in facilitating joint procurement. |
| *A.4.2 Additional period of data protection [6 months] if proven that the product has been placed on the market in all Member States within 6 years of authorisation.* |
| If the incentive succeeds in encouraging MAHs to place their products in a greater number of EU markets, this can have substantial positive impacts on access to medicines and consequently on the health and wellbeing of people in previously unserved markets. These impacts scale with the size of the target populations that would be reached but are also dependent on the ability of health systems in those markets to adequately diagnose conditions and provide appropriate treatment. As such, not all countries stand to equally benefit from such incentives. The impacts will also depend on product characteristics, whereby expanded access to medicines that address high unmet medical needs will have greater impact than other medicines.<br>The incentives, however, may carry a significant cost to national health systems and payers by potentially delaying generic entry. The cost of this to authorities, and conversely the value of the reward to MAHs, depends on by how much the additional period of regulatory data protection would extend the overall protection on the product that delays generic competition and on the likelihood of such competition emerging more generally (e.g. competition for biological and orphan medicines is often slow or non-existent even after expiry of any protections).<br>Although data protection can have significant (economic) value for innovators, in various consultations, industry stakeholders have suggested that additional regulatory protection of six months will not be an adequate incentive for wider market launch. Whether this will be the case will most likely depend on the balance between the expected ratio between the costs of doing business in less commercially attractive markets and the value of the incentive. |
| *A.4.3 Promote a voluntary reporting of market launches and a commitment to initiate pricing negotiations in all MSs within 2 years of centralised authorisation. (non-regulatory option)* |

[62] Cross-country collaborations to improve access to medicines and vaccines in the WHO European Region, (2020).

It is assumed that the EMA would serve as the central point of contact for reporting but that the information may then be shared also with authorities in each of the Member States. The policy element additionally intends to obtain a commitment from MAHs to initiate price negotiations in all MS. However, it is assumed that neither the EMA nor any other regulatory authority will be granted powers to monitor or enforce these (voluntary) commitments and that there will be no sanctions on MAHs when these commitments are not fulfilled. As such, it is difficult to see how this measure intends to achieve the desired impact of launch in a greater number of countries or earlier launch and, consequently, increased access.

Nonetheless, if the measure succeeds in obtaining commitments from MAHs to initiate price negotiations in all MSs within two years of granting of the MA, this may lead to earlier and wider access. It is expected that other factors (e.g. market characteristics and price policies) that currently influence where and when MAHs enter a market will continue to shape decision-making. As such, the impact of such a non-regulatory and voluntary measure on access may be rather limited.

*A.4.4 Allow generic competition entry in the EU market, in case a centrally authorised medicine is not placed on the market in the majority of Member States (small markets included) within 5 years of granting the MA*

Any measure that promotes market entry into a greater number of EU countries or accelerates access, will be beneficial to patients who are otherwise unable to access these medicines. The impacts of this measure will scale with the number of countries and patients reached and with the importance of the medicine. Earlier access to generic medicines will also improve patient access to (generic versions of) these medicines when generic competition comes in, provided that those generic versions will be placed on these markets.

Pressure to enter a set number of markets, at the threat of generic competition, may force companies to market these products in countries where it does not make commercial sense to do so. The question is whether the threat of loss of protection and earlier generic competition will be sufficient to overcome the lack of financial incentive for MAHs to enter such markets voluntarily. SPCs, orphan market exclusivity and regulatory data protection each carry a significant financial value and industry has often cited these instruments as essential to stimulate innovation. Limiting access to these protections, by making them conditional, could thus risk slowing down innovation.

Changes to the entire system of intellectual property and regulatory protections for medicines to make them contingent on market placement should be expected to make the system considerably more complex. It will require regular reporting by MAHs on market launches and potentially verification of this information by regulatory authorities to determine whether the MAH has fulfilled all the conditions to be, or remain, eligible for such protections. Questions also remain as to how eligibility for protections would be affected if countries decide not to admit the medicine into the package of reimbursed care (and consequently there is no possibility for the MAH to place the product on that market) or if the duration of the decision-making on reimbursement is such that the 5-year period after granting of the MA is exceeded. In these cases, the MAH may lose its protection from generic competition because of factors outside of its immediate control. This may introduce unpredictability into the system that could discourage companies from entering the EU market, although the risk of this may still be limited as the EU represents a major pharmaceutical market which MAHs are unlikely to forego.

### Summary assessment of the principal costs and benefits by impact type

Table 24 presents a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under Option A, for each impact type.

*Table 24 Option A - Summary assessment of access elements*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| A.4.1 | ++ | + | +/- | + | ++ | +/- | + | + | +/- |
| A.4.2 | ++ | - | +/- | - | + | +/- | +/- | + | +/- |
| A.4.3 | +/- | - | +/- | +/- | +/- | +/- | - | + | +/- |
| A.4.4 | --- | -- | +/- | -- | +/- | - | ++ | ++ | +/- |
| Overall impact | +/- | --- | +/- | -- | ++ | - | ++ | +++ | +/- |

- Facilitating the use of multi-country packs is expected to result in cost savings for MAHs by reducing the need for country-specific packaging and presentations and streamlining production lines. It may also facilitate the movement of medicines within the EU internal market, thereby promoting competition.

- Access to additional incentives for market entry in all EU countries grants MAHs a longer period of exclusive prices, representing increased revenue.
- An expectation to place centrally authorised medicines on the market in a majority of EU MS and a concomitant disincentive for not doing so in the form of loss of protection, may result in loss of revenue for innovator companies. This may make the EU market overall less attractive to these companies. Generic manufacturers on the other hand may benefit from this measure, as they may be granted earlier market access in the whole of the EU.
- MAHs will have to provide additional information to regulators to demonstrate their eligibility for incentives. This implies increased administrative costs. Increasing the number of MS in which the MAH places a product on the market may also increase the administrative cost of filing for (MRP/DCP) authorisation and the subsequent costs for interacting with regulatory agencies and health technology assessment bodies in these countries.
- The existence of intellectual property rights and regulatory protections is generally considered a driver for research and development of new medicines. By making access to these market protection mechanisms conditional and forcing MAH to operate in markets where they have no commercial interest, developers could be discouraged from investing in R&D.
- To determine eligibility with new incentives and qualification for existing protections, regulators (presumably the EMA) would incur greater costs due to an increased workload. Regulatory authorities in the MS where products are placed in the market will see an increase in cost due to a greater number of medicines for which they provide regulatory oversight. Similarly, HTA bodies will have to conduct a greater number of assessments.
- The intended and expected impact of increased access to medicine is that patients will be provided with earlier and wider access to more effective and safer treatments. This will have a positive impact on their health status and wellbeing. Whilst increased access to medicines is an intended positive outcome, it may result in increased health care expenditure. At the same time, new medicines may displace less (cost-)effective treatments, resulting in net savings. Further indirect savings from increased access to medicines may result from improved health and productivity.
- Granting of additional incentives (extension of regulatory data protection) that delay access to cheaper generic versions of medicines will lead to higher costs to payers / health systems. Conversely, allowing earlier generic entry when launch expectations are not sufficiently met, represents a cost saving.

### Assessment of any synergies and tensions within the Policy Block

Facilitating the wider use of multi-country packs not only may be a way to address problems with selective market launches that ignore the needs of smaller markets but could also facilitate the movement of product between countries in case of supply disruptions and shortages. It therefore is synergistic with other measures to improve supply chain security discussed in Block F.

Extending the regulatory data protection period as an incentive for wider market launch needs to be considered alongside other proposed revisions to the system to incentivise innovation, in particular in areas of unmet medical need (e.g. Policy element B.1.4).

Introducing a market placement expectation and allowing earlier generic entry in case the expectation is not fulfilled will require simultaneous revision of several other parts of the EU pharmaceutical legislation for medicines, in particular the EU Orphan and Paediatric Regulations.

### *12.3.5 Policy Block E (A.E): Competition*

Policy Option A is a refinement of the current legislative arrangements for encouraging competition, with only one change overall: A new simpler regulatory pathway for generics.

No other changes to the current situation are envisaged, including to the current conditions for duplicate MAs.

#### Assessment of the key impacts for the policy elements

Table 25 presents our assessment of the key impacts of each of the proposed measures, drawing on our consultations, desk research and targeted literature review.

*Table 25 Option A - Assessment of the proposed measures for competition*

| **Assessment** |
|---|
| A.5.1 New simpler regulatory pathway for generics |
| The key impact from a simpler regulatory pathway with shorter approval times will be faster availability of generics to patients. It should create more clarity and potentially less administrative burden for marketing authorisation applicants, encouraging more applications and increased development activity for generics.<br>We assume that generics will be on the market soon after approval and access to generics will be similar in all member states. The latter assumption has been adopted for ease of analysis as generics market penetration varies considerably across member states[63] and would add uncertainties to our assessment. |
| A.5.2 No change to current situation and no restriction on duplicate marketing authorisations |
| This is business as usual (BAU) and as such there would be no additional impact, as compared with the baseline policy option. As such we assume that the types of products being developed will not change (as no change in Bolar provision) and behaviour around duplicate marketing authorisations will also remain the same. |

#### Summary assessment of the principal costs and benefits by impact type

Table 26 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block A under Policy Option A and for each impact type.

*Table 26 Option A - Summary assessment of the proposed measures for competition*

| **Policy elements** | **COB** | **Admin** | **SMEs** | **CTI** | **Int Mar** | **I&R** | **PA** | **H&S** | **Sust** |
|---|---|---|---|---|---|---|---|---|---|
| A.5.1 | + | + | + | + | + | + | + | + | -/+ |
| A.5.2 | -/+ | -/+ | -/+ | -/+ | + | -/+ | + | + | -/+ |
| Overall impact | + | + | + | + | + | + | + | + | -/+ |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

The following key impacts are envisaged based on interviews (industry representatives and payers) and literature:

- Greater certainty for businesses in terms of their development cycles and application requirements for generics with reduced complexity of the submission because of the simplified pathway. This would improve the situation compared to the lack of clarity that

[63] Wouters OJ, Kanavos PG, McKEE M. Comparing Generic Drug Markets in Europe and the United States: Prices, Volumes, and Spending. Milbank Q. 2017 Sep;95(3):554-601.

has been reported regarding which current abridged application procedures (generic or hybrid) should be followed[64]

- A high likelihood of positive impact through making medicines more readily available to those that need them and reducing costs for health systems (generics represent around 80% cost reduction compared to originators, and entry of a generic also reduces price of the off-patent medicine by 61%[65]; biosimilars are 20% cheaper[66] compared to originator products)
- Benefit to patients (and public health) through the greater likelihood that getting MA for generics will be easier and quicker, and thus access to medicines will be improved

#### Assessment of any synergies and tensions within the Policy Block

This option does not present major changes compared to the current legislation, hence the opportunity for added impact in combination with other blocks is limited. Fundamentally, increasing competition via market entry of generics and biosimilars increases access and affordability and thus has added value in terms of improved patient health and lower costs for health systems. However, this added value will be in line with current benefits.

There is synergy with the horizontal measure of streamlining and harmonisation with making the regulatory pathway for generics simpler. No change to the duplicates regime creates some tensions with regard to timely availability of biosimilars on the market and thus access.

### *12.3.6 Policy Block F (A.F): Supply Chain Security*

Option A includes a variety of measures aimed at improving the availability, quality, timeliness, and exchange of information about (potential) shortages (A.6.1, A.6.2, A.6.4, A.6.5). The underlying idea is that such information will allow authorities and other parties to better mitigate the impact of supply disruptions and thereby reduce negative health impacts and costs. It would furthermore also improve the understanding of the causes of shortages and of what products are at increased risk.

The option additionally seeks to preserve the availability of medicines that the MAH intends to withdraw from the market by mandating that the MA is first offered to another party (A.6.3).

#### Assessment of the key impacts for the policy elements

Table 27 presents our assessment of the key impacts of each of the proposed measures, drawing on our consultations, desk research and targeted literature review.

*Table 27 Option A - Assessment of the proposed measures for Supply Chain Security*

| **Assessment** |
|---|
| A.6.1 Encourage the use of HMA/EMA guidance definitions |
| Overall, encouragement of the use of standardised guidance definitions can help create a more harmonised system of shortage monitoring across the EU. It should be noted though that adoption of such a definition itself cannot directly reduce the incidence of shortages, but rather is a stepping-stone in the introduction of further harmonisation measures. If wider adoption of a single harmonised definition contributes to improved information sharing between MS about shortage situations, this may in turn support earlier identification of potential supply disruptions and more effective mitigation strategies. The impact of this will still depend to a large extent on how national authorities further operationalise these guidance definitions within their own notification systems. |

[64] *Klein, K., Stolk, P., De Bruin, M.L., Leufkens, H.G., Crommelin, D.J., & de Vlieger, J.S. (2019). The EU regulatory landscape of non-biological complex drugs (NBCDs) follow-on products: Observations and recommendations. European Journal of Pharmaceutical Sciences, 133, 228–235.*

[65] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

[66] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilarsv

| Assessment |
|---|
| A.6.2. Notifications two months in advance, encouraging the use of the HMA/EMA reporting template. |
| The current notification timeframe under Article 23a of two months stipulates the minimum in all EU countries. As such, A.6.2. does not constitute a change to the current timing of notification. It also emphasises the use of the HMA/EMA reporting template. The main foreseeable impact thus relates to the type and amount of information MAHs may be expected to provide. Whilst possible that, compared to the current situation, the information requirements would increase in some MS, standardisation of requested information is more likely to facilitate central coordination of shortage reporting, thereby reducing transactional costs.<br>Potential impacts on the security of the supply of medicines are primarily indirect. Greater standardisation of information collected as part of shortage notifications likely will improve information sharing between countries and allow for a better understanding of the causes of shortages. This may allow for the development of more tailored policy approaches to address the issue of shortages at both EU and national levels and ultimately improve security of supply. |
| A.6.3 Marketing authorisation offered for transfer to another MAH before a permanent withdrawal |
| Requiring a MAH to offer the MA to another party before allowing it to withdraw the product from a specific market could delay the original MAH's withdrawal decision, as it seeks to avoid enabling its own competitors.<br>Hypothetically, requiring MAHs to offer the MA to another manufacturer could benefit such manufacturers who are enabled to market a product that already has an established patient base. However, as indicated previously, a large proportion of product withdrawals can be traced to low product-level profitability[67]. It is not clear to what extent a MA transfer could effectively address these underlying profitability issues. Such transfers would only be feasible/interesting in case a product remains commercially interesting for the new MAH or if commercial viability is not required for another party to take over the MA (e.g. in case of transfer to a not-for-profit entity).<br>The study team has identified no experiences with similar measures that could inform a (quantitative) estimation of potential impact. Moreover, the EU trade association for the generics industry (Medicines for Europe) has indicated that it considers this proposal unconstitutional and not compliant with the proportionality requirements of EU treaties. It indicates that permanent withdrawals for commercial reasons are often necessitated by national market conditions, such as pricing and reimbursement policies (e.g. price cuts, reference pricing, claw backs and rebates), that are imposed by Member States and over which the MAH has no control. Mandating that the MAH offers the authorisation to another party before allowing it to withdraw is therefore considered a form of regulatory expropriation in violation of Art. 16 of the European Charter of Fundamental Rights. |
| A.6.4. Use of the Falsified Medicines Directive (FMD) system to monitor shortages |
| EU-wide monitoring of shortages could reduce the need for decentralised notification and improve the quality of information available to stakeholders. Similar to B.6.1, better quality information could contribute to more effective prevention and mitigation strategies.<br>Given the fact that the European Medicines Verification System (EMVS) is currently not yet deemed fit for purpose, this measure is likely to require a significant investment to develop the system in this direction.<br>Some industry stakeholders have also called attention to the need for accelerating the implementation of IDMP/SPOR (IDentification of Medicinal Products[68]/Substances Products Organisations and Referentials) standards, which could improve data standardisation and linkage across systems and offer regulators more insight into supply chain structures, supply levels and demand. |
| A.6.5. EU coordination to exchange information on supply and supply chains to identify areas of consolidation |

## Summary assessment of the principal costs and benefits by impact type

Table 28 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block F under Policy Option A and for each impact type.

*Table 28 Option A - Summary assessment of the proposed measures for supply chain security*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|

[67] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages* (Issue December).

[68] IDMP is a suite of five standards developed within the International Organization for Standardization (ISO)

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| A.6.1. | +/- | +/- | +/- | +/- | +/- | +/- | +/- | + | +/- |
| A.6.2. | +/- | + | +/- | +/- | +/- | +/- | +/- | + | +/- |
| A.6.3. | - | - | +/- | - | +/- | +/- | +/- | ++ | +/- |
| A.6.4. | - | + | +/- | +/- | +/- | +/- | - | ++ | +/- |
| Overall impact | - | +/- | +/- | - | +/- | +/- | +/- | ++ | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

The following key impacts are envisaged:

- Collectively, the proposed measures are expected to allow for improved decision-making to prevent and mitigate the impact of shortages (A.6.1, A.6.2) and offer public authorities additional tools for protecting the domestic supply of medicines (A.6.3). If successful, this will in turn result in greater continuity of supply for medicines that are needed to offer appropriate healthcare to patients. Health care costs resulting from shortages would also be reduced.
- The costs associated with industry players are lower than in other policy options given that most measures are formulated in a non-binding language. The impact on industry players is therefore expected to be limited.

### Assessment of any synergies and tensions within the Policy Block

The policy elements proposed for Security of Supply under the Option A are overall synergistic. The are no major areas where tensions are expected to arise if all these elements are implemented together.

### *12.3.7 Policy Block G (A.G): Quality and manufacturing*

### Assessment of the key impacts for the policy elements

Table 29 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing mainly on desk research and targeted literature review.

*Table 29 Option A - Assessment of the proposed measures for quality and manufacturing*

| **Assessment** |
|---|
| A.7.1. Strengthen enforcement of responsibilities of MAH as regards the quality of the products by introducing harmonised system of sanctions |
| There is potential for more robust internal assessment before sanctions and less heterogeneity of sanctions across Member States. This would have a positive effect on quality standards in the long-term, with MAHs making sure to fulfil their obligations to avoid penalties. The harmonisation of sanctions may also positively impact the workload of the relevant competent authorities by streamlining the process.<br><br>There may also be short and long-term negative effects on the EU pharma industry due to the financial costs of penalties incurred and reduction in international competitiveness of the sector if the sanctions regime is considered too severe. The burden of sanctions or threat thereof could present barriers for smaller actors such as SMEs, which could lead to companies leaving the sector or the EU. |
| A.7.2. Inclusion of the information on the sustainability performance of supply chains actors by using international standards in the application dossiers |
| The proposed measure would improve the sustainability of production of medicines, which would be favourable for the environment. However, companies (MA applicants) would be negatively affected due to the additional burden of collating and submitting this information and complexity of submission to comply with the environmental |

| Assessment |
|---|
| requirements. It may encourage more supplies to be sourced from the EU and will also have an impact on manufacturers in third countries.[69] |
| A.7.3. Adaption of legislation/inclusion of specific provision covering new manufacturing methods (decentralised, continuous manufacturing, etc) to ensure levels of quality and safety equivalent to current methods. |
| The proposed measure has the potential to bring several product categories that are currently excluded from the legislation into the fold and provide regulatory certainty to manufacturers. These include magistral formulae (pharmacy-based preparation for an individual patient), radionuclides in sealed sources, hospital-manufactured medicines, and single-batch medicines. In addition, manufacturing methods such as decentralised manufacturing (where manufacturing occurs at different locations) and 3D printing-based methods could be accommodated.<br><br>Covering new manufacturing methods in the general pharmaceutical legislation has the main advantage of helping to standardise the methods themselves, quality control of the methods and resultant products and associated regulatory pathways at the EU level. Thus, there is a harmonisation benefit. Moreover, accommodating new technologies sends a positive signal to innovators as well as companies and will encourage more innovation and research activity and adoption of the new methods. There will be further knock-on effects on competition, competitiveness, and access to medicine. If greener manufacturing methods are used there will be an impact on environmental sustainability, but the likelihood and extent of that is unclear.<br><br>With more certainty over the manufacturing methods and the resultant products as well as more medicine developers adopting these methods, we could imagine a very high increase in the number of new therapies in comparison to the baseline. |

## Summary assessment of the principal costs and benefits by impact type

Table 30 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block G under Policy Option A and for each impact type.

*Table 30 Option A - Summary assessment of the proposed measures for quality and manufacturing*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| A.7.1 | - | - | - | - | - | -/+ | + | +/- | +/- |
| A.7.2 | - | - | - | - | + | +/- | +/- | +/- | + |
| A.7.3 | -/+ | -/+ | -/+ | + | + | + | -/+ | + | -/+ |
| Overall impact | - | - | - | - | + | + | + | + | + |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

Some of the key costs and benefits are

- Additional transaction, compliance and administrative costs for businesses to adapt to the new regulatory and data requirements. These costs along with the threat of sanctions may have effects on international competitiveness and internal markets (e.g. security of supply)
- Future proofing for new manufacturing methods within the legislation could increase the competitiveness of the EU pharmaceutical sector, promote innovation and help improve sustainability (if new methods are greener)

[69] Eeb. (2018). Policy options for regulating pharmaceuticals in the environment.

- There is potential for public health impacts through improved sustainability (lower CO2 emissions) and new products coming on board (those manufactured using novel methods)

### Assessment of any synergies and tensions within the Policy Block

There could be tensions between policy elements A.7.1 (harmonised system of sanctions) and A.7.3 (adaption of legislation for new manufacturing methods). While A.7.3 should ensure quality and safety standards of new manufacturing methods, which should result in more therapies being developed, A.7.1 may reduce this positive effect if the sanctions are not appropriately designed.

#### *12.3.8 Policy Block H (A.H): Addressing environmental challenges*

Policy Option A involves no changes to the ERA compared to the baseline. As such, there should be no change in impact compared with the baseline.

*Table 31 Option B – Assessment of the proposed measures for addressing environmental challenges*

| **Assessment** |
|---|
| A.8.1. No legislative change; Continue the implementation of the actions under the EU Strategic approach to pharmaceuticals in the environment. |
| There should be no major change in impacts and costs compared to the baseline scenario except for positive environmental sustainability impacts to some extent owing to implementation of actions under the EU Strategic approach to pharmaceuticals in the environment outside the legislation. |

### Summary assessment of the principal costs and benefits by impact type

The table presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block H under Policy Option B for each impact type.

*Table 32 Option A – Summary assessment of the proposed measures for environmental challenges*

| **Policy elements** | **COB** | **Admin** | **SMEs** | **CTI** | **Int Mar** | **I&R** | **PA** | **H&S** | **Sust** |
|---|---|---|---|---|---|---|---|---|---|
| A.8.1. | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | + |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

#### *12.3.9 Policy Block I (A.I): Lessons from COVID-19*

Policy Option A refers to the EMA's extended mandate, which is the same as the baseline, and as such, the assessment of likely future benefits under the baseline / Option A is already presented above.

## 12.4 Policy Option B

#### *12.4.1 Policy Block A (B.A): support for innovation, including unmet medical needs*

### Assessment of the key impacts for the policy elements

Policy Option B includes 3 sub-fields and 8 policy elements relating to Policy Block A and the legislation's support for innovation including unmet medical needs (UMNs).

*Table 33 Option B - Assessment of the proposed Incentives for Innovation*

| **Assessment** |
|---|
| Expedited regulatory schemes |
| B.1.1. Codification of PRIME in the legislation |
| The inclusion of the PRIME scheme within the legislation would give a strong signal to developers that the EU is committed to increasing support for UMNs.<br>It will also reassure developers that the scheme is permanent and that they continue to benefit from the active support that comes with PRIME designation (which is focused on medicines that promise a major therapeutic advantage in an area of unmet medical need). The scheme is well regarded by stakeholders (industry, regulators, health systems) and the EMA analysis of its first five years of operation found that PRIME designation is associated with faster assessment times and an improved likelihood of a positive recommendation for authorisation.[70]<br>There should be no significant additional administrative or compliance costs for businesses, when compared with the current situation.<br>Codification may increase the popularity of the scheme still further, and that may increase the number of companies that have to bear the administrative costs associated with making an unsuccessful PRIME-eligibility request. The popularity of the scheme has increased in the recent past (+15% between 2019 and 2020), and we would expect to see further growth in future. This would be even more likely should the EU implement an additional period of regulatory protection for UMNs. These additional costs (linked with unsuccessful requests) are being limited by an equivalent expansion in the number of medicines accepted onto the scheme, which has also increased (from 23% in 2018 to 33% in 2020).<br>The impact on regulators should be broadly neutral, as while the scheme does involve additional effort to businesses with advice on the development of their PRIME-designated medicines, the resulting applications tend to be better framed and evidenced, making assessment more efficient and improving success rates for submissions (improving EMA productivity in this important area of UMNs).<br>Small biopharma firms have a particular interest in advanced therapies relevant to UMNs, and the codification and expansion of PRIME ought to have positive impact of SMEs. They benefit disproportionately from EMA advice, where larger developers have considerably more experience in preparing an application for assessment. Moreover, for some startups (e.g. cell and gene therapy companies), PRIME may have the effect of a 'seal-of-approval,' which could improve their investability and market value.<br>In the longer term, codification should reinforce the regulator's wider efforts to reduce UMNs, improving treatments, reducing hospitalisations and improving patients' quality of life.<br>As with the other regulatory proposals designed to focus developers' attention on UMNs, there is a small risk this will displace investment in other areas of medical research, possibly even slowing down the rate of progress in other disease areas that have good treatment options currently, but which still constitute a major health burden. |
| Repurposing |
| B.1.2. Establish a binding system for scientific assessment of evidence |
| A binding system would increase the numbers of older off-patent and off-label medicines where available scientific evidence is brought together for assessment by the EMA, such that the wider EU healthcare system is informed about the safety and efficacy of medicines being used in for new indications.<br>While the costs of obtaining the new evidence would have been incurred already by clinical researchers or academics, there may be some additional costs for MA holders where they look to review, replicate or challenge the new evidence.<br>This element would work in conjunction with B.1.3, obliging MA holders to include a new indication when supported by new evidence.<br>EMA statistics show an upward trend in the annual number of extensions of indications it is recommending (87 in 2021, up from 83 in 2020 and 60 in 2019), with an annual growth rate of 5-10%.<br>We assume a binding system for new evidence may nudge that growth rate up by 1-2 percentage points annually, and more if applied in conjunction with B.1.3., perhaps reaching 8-15% CAGR within 3-5 years.<br>This policy element will help broaden access to what are otherwise rather selective and uneven use of safe and effective medicines off-label. It will be a much stronger intervention than the non-binding system. In the longer term, we may see more treatment options for patients and improved geographical access. |
| B.1.3. Obligation for marketing authorisation holders to include a new indication when supported by scientific evidence and assessment. |

[70] https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience_en.pdf

| **Assessment** |
| --- |
| The *obligation* for MAHs to include new indications when supported by scientific evidence will help reducing the problem of companies deciding selectively on which indications to include on-label.71 As such, it should help broaden patient access across the EU to safe and effective medicines that are used successfully off-label currently, but only in some but not all healthcare settings.<br>This policy element would impose additional costs on MA holders, as they will be required to make an application for an extension that they would not have done otherwise. For originators, this might trigger a process that could take several years and costs tens of millions of Euros to conclude. The academic evidence may reduce the costs for developers, in some degree, however there will be additional information demands relating to the application – and possibly a need to replicate trials in order to manage the liability issues. There would also be post authorisation processes and additional administrative costs are expected related to pharmacovigilance. While the additional costs may be similar on average for any MA holder, they may prove more problematic for generics companies, or developers that have withdrawn fully from a market, where the sales volumes / prices of the existing uses may not underwrite the costs for its extension to a new indication.<br>EMA statistics show an upward trend in the annual number of extensions of indications it is recommending (87 in 2021, up from 83 in 2020 and 60 in 2019), with an annual growth rate of 5-10%.<br>We assume a non-binding system may nudge that growth rate up only marginally, perhaps to 12-22%<br>In the longer term, we may see more treatment options for patients and improved geographical access. |
| Incentives: Adaptation of the period of regulatory protection |
| B.1.4. Reduce the duration of incentives for originators from 8+2 years to a new combination (6+2 years) taking into account the interaction between data protection and intellectual property rights. |
| For originators, a reduction in the period of regulatory protection will reduce overall income and profitability for new medicines since generics companies will be able to enter markets and begin to erode monopoly prices a year earlier. The new period of protection may prompt developers to increase prices in general to protect their current business model or otherwise rebalance their portfolios towards those market segments with greater commercial potential.<br>SMEs originators may find it more difficult to invest in riskier novel medicines given the reduction in future returns on investment and their relatively weaker market position when it comes to negotiating prices.<br>It could weaken the global competitiveness of EU based originators overall, compared with the current situation, unless prices are adjusted upwards to reflect the new protection period, and ensure global ROI norms can continue to be achieved.<br>The threat to EU-based originators will be offset to some degree by giving a boost to Europe's generic industries, broadening their portfolios and potentially creating a prime-mover advantage in global markets.<br>Considering that this policy element affect SMEs more than larger firms and the latter are based in bigger economies, while the former may be based in smaller economies this may affect the functioning of the internal market and limit access to medicines across Europe. This will also be the case if some companies adjust prices upwards in response.<br>Health payers may benefit from lower average lifetime costs for medicines due to earlier generic entry and patients may benefit if those savings are used in the health care sector. The extent of these benefits will depend on originators response to the reduced incentives, and it is highly likely that average prices will be adjusted upwards in some degree to offset the shortened period of protection. |
| B.1.5. Authorised medicines with demonstrated ability to address UMN get +2 years data protection. Other medicines will be entitled to additional protection only if they can demonstrate no return on investment in view of investment costs (including for research and development). |
| A +2 year period of premium pricing will offset the higher development costs and / or lower market volumes associated with a proportion of UMNs, whereby a larger number of all UMNs would pass the private sector's ROI thresholds. While companies cannot determine in advance which products will be successful and make a smaller or larger positive contribution to their overall income and profitability, the additional period of regulatory protection will have a positive impact on estimates of potential income and profitability used in stage-gate assessments.<br>The additional period of protection would improve the competitiveness and investment flows towards EU based originators producing UMN medicines.<br>Increasing developers focus on UMNs may increase their development and regulatory costs, in some limited degree, as applicants would need to meet the UMN criteria<br>For other developers, with products that do not address a UMN, the focus would be on demonstrating the absence of a return on investment from their R&D should they not be able to secure a period of additional regulatory protection. This would increase administrative cost associated with the data-hungry and exacting ROI |

[71] https://www.fiercepharma.com/sales-and-marketing/sanofi-pulls-campath-to-clear-way-for-higher-priced-lemtrada

| **Assessment** |
| --- |
| methodology businesses would need to follow). This would also imply higher administrative costs for the EMA and NCA partners involved in checking compliance with the ROI test.<br>This incentive is expected to increase investments in R&D resulting in a higher number of novel medicines addressing UMNs as compared with the baseline and an increase in treatment options, treatments and improved patient health. |
| B.1.6. Breaking market protection in case of urgency and insufficient coverage by authorised medicines (compulsory licensing) |
| There has only been one instance of an EU member state using a Compulsory Licence,[72] as such this is an ultra-low probability event, and the link with the EU general pharmaceutical regulation is about ensuring external coherence.<br>There should be no or minimal direct impact on EU pharma in general, given it would be implemented indirectly and by exception and for a localised and time limited period.<br>It may increase burden on regulators and expand the numbers of government bodies that have to become involved in explaining their use of this regulatory exception<br>The time and costs involved in developing safe and effective copies of protected medicines may mean that the policy lacks the speed or certainty to respond with confidence to public health crises |
| **B.1.7. Require public transparency on any relevant public contribution or funding, including of research and development costs** |
| Commercial sensitivity around companies' willingness to disclose information about their use of public funding and tax reliefs to underpin their development costs makes it difficult for governments and healthcare organisations to judge the distance between manufacturers' costs and the prices they seek to realise.<br>Greater transparency around public support for medicines development may strengthen reimbursement agencies' position when negotiating with MA holders, helping to place a downward pressure on prices and thereby helping to maintain or improve access to medicines with concomitant benefits to patient health.<br>Indirectly and in the longer term, greater transparency may help public authorities justify higher healthcare budgets and thereby drive support for publicly funded medicines development. This in turn may increase the number of developers in the market and raise competition.<br>The private sector may resist such measures where they require disclosure of commercially sensitive information that could be used by their competitors within the EU and globally. Moreover, the link between R&D grants / tax reliefs and individual medicines is complex and would demand the development of new costing models and assessment frameworks. The proposal to make this information available to the public may be in tension with EU competition and IP law and could result in legal challenges.<br>Moreover, the proposal implies the EU pharmaceutical industry would need to tolerate a switch to cost+ pricing strategies in its dealings with EU payers as compared with value-based pricing that is in use currently and applies across all open markets globally.<br>There may be substantial additional administrative costs for firms needing to prepare the required information using the templates and rules of thumb on the attribution of wide-ranging public supports to specific medicines.<br>There would be substantial additional costs for the EMA compliance teams that need to develop the new procedures and tools (one off costs) and implement / assure the implementation of those protocols, including possibly upgrading the EMA's existing portals to provide better public access to individual dossiers. |
| B.1.8. Give regulators the possibility to impose a post authorisation obligation for additional studies on the effectiveness compared to the standard of care |
| Imposing a post-authorisation obligation for MAHs to include new information about the effectiveness of the medicines (i.e comparative clinical trials) may impose additional costs on MA holders, albeit this may be a matter of timing and degree, as many businesses carry out additional research on the cost-effectiveness of their medicines with a conditional approval. The EMA annual reports show that around one third of all medicines that have been granted a CMA since 2006 have gone on to be granted a full marketing authorisation (i.e. sufficient additional evidence has been gathered to confirm effectiveness). As such, it may increase and bring forward costs associated with such studies for tens of businesses. Those costs might amount to €20-€50m for each product.<br>MA holders will have to bear some additional costs and there may be a small increase in the number of medicines that are found to be less cost-effective than had been anticipated. This last point could impact on the ability of individual companies to raise finance or otherwise weaken their competitive position, but there would be no substantive impact – positive or negative – on overall competitiveness, or the functioning of the internal market.<br>This obligation would help to confirm the relative effectiveness of the products in question several years earlier than is the case currently. The EMA annual report (2020) shows that the 30% of CMAs that have been granted full |

[72] https://www.keionline.org/35558

| Assessment |
|---|
| marketing authorisation took an average of 3.5 years post-authorisation to get their products fully authorised. This would allow more timely action in respect to individual medicinal products – e.g. withdrawal or more widespread use – and would indirectly give HTAs and payers greater confidence in the CMA pathway.<br>There would be some additional administrative costs for the EMA and NCA staff working with them following from the increasing numbers of assessments of these additional studies and consideration of the case for granting full authorisation.<br>The improved clarity as regards the relative cost-effectiveness of medicines should increase confidence across health systems in making full use of those products, and thereby benefiting patient health. |

### Summary assessment of the Incentives for innovation

Policy Option B foresees several important changes to the current arrangements. With regard to the incentives for innovation, this option reviews the current protection periods with reduced standard regulatory protection periods and modulation subject to certain conditions. Authorised medicines with demonstrated ability to address UMN are entitled to longer protection than the standard protection.

Other medicines will be entitled to additional protection only if they can demonstrate no return on investment in view of investment costs, including for research and development.

MAH are given increased obligations regarding the repurposing of off-patent medicines. It gives regulators the possibility to impose a post-authorisation obligation for comparative studies on the effectiveness compared to the standard of care. This will facilitate decision-making throughout the lifecycle of medicines.

*Table 34 Option B - Summary assessment of the Incentives for innovation*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.1.1. | + | +/- | + | +/- | +/- | + | - | - | +/- |
| B.1.2. | +/- | - | - | +/- | + | + | +/- | + | +/- |
| B.1.3. | - | -- | -- | +/- | ++ | +/- | +/- | + | +/- |
| B.1.4. | -- | +/- | -- | -- | - | --- | + | - | +/- |
| B.1.5. | ++ | -- | -- | + | +/- | + | - | + | +/- |
| B.1.6. | - | - | - | - | - | - | - | +/- | +/- |
| B.1.7. | - | -- | - | - | +/- | - | - | +/- | +/- |
| B.1.8. | +/- | - | - | +/- | +/- | + | - | + | +/- |
| Overall impact | -- | --- | -- | -- | + | - | - | + | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### Assessment of any synergies and tensions

Within the Innovation Policy Block, the policy elements proposed under Policy Option B are largely complementary to each other, whereby the proposal to reduce the period of regulatory protection for the standard innovative medicines pathway (by 2 year) is mirrored by a policy element to provide a +2 year special bonus for new medicines relevant to UMNs.

The ability to impose a requirement for additional studies would complement existing provisions relating to the EMA's various expedited regulatory pathways building support among member states (HTAs, health payers) for CMAs in particular.

### *12.4.2 Policy Block B (B.B): Antimicrobial Resistance*

#### Assessment of the incentives for innovation and prudent use of antimicrobials

Policy Option B encourages the development of antimicrobials through novel incentives. It introduces a 'pay or play' model. Either a company holds an antimicrobial in its portfolio, or it pays to a fund that is destined to finance the development of novel antimicrobials. It includes measures for prudent use of antimicrobials as well as monitoring consumption and use of human antimicrobials.

*Table 35 Option B - Assessment of the proposed incentives for Innovation and prudent use of antimicrobials*

| **Assessment** |
|---|
| B.2.1 Make the central procedure mandatory for new antimicrobials. |
| As this policy element largely formalises what happens in practice already, there would be little or no additional impact on the development of novel antimicrobials or their more prudent use. |
| B.2.2. PRIME like support scheme, including rolling review |
| If the system in place for rolling reviews is easy for SMEs and large companies to navigate and flexible, there is potential for a large positive effect on EU pharma businesses by increasing company-regulator interactions in areas that may not be currently attractive for business to invest in R&D. This could result in a positive impact on innovation rates and overall EU pharma industry output.<br>The targeted survey revealed that industry respondents were broadly in favour of codifying rolling reviews, in particular for new technologies or major innovations in medicinal products. However, the demands on Rapporteurs are high, with significant increase in workload; one NCA interviewed stated that the COVID-19 pandemic rolling review required approximately 50% increase in resources/workload. The demands on companies are also relevant, as the process requires more communication and clarifications (data packages may not be structured, may contain errors, etc). Furthermore, rolling reviews bring uncertainty on the added therapeutic value of medicines and inequity of access is larger for orphan medicines73. Considering these reasons, some civil society and public authority respondents were against codifying rolling reviews in a way that would expand the scope of use of this procedure outside exceptional medical conditions and public health emergencies. |
| B.2.3. Optimise package size |
| This policy element would encourage the use of smaller package sizes, thereby increasing manufacturers' costs relating to product packaging and distribution.<br>It may also increase the cost of antimicrobials for health payers (smaller package sizes are more costly), including an increase in average prices for a course of treatment for an individual patient, albeit these price increases should be offset in some small degree by lower levels of consumption.<br>It may have implications for storage costs (more space required) but may ease dispensing and take pressure off pharmacists' local storage requirements.<br>We don't foresee additional extra administrative costs on the side of businesses and authorities.<br>By helping to reduce overall levels of consumption, this policy element may contribute in some small degree to reducing AMR and avoiding AM releases to the environment. The smaller pack sizes will increase packaging waste, which would increase costs associated with waste management and recycling. |
| B.2.4. Stricter rules on disposal |
| The legislation and accompanying guidelines would have no direct impact on EU pharmaceutical manufacturers, wholesalers or pharmacies, indirectly it may lead to an expansion in overall sales volumes and income, as pharmacies buy smaller volumes more frequently, prescribers push for smaller pack sizes, and patients a less likely to self-medicate. In the longer term, and indirectly, the initiative should encourage industrial actors across the value chain and across member states to give more weight to these issues and adhere more closely to applicable legislation and professional guidance.<br>Stricter disposal rules would bring additional costs for public authorities, with a substantial one-off cost for EU / MS authorities in developing and championing the roll-out / adoption of the guidelines and additional ongoing costs for national authorities in maintaining / monitoring adherence and for the EMA and its advisory groups in tracking developments and giving ad hoc advice. |

[73] https://www.efpia.eu/media/602652/efpia-patient-wait-indicator-final-250521.pdf

| **Assessment** |
|---|
| Stricter disposal rules / smaller pack sizes may increase the unit costs of antimicrobials and stricter management of stocks may also add costs and even increase susceptibility to shortages. Patients should see a benefit from a reduction in self-medication using unused and out of date medicines.<br>Given the high proportion of citizens that hold onto medicines indefinitely or otherwise dispose of them inappropriately[74], improved advice and collection should reduce poor disposal and indirectly benefit the environment and help to curtail an important vector for AMR |
| **B.2.5. Tighten prescription requirements for antimicrobials** |
| While prescribing policies are a matter for national authorities in the first instance, the legislation can invite member states to do more to bring practice in line with international standards.<br>These obligations and guidelines do not affect industry directly. Indirectly, and if successful, better prescribing would accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for the pharmaceutical industry overall and particularly those generics companies that supply older, lower-cost, broad-spectrum antimicrobials.<br>Indirectly, there may be a differential impact on the generics industry and particularly that sub-set of pharma businesses that include older, broad-spectrum antimicrobials in their portfolio. There may be a small benefit for MA holders with more specific antimicrobials, if prescribers both reduce overall prescription numbers and switch from cheap, broad-spectrum medicines to more specific (more expensive) antimicrobials.<br>Indirectly, tighter prescription is likely to reduce usage and that may weaken the return on investment for antimicrobials in general, worsening the investment case in an area of medicines research that is already regarded as being uneconomic.<br>Indirectly, health systems may see savings because of better prescription practices and reduced consumption, albeit this may be offset by increased costs associated with diagnostic tests and a switch to more costly antimicrobials. If successful, this policy element should reduce consumption and that in turn should reduce the potential for negative environmental impacts. |
| **B.2.6. Mandatory use of diagnostics prior to prescription of antimicrobials** |
| Similar impacts as with B.2.5 but since this policy element is seeking to encourage EU member states to make the use of diagnostics a mandatory requirement, there may be a greater impact on prescribing behaviour and consumption (albeit, as with prescribing practice in general, the use of diagnostics is a matter for member states in the first instance, with many wider factors determining the use of such screening techniques[75]).<br>There may be territorial issues around access and affordability with respect to diagnostic tests, whereby some of the proportionately largest consumers of antimicrobials are central and southern European member states, that rely heavily on low-cost broad-spectrum antibiotics supplied by generics manufacturers, and where there is less good access to more specific and costly branded antimicrobials and a similarly less good access to point-of-care tests, microbiologists, and test labs. These countries also have a stronger tradition in prescribing antibiotics as a first line of defence.<br>Greater use of diagnostic tests should improve prescribing practice in some degree, which should have a positive impact on patients, avoiding unnecessary medication or poor therapeutic outcomes that result from using the wrong anti-microbials. Depending upon the success of the proposed legislation and guidelines, these changed practices could reduce consumption considerably and make a significant contribution to efforts to contain AMR. |
| **B.2.7. Pay or play model: either a company holds an antimicrobial in its portfolio, or it pays into a fund that is destined to finance the development of novel antimicrobials.** |
| A pay or play model would impose additional costs on EU pharma businesses, and while a minority may look to avoid a levy by beginning to develop antimicrobials, or by acquiring businesses with an antimicrobial in the portfolio, the majority would be likely to view the surcharge as an unavoidable additional cost to be factored into their wider pricing policies.<br>Additional administrative costs related to the pay or play model are expected to be relatively small, with the sub-set of firms that are developing or supplying antimicrobials needing to certify that fact in order to avoid the surcharge.<br>SMEs would not be impacted directly by this policy since it is expected that EMA continues to put in place preferential policies for these firms. Indirectly, and over time, the system could lead to a series of acquisitions and an expansion in demand among larger developers for the results of early-stage R&D involving SMEs. |

[74] Mitkidis, K., Obolevich, V., Chrysochou, P. and Mitkidis, P., 2021. Harmonisation of Pharmaceutical Take-Back Systems in the EU. *European Journal of Health Law*, pp.1-27.

[75] https://www.imi.europa.eu/projects-results/project-factsheets/value-dx

| **Assessment** |
| --- |
| The proposed pay or play model would raise the cost of doing business in Europe, this could affect the competitiveness of pharma companies in Europe relative to US companies.<br>It may encourage developers willing to avoid the fees to broaden their product portfolios through commercial activities (e.g. mergers, acquisitions, licences, etc. with smaller biopharma companies that develop antimicrobials). It will incentivise competition between large pharmaceuticals to win the research and development grants financed by the fund.<br>The EMA would need to establish a new unit to decide on the allocation of the research grants to the best suited developers.<br>This pay or play model would not increase substantially the number of novel antimicrobials in the market and may risk increasing prices in other markets, creating substantial social costs. |
| B.2.8. Establish a monitoring system for data collection on human antimicrobial consumption and use and potentially on the emission of APIs to the environment |
| Expanded surveillance would have no direct impact on EU pharmaceutical companies conduct of business. Indirectly, and in the longer term, improved surveillance data may help to accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for industry overall.<br>Expanded surveillance would have no direct impact on EU pharmaceutical companies' administrative costs. Indirectly, and in the longer term, improved surveillance may facilitate the more robust scrutiny of MAH environmental risk assessments (ERA) and this would be expected to require all businesses to develop more comprehensive - possibly more costly - ERA presentations as part of their submissions to the EMA.<br>This policy element would not have a direct impact on SMEs, however, indirectly, any implications for enhanced environmental risk assessments could be more challenging for SMEs to carry out / afford.<br>Expanded surveillance would have no direct impact on EU pharmaceutical companies conduct of business. Indirectly, and in the longer term, the improved surveillance data would be expected to facilitate more robust scrutiny of MAH environmental risk assessments. More and better data may also accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for industry overall, but possibly with a relatively bigger negative impact on generic companies.<br>This policy element would have no direct impact on the functioning of the single market; however, it is conceivable that an expanded surveillance system would reveal environmental hot spots across the EU that could trigger referrals to the EC / EMA and possibly change national procurement behaviour, with more interest in sourcing medicines from producers with the best environmental record no matter where they are based.<br>Expanded surveillance would have no direct impact on EU pharmaceutical research and innovation. Indirectly, it is likely to reduce overall demand and thereby worsen the market failure associated with the development of new antimicrobials<br>An expanded surveillance system could have a significant impact on the costs borne by public authorities, both one off and in the longer term. The additional costs would fall most heavily on national agencies. Environmental impacts go far beyond the mandate and competence of the network members and given the many routes by which such active ingredients may come into the environment (e.g., agriculture), there would need to be a considerable amount of work done to agree definitions and set up data collection systems. There would also be questions around the interpretation of the results and any causal relationship between the pharma legislation, human use and the environmental signature.<br>An expanded surveillance system would not have a direct benefit to public health, however, indirectly it may provide a small additional impetus to encourage more prudent use of antibiotics. In this way, and in the longer term, it may help to combat AMR to some limited extent. On the negative side, and indirectly, it could weaken incentives slightly for industry to invest in the kinds of novel antibiotics that are needed to combat AMR more robustly.<br>An expanded surveillance system could provide a good platform from which to improve the management of antimicrobial production and consumption, with more prudent use and more informed production and disposal helping to reduce the level of human-related active ingredients getting into the environment. |
| B.2.9 same as A.2.3. Consider adapted system for authorisation of phage therapies and other alternative products |
| This policy element would create the regulatory space to encourage an increase in ongoing efforts to develop phage therapies for routine use in human medicine, potentially increasing the number of companies willing to invest and develop these emerging alternatives to conventional antibiotics.<br>In the longer term, the adaptation should ensure novel therapies can be authorised and this will in turn increase investment, develop a new market segment where the EU industry enjoys a competitive advantage, while also reducing prices of these therapies such that they will become affordable. |

| Assessment |
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| In the longer term, the emergence and growing use of phage therapies may also reduce healthcare costs/budgets since phages are an inexpensive natural resource present in the environment and offer potential as an alternative when antibiotics are rendered ineffective due to bacterial resistance (AMR).[76]<br>Finally, by reducing the use of antibiotics it would help reduce the presence of antibiotics in the environment. |

### Summary assessment of the incentives for innovation and use of antimicrobials

Policy Option B is largely concerned with enhanced prescribing practices and stewardship, which will have limited direct impact on industry or markets – beyond reinforcing the downward pressure on demand for antimicrobials in general – but should have benefits for patients and the environment. There is no substantive direct support for innovation, but rather Policy Option B proposes introducing a Pay or Play model to create a fund for reinvesting in AM R&D, which would add costs and administrative burden for industry in general without generating the volume of funds necessary to impact the AM pipeline. The adaptation of the system for the authorisation of phage therapies may catalyse increased investment in this emerging and innovative technology.

*Table 36 Option B - Summary assessment of measures for innovation and use of antimicrobials*

| Policy elements | COB | Admin | SMEs | CTI | Internal Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.2.1 | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| B.2.2. | + | - | + | +/- | +/- | + | - | + | +/- |
| B.2.3. | - | +/- | +/- | +/- | +/- | +/- | - | + | + |
| B.2.4. | +/- | +/- | +/- | +/- | +/- | +/- | - | + | + |
| B.2.5. | +/- | +/- | +/- | +/- | +/- | +/- | - | + | + |
| B.2.6. | +/- | +/- | +/- | +/- | +/- | +/- | - | + | + |
| B.2.7. | - | -- | -- | - | +/- | + | - | +/- | +/- |
| B.2.8. | +/- | +/- | +/- | +/- | +/- | +/- | - | +/- | + |
| B.2.9 | + | +/- | +/- | + | + | + | - | + | + |
| Overall impact | +/- | -- | - | +/- | +/- | + | - | + | + |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element. Policy Option C – Summary assessment of the Incentives for innovation

### Assessment of any synergies and tensions

Within the AMR Policy Block, the policy elements proposed under Policy Option B are largely complementary to each other, with the mandating of the use of the Central Procedure dovetailing with the proposal for the EMA to create a PRIME-like scheme for AM products, while also introducing the Pay or Play model to create a fund for reinvesting in AM R&D. The adaptation of the system for the authorisation of phage therapies is a further complementary initiative that recognises the potential for this emerging and innovative technology to make a

[76] https://www.nesta.org.uk/blog/when-the-drugs-dont-work-could-bacteriophages/?gclid=Cj0KCQjw_4-SBhCgARIsAAlegrUn5LXTOVza5VKzwfA4XcfpeUXcHW8jiSFfDhOBM2_MUMNcQ0GrXVQaAtQVEALw_wcB

substantial contribution to combatting AMR through support for the development of a non-traditional technology trajectory. Moreover, the proposals on prescribing practices, package size, and disposal all work well together in supporting more prudent use. The expansion in the scope of the existing surveillance system would also provide an important means by which to track progress in optimising consumption across the EU.

Under Policy Option B, there is no specific policy element that will reward innovators with an additional period of regulatory protection, however, the proposals under the Innovation Policy Block do include a policy element to provide a +2 year special bonus for new medicines relevant to UMNs. This would be an important synergy across these blocks, assuming most innovative antimicrobials would be considered as being relevant to an UMN (e.g. targeting a WHO priority pathogen where there are no or too few effective treatment options) and therefore eligible for the additional protection.

### *12.4.3 Policy Block C (B.C): Future Proofing*

Policy Option B is a refinement of the current arrangements, with four principal interventions.

Table 37 presents our schematic overview of these proposals, noting the key design assumptions and strengths/weaknesses of each one.

*Table 37 Option B - Assessment of the proposed measures for Future Proofing*

| **Assessment** |
|---|
| 1. Scope and Definitions |
| B.3.1. Adapted regulatory framework for certain categories of novel products/technologies or low volume products (hospital preparations) on the basis of well-defined conditions and respecting the principles of quality/safety/efficacy. Such frameworks could be adapted or expanded through delegated acts to set the technical framework that can be adapted to emerging scientific and technical advances (adaptive framework).<br>Where applicable, such delegated acts should be developed in close coordination with other relevant competent authorities such as e.g. medical devices, IVDs or substances of human origin) |
| As changes to legislation can be lengthy with a high administrative burden especially in the case where legislation needs to change regularly (for example to adapt to emerging technologies) adaptive legislation can be an option. In an adaptive framework change can be more iterative and responsive, 'soft-law' tools such as best-practice guidance can be employed and can be developed more collaboratively with stakeholders (who bring in depth technical knowledge) and later certified or adopted by regulators.<br>For novel products or technologies this is to respond to the emergence of new technologies that do not fit the legislation scope or definitions to ensure the legislation remains relevant. For low volume products this is assumed to respond to challenges with hospital preparations (via the hospital exemption, pharmacy exemption or as bedside manufacturing of a centrally authorised product) where regulatory gaps currently exist due to manufacturing process being out of scope or unsuitability of some aspects of GMP for hospital context.<br>B.3.1. has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. It would also address the issues of current technological advancements that are not adequately legislated for and provide the legislation with a mechanism of keeping pace with technology through both facilitating adaptation and drawing on the expertise of deeply engaged stakeholders with in-depth technical knowledge of emergent areas. However, there would be an associated increase in administrative burden due to a likely expansion of the number of specific non-legislative (soft law) tools that would require development, maintenance, review etc. and ongoing need for feedback loops, iteration and adopting delegated acts. EMA and the regulators need to stay in control and ensure that the soft law tools are meeting the overall objectives of the legislation since the incentives and alignment of all stakeholders (some of whom have valuable technical expertise that this framework is designed to harness) is not implicit. With respect to low volume products specifically this will represent an increase in regulation and associated regulatory burden but will reduce gaps in the legislation and improve patient safety while providing the legislation with the tools to consistently adapt to this rapidly paced area of technological change (e.g. pharmacoprinting, bedside manufacture, personalised medicines etc.) contributing to hospital preparations as a legitimate and robust production mechanism. |
| 2. GMO |

| **Assessment** |
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| B 3.2. Same as A.3.2 but for clinical trials: Where required, the assessment of the GMO aspects of investigational medicinal products is performed at Member State level, within the maximum timelines defined in the Clinical Trial Regulation (decentralised assessment). |
| This is as A3.2 however with the understanding that the assessment would take place at the Member State Level rather than EMA level.<br>This element would likely have less potential to improve efficiency of assessment and thus speed of authorisation of GMO-containing medicinal products. This is because complications with assessments may arise if NCA apply risk-based approach differently. However, if implemented well regulatory efforts would be focused on assessing GMO containing medicines that pose greatest threat to the environment. |
| B.3.3. Adapt certain definitions, including that of medicinal product and *delink scope from industrial process* to address technological developments, gaps/borderline questions, taking into consideration the views of regulatory authorities for other relevant legal frameworks (e.g. medical devices and blood, tissue and cells) - linked to scope of the legislation. |
| The 2004 Directive 2001/83/EC covers all 'medicinal products' that are "either prepared industrially or that are manufactured by a method involving an industrial process". By "delinking" we assume removing the manufacturing process specification from the legislation scope such that it will automatically bring into scope products that could be considered as being exempted purely through not meeting that definition. By adapting 'certain' definitions we assume this is firstly 'medicinal product' to be less specific and more similar to that found fit for purpose in other markets, secondly 'batch' which is a cornerstone of GMP but ill-fitting for continuous manufacturing processes in addition to other more specific ones around different categories of medical product.<br>This element has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. Delinking scope from industrial process would immediately bring under regulation a number of excluded or potentially excluded products and processes – most notably novel manufacturing such as bedside such as pharmacoprinting. It would be important that upon their being brought in scope the GMP was able to accommodate them or that sufficient alternative tailored guidance was available: the adaptive framework for low volume products in element B3.2 could be a facilitator to this. Addressing gaps in the legislation would impact positively on patient safety though could cause a (likely short term) reduction or delay in access while adaptations for compliance to greater regulation were made. There would be additional regulatory burden to implement the extended scope of the legislation. However, long term the efficiencies and predictability are anticipated to increase investment and innovation, reduce the time to access and improve patient safety. |
| B.3.4. Create a central *classification mechanism* for advice on whether products are medicines or not, building on the current EMA Committee for Advanced Therapies (CAT) mechanism for ATMPs to all medicinal products (borderline products) in close coordination with other concerned authorities in particular in the frameworks of medical devices and substances of human origin. |
| Medicines are increasingly being used in combination with a medical device, usually to enable the delivery of the medicine. However, these combinational products have brought regulatory difficulties for NCAs in terms of uncertainty whether they should be classified as a medical product or medical device and what regulatory framework applies.<br>B.3.4 would improve consistency of the classification of borderline products and the resulting choice of the most appropriate pathway through the EMA committee structure. This should harmonise coordination between concerned authorities in particular in the framework of medical devices and substances of human origin, and thereby deliver some small efficiency gains and avoid assessment committees being distracted from their assessment work by definitional questions. It may also improve the overall timeliness of assessments. The creation of a central screening mechanism may be timely as more definition questions arise: for example, 1 in 4 centrally approved medicines typically include a medical device component[77]. Success would depend on EMA finding the capacity to deliver relevant advice at speed. |

[77] European Medicines Agency. (2020). *ANNUAL REPORT 2020*.

### Assessment of the key impacts for the policy elements

Table 38 provides a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under option B.

*Table 38 Option B - Summary assessment of future proofing*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B3.1 | ++ | + | + | ++ | + | ++ | -- | ++ | +/- |
| B3.2 | +/- | +/- | + | +/- | + | ++ | - | + | +/- |
| B3.3 | + | + | +/- | + | ++ | + | - | ++ | +/- |
| B3.4 | + | + | + | + | + | + | +/- | + | +/- |
| Overall impact | + | + | + | + | + | + | - | + | +/- |

### Assessment of any synergies and tensions

Within this block there is tension around significant ongoing administrative burden for legislators (and other stakeholders in complex novel technologies) associated with regular and continuous amendments via delegated acts. While this undoubtedly has positive impacts regarding efficiency of applications, reduction of legislative gap and therefore products reaching the market more quickly and better regulated it should be recognised that it does represent a transfer or trade-off of administrative burden (from scientific committees and applicants in navigating an ill-fitting framework) that it represents any overall reduction. This also creates a tension with some of the horizontal streaming measures looking to reduce administrative burden where otherwise there are synergies with B3.3 and B3.4 very much related to streamlining and reduction of burden.

The relationship of all medicinal products with industrial process is not the same. While generally a delinking from industrial process was regarded positively in stakeholder consultation and according to our research would have positive impacts overall particularly for resolving scope issues and preventing legislative gaps around novel manufacturing processes, certain sectors (plasma in particular) suggest this would for them create regulatory uncertainty.

Future proofing elements in this policy element related to improved mechanisms/approaches for innovation to promote access to novel medicines (B3.2, B3.3) complementing measures in Block A – innovation for UMN, Block D-access as well as competition (Block E). There are also definition synergies with Block F (Introduce EU definition of a shortage and a definition of a critical medicine (B6.1)) and G (Adaption of legislation/inclusion of specific provisions covering new manufacturing methods (B7.4)).

#### *12.4.4 Policy Block D (B.D): Access*

Under Option B, four elements are included. The first (B.4.1) is aimed at regulating access to products that have been conditionally authorised by giving regulators greater powers to act when the generation of new evidence post-approval is not satisfactory or in case benefit is not confirmed. The other three measures (B.4.2, B.4.3 and B.4.4) have similar objectives to the elements previously discussed in Option B in that they are aimed at expanding the number of EU markets where products are launched. Unlike Option A, however, the measures under Option B exclusively focus on imposing greater requirements on MAHs and do not include incentives or voluntary options. Furthermore, whilst obligations under Option A were linked exclusively to products authorised through the centralised procedure, Option B also targets those that are authorised through the MRP/DCP route (B.4.4).

## Assessment of the key impacts for the policy elements

Table 39 presents our high-level assessment of the likely costs and benefits of each of the proposed legislative actions. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

*Table 39 Option B - Assessment of the proposed elements to improve access*

| **Assessment** |
|---|
| *B.4.1* Conditional Marketing Authorisation: introduce more powers to regulators to take measures in case of non-compliance with obligations for post-market evidence generation or in case benefit is not confirmed |
| Whilst available evidence primarily points in the direction of issues with the *standards* of evidence imposed on post-market evidence generation, policy element B.4.1. aims at increasing the ability of regulators to *enforce compliance* with the SOB. For the measure proposed under B.4.1 to have meaningful impact on access to medicines, whilst maintaining rigorous standards of effectiveness, quality and safety it must thus be assumed that:<br>• The standards for evidence generation imposed through the SOB are sufficient or will be further raised to a level whereby post-market evidence can better inform assessment of the risks and benefits<br>• Delays in submitting data in compliance with the SOB are due to insufficient commitment on the part of the MAH to meet specified timelines and there is scope to accelerate fulfilment of the requirements.<br>If regulators exercise their expanded powers to impose stricter obligations on the generation of post-marketing evidence (e.g. better quality study designs) and/or better enforce compliance with the SOB, this may raise the quality of evidence generated with regards to a medicine's effectiveness and safety. Earlier access to such information could mean that ineffective or unsafe medicines are removed from the market more quickly. This will have a positive impact on public health, as well as reduce the costs from use of ineffective or unsafe treatments. Conversely, when the generated evidence supports the conversion of the authorisation from conditional to full, this too will be beneficial for patients and health providers who can be better guaranteed of the medicine's continued availability. It also provides more certainty to payers and health systems about future health expenditures on such medicines. |
| *B.4.2* Require the MAH to notify regulators, during the authorisation process, of their market launch intentions through a roll out plan for all centrally authorised medicines |
| The requirement to report on launch intentions is similar to the (voluntary) reporting proposed under A.4.3 except that voluntary reporting has here been converted into a requirement. It further differs in that it does not ask for a commitment to initiate pricing negotiations. In this regard it is both a stricter and a narrower proposal.<br>Earlier notification of launch intentions allows regulators, health systems and payers to better prepare for (potential) entry of new medicines into the package of reimbursed care. It also facilitates timelier discussion between the MAH and authorities about pricing and reimbursement.<br>It has been assumed that this requirement does not come with powers to regulators to enforce MAHs to follow up on their expressed launch intentions, nor imposes sanctions on MAH for not doing so. It is therefore highly uncertain whether, on its own, this measure could increase the number of markets in which MAH launch or encourage earlier launch. Additional obligations such as those proposed under B.4.3 would be needed to support this measure. |
| ***B.4.3* Obligation to place a centrally authorised medicine on the market in the majority of Member States (small markets included) within 5 years of authorisation** |
| The proposed obligation is similar to that specified under A.4.4. but is less explicit in that it does not indicate what the sanction is for non-compliance. In the absence of this information, it is assumed the sanction will be withdrawal of regulatory protection that would allow generic competition from year 6.<br>Any measure that promotes market entry into a greater number of EU countries, will be beneficial to patients who are otherwise unable to access these medicines. The impacts of an obligation to place centrally approved products on the market will scale with the number of countries and patients reached and with the importance of the medicine.<br>A potential risk is that MAHs of products that are within the optional, but not compulsory, scope of the CP will avoid the CP authorisation route to not fall under the obligations. This could result in a reduction in the number of countries where the product is authorised and decrease rather than promote equitable access. |
| *B.4.3.1* Requirement to offer products to a majority of national health systems (including small markets)] within 5 years from authorisation |
| This element is offered as an alternative to B.4.3. The main difference is that it requires MAH only to *offer* the product to national health systems but does not make fulfilment of this obligation contingent on whether this results in actual market placement. Whilst not explicitly stated, it is assumed that – as an alternative to B.4.3 – this requirement would apply only to centrally authorised medicines.<br>This element imposes somewhat less stringent obligations on MAHs by making its fulfilment dependent only on whether an MAH has entered into discussions with national authorities about pricing and reimbursement but not |

| |
|---|
| on a successful outcome of those discussions. Since this still allows MAHs to refrain from market entry if no mutually acceptable agreement can be reached, the direct impact of this element on improved access will likely be smaller than under option B.4.3. It may, however, be less of a deterrent for MAHs of products in the *optional* scope of the CP than B.4.3. |
| B.4.4 Requirement on MAH applying for MRP/DCP to include small markets (in particular address the post-BREXIT challenges) or possibility for MS to opt-in a pending MRP/DCP procedure |
| Most generic medicines are currently approved through the MRP/DCP route[78]. Because of this, these products would not fall within the scope of the requirements imposed by B.4.2 and B.4.3. By also extending greater obligations for inclusion of smaller markets in the application for approval via the MRP/DCP, the Commission aims to increase access to a wider group of products, in particular generic medicines, than would be achieved via marketing obligations on centrally approved medicines alone. It is assumed that the proposed element intends only to require the applicant to include specific countries into the MRP/DCP application, such that there is a valid MA in these markets, but does not require the applicant to directly place products on these markets.<br>Requiring MAHs applying for an authorisation via the MRP/DCP route to include specific markets – or allowing countries to opt-in – will enable these countries to obtain medicines more easily from other EU MS (through parallel distribution), even when the MAH does not place the product directly on the market. This may have the effect of increasing access to medicines that are not within the scope of the CP, especially generic medicines. This, in turn, may be expected to positively affect both health outcomes for patients and the affordability of treatment by increasing access to low-cost generic versions. It will also improve security of supply for included countries by facilitating redistribution in case of shortages. |

### Summary assessment of the principal costs and benefits by impact type

Table 40 presents a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under Option B.

*Table 40 Option B - Summary assessment of Policy Block D (Access)*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.4.1 | -- | - | - | -- | +/- | ++ | ++ | ++ | +/- |
| B.4.2 | +/- | - | +/- | +/- | +/- | +/- | + | + | +/- |
| B.4.3 | --- | -- | -- | -- | + | - | ++ | +++ | +/- |
| B.4.3.1 | -- | -- | -- | - | + | - | ++ | ++ | +/- |
| B.4.4 | --- | -- | - | -- | + | - | ++ | +++ | +/- |
| Overall impact | --- | --- | -- | -- | ++ | - | +++ | +++ | +/- |

- Greater obligations on the quality of evidence generated may require additional activities by the MAH (e.g. larger and additional trials), that would increase the cost for conduct of business to the MAH. Estimation of the magnitude of any potential impact would require insight into the size and type of additional activities that would be requested to raise the post-market evidence generation to a more widely accepted level.
- Obligations on MAHs to place centrally authorised medicines on the market in a majority of MS, presumably at risk of penalty in case of non-compliance, may carry substantial costs to the MAH. They may either be required to operate in markets where they cannot generate a sufficient ROI or incur fines if they refuse to do so. The MAH will also have to

[78] European Medicines Agency. (n.d.). *Authorisation of medicines*. Retrieved April 4, 2022, from https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

provide additional information to regulators to demonstrate their compliance with obligations. This implies increased administrative costs.

- Increasing the number of MS in which the MAH places a centrally approved product on the market will increase the costs to MAHs for interacting with regulatory agencies and HTA bodies in these countries. Obligations for market placement in a minimum number of MS, including smaller markets, may be more challenging to meet for SMEs that do not yet have market presence or distribution channels in such markets.
- For products approved via the MRP/DCP, a separate fee for each country in which the application is recognised will also be required. Further fees are required to annually renew the authorisation and to submit variations. However, to promote inclusion of smaller MS, special procedures with shortened time schedules and reduced fees exist (20).
- The policy elements included under Option B impose a number of additional obligations on MAHs and do not offer any incentives in return. As such, they are likely to present a significant cost for any company operating in the EU. This will reduce the competitiveness of EU-based companies compared to those in, for instance, the United States.
- Inclusion of additional countries, in particular smaller MS, in the MRP/DCP application will facilitate the movement of medicines between markets where the product has been authorised. As such, this measure may be expected to promote the functioning of the EU internal market.
- Regulatory authorities in the MS where products are placed in the market will see an increase in costs due to a greater number of medicines for which they provide regulatory oversight (B.4.3 and B.4.4). Similarly, HTA bodies will have to conduct a greater number of assessments. Expansion of the number of countries included in MRP/DCP applications will result in more work for authorities in those countries to process applications. The resulting costs may be offset, at least in part, by application fees.
- The intended and expected impact of increased access to medicine is that patients will be provided with earlier, more effective and safer treatments. This will have a positive impact on their health status and wellbeing. Whilst increased access to medicines is generally positive, it may result in increased health care expenditure. At the same time, new medicines may displace less (cost-)effective treatments, resulting in net savings. Further indirect savings from increased access to medicine may result from improved health and productivity.

#### Assessment of any synergies and tensions within the Policy Block

Requiring additional, and in particular smaller, countries to be included in the MRP/DCP application procedure (or allowing countries to opt-in) may be considered synergistic with the objectives of the policy elements in Block F to improve supply chain security, by facilitating the import of medicines from other EU countries in case of shortages.

### *12.4.5 Policy Block E (B.E): Competition*

Policy Option B involves several changes to the current legislative arrangements for encouraging competition with a view to improving time to market entry for generics and biosimilars.

#### Assessment of the key impacts for the policy elements

Table 41 presents our assessment of the likely impacts (costs and benefits) of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected.

*Table 41 Option B - Assessment of the proposed measures for competition*

| **Assessment** |
|---|
| B.5.1 New simpler regulatory pathway for generics (adapted EMA/CHMP working methods, shorter approval timelines, potentially distinguishing between complex generics/biosimilars – reducing requirements for known biologics) |
| As described for A.5.1.<br>The key impact from a simpler regulatory pathway with shorter approval times will be faster availability of generics to patients. It should create more clarity and potentially less administrative burden for marketing authorisation applicants, encouraging more applications and increased development activity for generics.<br>We assume that generics will be on the market soon after approval and access to generics will be similar in all member states. The latter assumption has been adopted for ease of analysis as generics market penetration varies considerably across member states and would add uncertainties to our assessment. |
| B.5.2 Interchangeability of biosimilars with their reference product will be generally recognised in guidance or e.g. through a recital in the legislation and will be scientifically assessed as part of the product assessment and indicated in the summary of product characteristics (SmPC, product information) to inform healthcare professionals and their patients as well as downstream decisions makers |
| Interchangeability, switching (by prescriber) and substitution (by pharmacy) of a reference medicine by its biosimilar currently fall within the remit of EU Member States. Guidance on interchangeability from one originator (reference) or biosimilar product to another at the EU level would enable all member states to make decisions on whether to allow switching and/or substitution for certain products, especially those countries where the relevant technical capacity is not available. There is potential to pool the best expertise from across the EU if product assessment is done as part of the centralised procedure, reducing burden on individual member state authorities. Inclusion of the guidance in a recital in the legislation and product information (SmPC) would inform prescribers, patients, and decision makers about interchangeability of specific products, potentially increasing uptake of biosimilars. This could improve access to biologics for patients and reduce health system costs if cheaper biologics were switched or substituted for more expensive ones.<br>It is not clear if additional data will be requested for the scientific assessment of interchangeability e.g. switch studies.[79] Our assumption is that no additional data will be required – a study by Kurki et al. (2021) which analysed post-marketing surveillance data suggests that biosimilars approved in the EU are highly similar to and interchangeable with their reference products.[80] A recent qualitative study also shows that European and UK regulatory, legal and policy experts do not see any added value in additional data or switching studies.[81] |
| B.5.3 Broader Bolar exemption – allow additional beneficiaries (companies, producers of active pharmaceutical ingredients (APIs) and non-industry actors) to conduct studies/trials |
| Overall, the broader Bolar exemption is likely to increase legal certainty, access to medicines, cost savings and research activity in the EEA compared with a narrower exemption.[82] |
| B.5.4 Extend Bolar exemption beyond generics – Allow repurposing studies/comparative trials without infringing patent rights |
| Overall, the extended Bolar exemption is likely to increase legal certainty, access to medicines, cost savings and research and innovation activity in the EEA compared to a narrower exemption.[82] |
| B.5.5 Specific (regulatory) incentive for a limited number of first biosimilars [market exclusivity for 6 months] |
| The key expected impact would be new biosimilars on the market as a result of additional research and innovation related to biosimilars undertaken to capture the benefits of the incentive. However, any such impact is likely to be extremely limited according to feedback from industry in the impact assessment workshop. According to industry, the incentive proposed is unlikely to significantly alter R&D activity or availability of biosimilars. This |

[79] Alvarez, D.F., Wolbink, G., Cronenberger, C. *et al.* Interchangeability of Biosimilars: What Level of Clinical Evidence is Needed to Support the Interchangeability Designation in the United States?. *BioDrugs* **34,** 723–732 (2020)

[80] Kurki, P., Barry, S., Bourges, I. *et al.* Safety, Immunogenicity and Interchangeability of Biosimilar Monoclonal Antibodies and Fusion Proteins: A Regulatory Perspective. *Drugs* **81,** 1881–1896 (2021).

[81] Druedahl LC, Ka'Ivemark Sporrong S, Minssen T, Hoogland H, De Bruin ML, van de Weert M, et al. (2022) Interchangeability of biosimilars: A study of expert views and visions regarding the science and substitution. PLoS ONE 17(1): e0262537.

[82] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

| Assessment |
|---|
| point is supported by literature – for example, a one-year extension of market protection for approval of a new indication has rather marginal effects.[83]<br>At this stage it is unclear, how the market exclusivity would work and whether it will be simultaneous or sequential as not all biosimilars within the group will enter the market at the same time. |
| B.5.6a Reforming the duplicates regime: No auto-biologicals<br>OR<br>B.5.6b Duplicates restricted to cases of intellectual property protection or co-marketing |
| The main effect of B.5.6.a will be increased competition in the biosimilars market with no monopoly conditions for the first entrant. This will mean greater choice for patients and health systems.<br>In case of B.5.6.b, there will be a reduction in barriers to competition and monopolisation of the market by the first generic/biosimilar of an originator product to receive an MA. Consequently, there will be no delay in the second generic/biosimilar coming onto the market once it receives approval. This will mean greater consumer choice and price competition. |

## Summary assessment of the principal costs and benefits by impact type

Table 42 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block E under Policy Option B and for each impact type.

*Table 42 Option B – Summary assessment of the proposed measures for competition*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.5.1 | + | + | + | + | + | + | + | + | -/+ |
| B.5.2 | -/+ | -/+ | -/+ | + | + | -/+ | ++ | ++ | -/+ |
| B.5.3 | + | + | -/+ | + | + | + | ++ | ++ | -/+ |
| B.5.4 | + | + | -/+ | + | + | + | ++ | ++ | -/+ |
| B.5.5 | -/+ | -/+ | -/+ | -/+ | -/+ | -/+ | -/+ | -/+ | -/+ |
| B.5.6 | -/+ | -/+ | + | + | ++ | + | ++ | + | -/+ |
| Overall impact | + | + | + | + | ++ | + | +++ | +++ | -/+ |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Some of the key expected impacts are as follows:

- Increased international competitiveness through creation of a more favourable regulatory environment for generics/biosimilars (simplified generics pathway, specific incentive for first biosimilars), which might encourage more MAHs to apply for first filing in EU. The broader scope of the Bolar exemption will increase the share of EU-based API producers and API manufacturing jobs and lower costs of supply for European generics.[84] The cost savings

[83] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, *Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe : final report*, Publications Office, 2018, https://data.europa.eu/doi/10.2873/886648

[84] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

would be more pronounced for European generics manufacturers of specialised products e.g. for oncology or central nervous system. Increased competitiveness may possibly encourage new entrants

- Improved consumer choice and competition through availability of both generics/biosimilars and originators on the market, resulting in lower prices and improved access for patients across member states. Modification of the duplicate regime will mean originator companies will not be able to severely undercut the price of potential biosimilar competitors through a duplicate authorisation for an autobiological while allowing the reference originator product to maintain a high price.[85]
- Market exclusivity for first biosimilars may allow higher prices to be charged[83]. It may also limit competition by preventing new biosimilars from entering the market during the exclusivity period. On the other hand, with protection being awarded to a set of biosimilars for the same originator product, price competition may also occur. The level of discounting is typically around 20% of the price of the originator product for a single new biosimilar entering the market, or 30–50 percent for multiple biosimilars entering the market simultaneously.[86]
- Increase in R&D for generics/biosimilars with regulatory pathway becoming quicker and clearer, Bolar exemption broadened to include additional beneficiaries, modification of the duplicate marketing authorisation regime and specific (regulatory) incentive for first biosimilars. The latter may encourage more investment in biosimilar development (there is a positive relationship between market protection and R&D investments by companies[87]), but this effect will be limited considering development costs[88] and only six months' market exclusivity as incentive.
- The extended scope of the Bolar exemption will increase returns to innovation and therefore increase incentives to innovate for European R&D based pharmaceutical companies in countries that currently have a narrow Bolar scope, such as Belgium, the Netherlands and Sweden. This might increase the number of regulatory tests/medicine trials conducted in these countries and can be expected to lead to an increase in the number of skilled jobs[84]
- A very high likelihood of positive impact on patients through making medicines more readily available and reducing costs for health systems (generics represent around 80% cost reduction compared to originators, and entry of a generic also reduces price of the off-patent medicine by 61%[89]; biosimilars are 20% cheaper[90] compared to originator products)
- An extended Bolar exemption will result in more timely access to medicines for patients.[91] If the measure leads to more clinical trials in a country, this will benefit the country patient population, as it has been shown that new medicine adoption is wider in countries where the clinical trial was run.[91]

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[85] https://www.biosliceblog.com/2019/11/update-on-eu-duplicate-marketing-authorisations/

[86] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilars

[87] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, *Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe : final report*, Publications Office, 2018, https://data.europa.eu/doi/10.2873/886648

[88] Mestre-Ferrandiz, J., Towse, A. & Berdud, M. Biosimilars: How Can Payers Get Long-Term Savings?. *PharmacoEconomics* **34**, 609–616 (2016).

[89] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

[90] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilarsv

[91] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

- Increased access to medicines and security of supply through alternatives being defined (interchangeability)

### Assessment of any synergies and tensions

There is synergy with the horizontal measure of streamlining and harmonisation with making the regulatory pathway for generics simpler. There is a high likelihood of synergistic effects on biosimilar adoption from the combination of interchangeability guidance and the other incentives and measures.

Changes to the duplicates regime should alleviate some tensions with regard to timely availability of biosimilars on the market and thus could improve access. On the other hand, the measures to promote earlier generic/biosimilar entry to the market e.g. extending/broadening the Bolar exemption and specific regulatory protection for first biosimilars may create tensions with the measures supporting innovation.

### *12.4.6 Policy Block F (B.F): Supply Chain Security*

Compared to Option A, Option B introduces a considerably more extensive set of measures that introduce or increase various obligations and requirements on MAHs and wholesalers.

### Assessment of the key impacts for the policy elements

Table 43 presents our assessment of the key impacts of each of the proposed measures, drawing on our consultations, desk research and targeted literature review.

*Table 43 Option B - Assessment of the proposed measures for Supply Chain Security*

| **Assessment** |
|---|
| B.6.1. Introduce EU definition of a shortage, including a critical shortage and critical medicine |
| The measure has the potential to harmonise numerous definitions of shortages that exist across the EU. The clarification of criticality criteria can further help in making changes in shortage notification to cover shortages for most critical medicines. Overall, many stakeholders, and particularly industry representatives have advocated for the adoption of the concept of 'product criticality' into definitions of shortages and regulatory measures aimed at notification and prevention of shortages. The study of medicines shortages also called for the introduction of criticality criteria and further measures associated with it.[92]<br>The clarification of shortage criticality criteria can further help in making changes in shortage notification to cover the most impactful shortages. |
| B.6.2. Increase notification period to 6 months in advance using a common template for reporting withdrawals and shortages including details of root causes, alternatives medicines and impact. |
| This option differentiates between planned (permanent) market withdrawals and temporary supply disruptions, setting different notification timeframes for each. There is more explicit recognition of the fact that not all shortages can be foreseen 6 months in advance. It is uncertain whether this element will result in earlier notification than presently the case, given that most shortage notification are currently made with less than 2 months' notice, citing 'exceptional circumstances'. There is no clear reason why extending the notification period would remedy this situation. Where potential shortages are notified more in advance, these situations often are resolved before they result in an actual shortage. Extending the notification period may thus increase the number of 'false alarms'. There is also a risk that a longer notification period will increase the administrative burden on both MAHs and public authorities without clear benefits.<br>In some countries, parallel distributors also fall under a notification obligation. In consultation, this industry has indicated that a 6-month notification requirement would not be possible to meet since they typically do not hold stocks for more than 2-3 months.<br>Earlier notification of planned withdrawals may be more feasible and provide authorities more time to identify and source alternatives.<br>The obligation to utilise a common reporting template is received positively by the stakeholders. Common data collection approaches, particularly if linked to a standardised reporting portal and automatic sharing of information between MS could, in the longer term, result in cost savings for authorities. Greater standardisation of |

[92] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages*

| **Assessment** |
| --- |
| information may also enable a better understanding of the causes of shortages and allow for the development of better-tailored policy approaches to address the issue of shortages. |
| B.6.3. Shortage prevention and mitigation **plans added to GMP** for **all medicines** |
| Early identification of risks to the security of supply and of possible mitigation steps could reduce the occurrence and impact of supply disruptions. Fewer medicine shortages, as well as faster and more effective mitigation of the impact of shortages when these occur, improves patient access to (critical) medicines and leads to better health outcomes. The health system experiences fewer costs associated with dealing with medicine shortages.<br>Depending on the level of detail required and the degree to which risk mitigation steps (e.g. contractual agreements with backup suppliers) are expected, MAHs may make additional costs not only in drawing up the plans but also in implementing the actions therein specified.<br>Industry representatives have indicated that an important condition for the submission of shortage prevention plans would be that the company retains ownership of the plan, and that information remains confidential, as this could be commercially sensitive. |
| B.6.4. Stockpiling requirements for MAHs and wholesalers for unfinished critical medicines, as appropriate |
| Some further elaboration is needed to determine criteria to establish what constitutes 'as appropriate'. More detailing is also needed about the expected quantity of such stock, what state the product needs to be in (e.g. intermediates or finished but unlabelled/unpacked products), at what level the stock will be held (e.g. EU, national, regional), who has ownership and responsibility for the stock (e.g. MAHs, wholesalers or authorities) and whether stock may be redistributed according to need. All such factors may strongly influence the operational feasibility of this measure and its acceptability to involved stakeholders.<br>Among wholesalers there is a sense that a limited level of additional reserve stockholding (~2-3 weeks) – with reserves dynamically rolled into normal stock – for critical measures may be a cost-effective measure against supply disruptions, holding larger volumes of stock is both unfeasible and unnecessary.<br>It is expected that the costs of increased stock holding will either need to be shared between MAHs and public authorities, or if not, that MAHs will seek to recoup the increased costs by raising prices. For generic manufacturers, whose products are typically under strict price regulations and caps, this may not always be possible. Among generic manufacturers, there is therefore a fear that in the absence of a balanced cost/risk sharing arrangement, companies may be unable to continue operating in markets where these stock obligations apply. |
| B.6.5. Introduce an **EU shortage monitoring system** |
| Improved monitoring of supply and demand of shortages may enable earlier identification of potential supply problems and allow for mitigating actions to be taken before these can impact patients unduly.<br>EU-wide monitoring of shortages would reduce the need for decentralised notification and national (mirror) reporting systems, which should improve the overall consistency / timeliness / quality of information available to stakeholders. This can be expected to result in cost savings for parties under a notification obligation if it is assumed that notification into an EU shortage system negates the need to report to one or more individual national authorities and for those national agencies to maintain their own reporting systems.<br>Most shortages are limited in geographic scope and are not the result of global supply disruptions but rather inequitable distribution. Improved monitoring at the EU level could allow to improve the balance between supply and demand across the EU and can support the functioning of the internal market by matching excess supply in one location to unmet demand in another.<br>Standardisation of the information collected on shortages across the EU would overcome current reporting issues and would significantly aid research into understanding the characteristics of products most at risk and the causes of shortages. This, in turn, will inform better evidence-informed policy making. |
| B.6.6. Require specific **penalties** for breaking supply obligations. |
| If (the threat of) penalties are effective in improving the continuity of supply, this reduces the negative health and economic impacts to patients resulting from medicine shortages.<br>If levied, financial penalties for failure to meet supply obligations represent an additional cost to suppliers (MAHs and wholesalers). The height of penalties and the conditions under which these are imposed in practice will determine the economic impact of this. In past, penalties have been imposed only rarely and often are not financially significant for companies. (DG SANTE, 2021)<br>To enable more stringent monitoring of suppliers' obligations by authorities, suppliers will be expected to adequately document and communicate the steps they have taken to fulfil their responsibilities. This is likely to increase administrative costs associated with dealing with public authorities. |
| B.6.7 Expanded requirements for key suppliers and back-ups to diversify supply chain for critical medicines |

| Assessment |
|---|
| B.6.7. aims to force MAHs to diversify their supply chains to prevent shortages and thus improve the availability of medicines and overall patient outcomes.<br>Requiring more diverse supply chains most likely will result in increased production costs as MAHs may need to procure goods and services from less economically advantageous suppliers. These costs could be substantial, although no data was collected that would allow this impact to be quantified. There may be additional payments to backup suppliers, to reserve goods and space on production lines, even if not needed.<br>These additional costs occurred by the pharmaceutical industry may result in higher medicine prices and greater costs to health systems and patients. If requirements are introduced by individual MS rather than at the EU level, this could discourage MAHs from operating in markets with such requirements and contribute to inequitable access to medicine.<br>Importantly, the measure may not be feasible to implement for many medicines, for which globally a limited number of API and raw materials manufacturers exist, meaning that it may not be feasible for MAHs to sufficiently diversify their supply chains. Separate measures would be needed to enable this, e.g. economic incentives for industry to increase the manufacturing of APIs and raw materials. |
| B.6.8. Increase transparency of the supply chain, including:<br>1. active supply sites for all medicines,<br>2. volumes supplied, incl. supply quotas and remaining stocks for critical medicines upon request of NCA's/ EMA,<br>3. parallel traders and wholesalers' transactions for critical medicines upon request of NCAs/ EMA. |
| Improved transparency of the supply chain, at least for public authorities, has the potential of improving the security of supply by better matching supply and demand.<br>MAHs and parallel distributors each have a clear commercial interest in keeping (aspects of) information about their transactions confidential and are not generally welcoming of disclosing this to the other. For instance, parallel traders fear that full public disclosure of information about their transactions will render their trade practically impossible by allowing MAHs to throttle their supply to the level where no surplus is created.<br>For these parties to agree to share information with public authorities, it will be essential that strong agreements are made about what information is disclosed, for what purposes, how this will be used and who has access to it. Without this, it is unlikely that industry will cooperate. Mandatory disclosure of commercially sensitive information could furthermore distort competition between MAHs.<br>It may be assumed that regular sharing of information between supply chain actors and authorities – particularly when not done though an automated system – entails substantial administrative costs on all sides. |

## Summary assessment of the principal costs and benefits by impact type

Table 44 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block F under Policy Option B.

*Table 44 Option B – Summary assessment of Security of Supply elements*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.6.1 | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| B.6.2. | - | - | +/- | - | +/- | +/- | +/- | ++ | +/- |
| B.6.3 | - | + | +/- | +/- | +/- | +/- | - | ++ | +/- |
| B.6.4 | +/- | +/- | +/- | - | +/- | +/- | + | ++ | +/- |
| B.6.5 | +/- | + | +/- | +/- | +/- | + | + | ++ | +/- |
| B.6.6 | --- | -- | - | +/- | -- | +/- | +/- | ++ | +/- |
| B.6.7 | --- | --- | -- | -- | - | +/- | +/- | ++ | -- |
| B.6.8 | +/- | -- | +/- | -- | - | +/- | + | ++ | +/- |
| Overall impact | - | +/- | +/- | - | +/- | +/- | +/- | ++ | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and

production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

The following key impacts are envisaged:

- Collectively, the proposed measures are expected to allow for improved decision-making to prevent and mitigate the impact of shortages (B.6.1, B.6.3, B.6.4) and offer public authorities additional tools for protecting the domestic supply of medicines (B.6.2). If successful, this will in turn result in greater continuity of supply for medicines that are needed to offer appropriate healthcare to patients. Health care costs resulting from shortages would also be reduced. With added coordination at EU level and use of an EU-wide monitoring system, the public health benefits will be greater compared to Option A.

### Assessment of any synergies and tensions within the Policy Block

Overall, the elements are synergistic and do not contradict each other.

### *12.4.7 Policy Block G (B.G): Quality and manufacturing*

### Assessment of the key impacts for the policy elements

Table 45 presents our high-level assessment of the likely costs and benefits of each of the proposed policy elements.

*Table 45 Option B – Assessment of the proposed measures for quality and manufacturing*

| **Assessment** |
|---|
| B.7.1. Improve the oversight of the sites within a supply chain (including distributors and active pharmaceutical ingredients (APIs) manufacturing sites) by modifying provisions on inspections (frequency, content, triggering points) |
| This measure will strengthen end-to-end oversight of the supply chain and could improve GMP/GDP compliance. However, it could impose significant additional burden on businesses and competent authorities if the frequency of inspections is increased and the triggering points are changed such that in effect more inspections take place. This would substantially increase the workload of inspectors, which would need to be met with more resources. |
| B.7.2. Reinforcing Member States GMP and good distribution practices (GDP) inspections capacity by setting up a mandatory joint audit scheme |
| This policy element has the potential to increase inspection efficiency through more cooperation and knowledge transfer. This may have a positive effect on manufacturing and distribution practices within the EU and globally, which would ultimately positively impact public health in the long-term. |
| B.7.3. Stronger overall responsibilities of MAH vis a vis suppliers of raw materials and clarification of responsibilities of business operators over the entire supply chain. This would include transfer of information between each actor for each to fulfil their legal obligations with respect to quality, safety, efficacy. |
| Greater burden on MAHs and other business operators with additional responsibilities, complexity of submissions and costs could lead to reduction in international competitiveness and a decrease in companies within the sector, in particular SMEs. This may threaten security of supply of medicines.<br>Depending on the information required to be provided by the manufacturers/suppliers and the mechanism for receiving, analysing and sharing this information with the stakeholders, sufficient safeguards should be introduced to ensure that information sharing does not run counter EU antitrust rules. |
| B.7.4. Adaption of legislation/inclusion of specific provision covering new manufacturing methods (decentralised, continuous manufacturing, etc). to ensure levels of quality and safety equivalent to current methods. |
| Same as A.7.3<br>The proposed measure has the potential to bring several product categories that are currently excluded from the legislation into the fold and provide regulatory certainty to manufacturers. These include magistral formulae (pharmacy-based preparation for an individual patient), radionuclides in sealed sources, hospital-manufactured medicines, and single-batch medicines. In addition, manufacturing methods such as decentralised manufacturing (where manufacturing occurs at different locations) and 3D printing-based methods could be accommodated.<br>Covering new manufacturing methods in the general pharmaceutical legislation has the main advantage of helping to standardise the methods themselves, quality control of the methods and resultant products and |

| Assessment |
|---|
| associated regulatory pathways at the EU level. Thus, there is a harmonisation benefit. Moreover, accommodating new technologies sends a positive signal to innovators as well as companies and will encourage more innovation and research activity and adoption of the new methods. There will be further knock-on effects on competition, competitiveness, and access to medicine. If greener manufacturing methods are used there will be an impact on environmental sustainability, but the likelihood and extent of that is unclear.<br>With more certainty over the manufacturing methods and the resultant products as well as more medicine developers adopting these methods, we could imagine a very high increase in the number of new therapies in comparison to the baseline. |

### Summary assessment of the principal costs and benefits by impact type

Table 46 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block G under Policy Option B and for each impact type.

*Table 46 Option B – Summary assessment of the proposed measures for quality and manufacturing*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.7.1 | - | - | - | - | - | -/+ | - | +/- | +/- |
| B.7.2 | +/- | +/- | +/- | + | +/- | +/- | + | +/- | +/- |
| B.7.3 | - | - | - | - | +/- | +/- | +/- | +/- | +/- |
| B.7.4 | -/+ | -/+ | -/+ | + | + | + | -/+ | + | -/+ |
| Overall impact | - | - | - | +/- | +/- | + | -/+ | + | -/+ |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Overall, modifying provisions on inspections and expanding oversight to all sites within a supply chain (including distributors and API manufacturers) will create additional transaction, compliance and administrative costs which might result in smaller players leaving the market and thus loss of choice and competition. Moreover, NCAs will need additional inspection capacity and training to accommodate the changes in the provisions and actors. On the other hand, a mandatory joint audit scheme for member states will allow greater efficiency, cooperation, and knowledge transfer across NCAs.

Adaptation of the legislation or inclusion of specific provisions to accommodate new manufacturing methods will improve international competitiveness, encourage greater research and innovation, and increase choice and competition in the sector. It would also have a direct impact on patients by making more treatments available. The other measures improve oversight of manufacturing but the quality standards are already high so there is unlikely to be greater added benefit to public health.

### Assessment of any synergies and tensions within the Policy Block

Policy elements B.7.1, B.7.2 and B.7.3 have synergies as they aim to improve quality and safety of medicinal products through improved oversight. Stronger supply chain oversight through increased inspections should work well with setting up a mandatory joint audit scheme and should also help to enforce the stronger overall responsibilities of MAHs.

### *12.4.8 Policy Block H (B.H): Addressing environmental challenges*

#### Assessment of the key impacts for the policy elements

Table 47 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

*Table 47 Option B – Assessment of the proposed measures for addressing environmental challenges*

| **Assessment** |
|---|
| C.8.1 Include assessment of the environmental risk of manufacturing into ERA, including main supply chain actors (API, raw materials) |
| This measure represents considerable additional burden for medicine developers and supply chain actors, and public authorities in terms of compliance and administration costs and review costs respectively. On the other hand, it will allow tracking of the environmental risks of manufacturing across the supply chain providing a more comprehensive assessment of the potential environmental impact of a new medicine. For example, if risk associated with active pharmaceutical ingredient discharges from manufacturing sites is included in the ERA, it would increase the relevance of the assessments by including a part of the life cycle of the product responsible for the highest environmental concentrations detected.[93] |
| B.8.2 Strengthen the ERA requirements and conditions of use for medicines, while taking stock of research under the innovative medicines initiative |
| The proposed measure should enable robust assessment of the environmental risks of pharmaceuticals as well as promote prudent use, supporting sustainable consumption and helping to minimise the environmental footprint of medicines. However, this may place slight additional burden on public authorities for reviewing ERA submissions (in case of additional data requirements) and monitoring medicine use (if required) as well as on businesses and other stakeholders responsible for complying with said requirements and conditions. |
| B.8.3 Include the AMR aspects into GMP to address the environmental challenges |
| This measure would help minimise amounts of antibiotics entering the environment via manufacturing and thus prevent emergence of AMR from pharmaceutical manufacturing. Recent evidence indicates the presence of a selection pressure for AMR within environments receiving wastewater from antimicrobial manufacturing, as opposed to environments receiving wastewater from municipal sewage treatment plants (containing antibiotics from human use) that do not receive waste from antimicrobial manufacturing.[94]<br>There would be the additional costs for businesses to comply with the AMR requirements in GMP and data requirements and for public authorities for enforcement of the requirements. This could present barriers for smaller actors.<br>The KPI would be amount of an antibiotic in waste and wastewater in µg/l. Suggested annual mean value for an erythromycin environmental quality standard (EQS) is 0.2 µg/l.95<br>For the current impact assessment, we would assume that compliance with the measure will result in levels below the EQS and thus there is a high likelihood of impact on sustainable production (environmental impact). |

#### Summary assessment of the principal costs and benefits by impact type

Table 48 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block H under Policy Option B for each impact type.

[93] Eeb. (2018). Policy options for regulating pharmaceuticals in the environment.

[94] WHO Expert Committee. (2020). *Annex 6 Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance*.

[95] UBA – Umweltbundesamt (Hrsg.) (2018) Empfehlungen zur Reduzierung von Mikroverunreinigungen in den Gewssern, Hintergrund, February 2018, Dessau-Ro lau, https://www.umweltbundesamt.de/sites/default/files/medien/1410/publikationen/uba_pos_mikroverunreinigung_final_bf.pdf

*Table 48 Option B – Summary assessment of the proposed measures for addressing environmental challenges*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.8.1. | - | - | - | - | - | +/- | - | + | ++ |
| B.8.2. | +/- | +/- | - | - | - | +/- | +/- | + | ++ |
| B.8.3. | - | - | - | - | +/- | +/- | - | + | + |
| Overall impact | - | - | - | - | - | +/- | - | + | ++ |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Policy Option B is unlikely to impact on areas other than sustainability and waste management since it does not mark a major departure from current requirements. The impact on patients and health systems will be neutral owing to the uncertain health impacts of pharmaceutical residues in the environment as well as lack of direct impact of the proposed measures on quality and safety of medicines.

### Assessment of any synergies and tensions within the Policy Block

No synergies or tensions.

### *12.4.9 Policy Block I (B.I): COVID-19 lessons learnt*

### Assessment of the key impacts for the policy elements

Table 49 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

*Table 49 Option B – Assessment of the proposed policy elements for COVID-19 lessons learnt*

| Assessment |
|---|
| B.9.1. Refusal of immature marketing authorisation applications. |
| The most significant efficiency gains would be for public authorities, which could save time currently spent on assessing immature applications and resolving internal differences of opinion as regards their evaluability or suitability for processing through the CMA pathway. As per baseline, we assume that there could be **2 to 3** marketing authorisation applications every year that do not initially request a CMA despite not containing enough data for standard marketing authorisation. This would likely lead to 2 to 3 immature marketing authorisation applications refused every year in the first one or two years, possibly increasing to 5 to 10 refused applications every year in the next 3-5 years as the evidentiary threshold is established. Industry would begin to recalibrate the acceptable levels of evidence in parallel and the numbers of weak applications should fall back to some minimum within 5 years, perhaps never quite falling below 2-3 a year over the remaining years through to 2035.<br>Overall, assuming an average annual reduction of 3-5% in the total number of applications for assessment and 100-120 applications annually, which are increasing at 5-10% a year (as per EMA annual report 2020), cutting assessments by 3-5% might result in a reduction of EMA / NCA costs of 2-3% (the work of the EMA committees is a major cost driver).<br>There could be a negative impact on cost for developers that are currently submitting immature marketing authorisation applications for valid reasons. For example, addressing an UMN may be difficult in terms of conducting large clinical trials. This may discourage developers of medicinal products for UMN if it is not combined with other policy elements. On the other hand, less immature data means HTA bodies and P&R |

| Assessment |
|---|
| authorities would be more able to assess therapeutic value, which could have a positive impact on access and affordability. Thus, the impact on healthcare systems could be negative (less developers working on UMN) and positive (more streamlined and coherent procedure leading to faster market launch). |
| B.9.2 Codification of rolling review for UMN |
| The most significant benefit would be to developers of medicinal products for UMN. The increased interactions with regulators could reduce uncertainty, the timeline for EMA scientific opinion (baseline = 150 days) and the total approval time (baseline = 251 days).<br>The impact will depend on the implementation of the system and the specific timeframes proposed by the EMA to respond to each rolling review cycle. As per baseline (COVID-19 pandemic), the average number of rolling review cycles was 2 cycles[96], and the number of days spent by the EMA on each rolling review cycle was 30 days[97].<br>Other factors will also be important, such as the details of the definition of UMN that will be applicable to the rolling review system and the specific requirements for each data package. As such, there would be significant cost to public authorities, even with our assumption that resources would be made available, new ways of working would have to be implemented and adapted over the years.<br>It is expected that such system would streamline the process of evaluating evidence for medicinal products for UMN and therefore increase the number of medicinal products approved by speeding up the process and by attracting new investments areas of UMN. This could also result in a positive impact on innovation rates and overall EU pharma industry output.<br>While patients and healthcare systems would benefit from more medicinal products available, there could be a negative impact on access due to more post-marketing authorisation requirements to allow P&R authorities to assess therapeutic value. Therefore, there is a risk that this policy element would increase the gap/time between availability (centrally approved) and accessibility (Member State market launch), which could affect poorer/smaller Member States disproportionately. |

## Summary assessment of the principal costs and benefits by impact type

Table 50 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block I under Policy Option B for each impact type.

*Table 50 Option B – Summary assessment of the proposed policy elements for COVID-19 lessons learnt*

| Policy elements | COB | Admin | SMEs | CTI | Internal Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.9.1. | - | +/- | - | - | +/- | +/- | + | +/- | +/- |
| B.9.2 | + | + | + | ++ | +/- | + | - | +/- | +/- |
| Overall impact | +/- | + | +/- | + | +/- | + | +/- | +/- | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element. Policy Option C – Summary assessment of the Incentives for innovation

## Assessment of any synergies and tensions within the Policy Block

Within the COVID-19 lessons learned Policy Block, the policy elements proposed under Policy Option B are largely complementary to each other. Refusing immature marketing authorisation applications while codifying rolling reviews for UMN provides a clear pathway for developers to submit their immature data sets. In comparison to the current system, where immature data create challenges for regulators (often leading to ambiguous decisions and/or

[96] https://doi.org/10.1016/j.clinthera.2022.01.001

[97] https://doi.org/10.1016/j.clinthera.2022.01.001

nudging developers towards CMA), this policy block B should decrease uncertainty, and facilitate developer/regulator interaction.

## 12.5 Policy Option C

### *12.5.1 Policy Block A (C.A): support for innovation, including unmet medical needs*

#### Assessment of the proposed Incentives for Innovation

*Table 51 Option C – Assessment of the proposed Incentives for Innovation*

| **Assessment** |
|---|
| Expedited regulatory pathways |
| C.1.1. Codification of PRIME in the legislation |
| same as B.1.1<br>The inclusion of the PRIME scheme within the legislation would give a strong signal to developers that the EU is committed to increasing support for UMNs.<br>It will also reassure developers that the scheme is permanent and that they continue to benefit from the active support that comes with PRIME designation (which is focused on medicines that promise a major therapeutic advantage in an area of unmet medical need). The scheme is well regarded by stakeholders (industry, regulators, health systems) and the EMA analysis of its first five years of operation found that PRIME designation is associated with faster assessment times and an improved likelihood of a positive recommendation for authorisation.<br>There should be no significant additional administrative or compliance costs for businesses, when compared with the current situation.<br>Codification may increase the popularity of the scheme still further, and that may increase the number of companies that have to bear the administrative costs associated with making an unsuccessful PRIME-eligibility request. The popularity of the scheme has increased in the recent past (+15% between 2019 and 2020), and we would expect to see further growth in future. This would be even more likely should the EU implement an additional period of regulatory protection for UMNs. These additional costs (linked with unsuccessful requests) are being limited by an equivalent expansion in the number of medicines accepted onto the scheme, which has also increased (from 23% in 2018 to 33% in 2020).<br>The impact on regulators should be broadly neutral, as while the scheme does involve additional effort to businesses with advice on the development of their PRIME-designated medicines, the resulting applications tend to be better framed and evidenced, making assessment more efficient and improving success rates for submissions (improving EMA productivity in this important area of UMNs).<br>Small biopharma firms have a particular interest in advanced therapies relevant to UMNs, and the codification and expansion of PRIME ought to have positive impact of SMEs. They benefit disproportionately from EMA advice, where larger developers have considerably more experience in preparing an application for assessment. Moreover, for some start-ups (e.g. cell and gene therapy companies), PRIME may have the effect of a 'seal-of-approval,' which could improve their investability and market value.<br>In the longer term, codification should reinforce the regulator's wider efforts to reduce UMNs, improving treatments, reducing hospitalisations and improving patients' quality of life.<br>As with the other regulatory proposals designed to focus developers' attention on UMNs, there is a small risk this will displace investment in other areas of medical research, possibly even slowing down the rate of progress in other disease areas that have good treatment options currently, but which still constitute a major health burden. |
| *Repurposing* |
| C.1.2. Establish a binding system for scientific assessment of evidence for repurposing off-patent medicines (scientific opinions or monographs) that are used by marketing authorisation holders to include a new indication for their products. Plus simplify the obligations regarding certain activities associated with holding a market authorisation in order to facilitate non-commercial entities (e.g. academic) to become marketing authorisation holders. This could be combined with possibility for private, public partnerships for manufacturing and safety monitoring (e.g. for **repurposing** of authorised medicines or hospital preparations). |
| Same as B.1.2.<br>The policy might lead to developers investing more heavily in new indications of their recently approved medicines, with the additional costs of seeking better, earlier scientific advice being offset by a greater likelihood of seeing a new use authorised<br>There may be a reduction in administrative and compliance costs associated with repurposing, as compared with the authorisation of new medicines |

| **Assessment** |
|---|
| May provide opportunities for developers to cost-effectively expand their portfolio of medicines / indications (improving R&D productivity); may provide a platform for clinical researcher and academics to play a fuller role in development work and trials<br>MAHs can be reluctant to apply for new indications of existing older medicines close to the end of their period of regulatory protection or where going on-label for new indications could affect the commercial value of any existing medicines used for the same indications[98] or otherwise for liability reasons.<br>This policy element will help broaden access to what are otherwise rather selective and uneven use of safe and effective medicines off-label. It will be a much stronger intervention than the non-binding system. In the longer term, we may see more treatment options for patients and improved geographical access. Its impact would be strengthened by C.1.3 (a period of additional data protection for major public health interest) and C.1.4 |
| C.1.3. Additional data protection period for the new evidence generated to support repurposing of existing products if considered as major public interest for public health or innovation (i.e. criteria for accelerated assessment). |
| Industry may benefit from the (lower cost) of repurposing an existing medicine for use with an UMN, where that insight has arisen based in part on evidence gathered by healthcare providers or academics.<br>While repurposing costs are substantially lower than the costs for wholly new development programmes, the costs can run into the many tens of millions and take several years, and the ROI is often too weak for many older medicines. An additional period of data protection (+1 year becomes +2 years) could help offset that ROI challenge, at least for that subset of extensions where there is a major public health interest associated with an extension of an existing medicine.<br>May increase the workload for regulators (more assessments, more enforcements).<br>May increase the size of the medicines bill for health systems; may reduce the high costs associated with hospitalisations of people with complex conditions and no effective treatment. |
| *Adaptation of the regulatory protection* |
| **C.1.4. Reduce duration of incentives for originators from 8+2 to a new combination (e.g. 6+2) taking into account the interaction between data protection and intellectual property rights** |
| same as B.1.4<br>For originators, a reduction in the period of regulatory protection will reduce overall income and profitability for new medicines since generics companies will be able to enter markets and begin to erode monopoly prices a year earlier. The new period of protection may prompt developers to increase prices in general to protect their current business model or otherwise rebalance their portfolios towards those market segments with greater commercial potential.<br>SMEs originators may find it more difficult to invest in riskier novel medicines given the reduction in future returns on investment and their relatively weaker market position when it comes to negotiating prices.<br>It could weaken the global competitiveness of EU based originators overall, compared with the current situation, unless prices are adjusted upwards to reflect the new protection period, and ensure global ROI norms can continue to be achieved.<br>The threat to EU-based originators will be offset to some degree by giving a boost to Europe's generic industries, broadening their portfolios, and potentially creating a prime-mover advantage in global markets.<br>Considering that this policy element affect SMEs more than larger firms and the latter are based in bigger economies, while the former may be based in smaller economies this may affect the functioning of the internal market and limit access to medicines across Europe. This will also be the case if some companies adjust prices upwards in response.<br>Health payers may benefit from lower average lifetime costs for medicines due to earlier generic entry and patients may benefit if those savings are used in the health care sector. The extent of these benefits will depend on originators response to the reduced incentives, and it is highly likely that average prices will be adjusted upwards in some degree to offset the shortened period of protection. |
| **C.1.5. Authorised medicines with demonstrated ability to address UMN get +1 year data protection** |
| A +1 year period of premium pricing (during the extra year of data protection) will offset the higher development costs and / or lower market volumes associated with a proportion of UMNs, whereby a larger number of all UMNs would pass the private sector's ROI thresholds.<br>While companies cannot determine in advance which products will be successful and make a smaller or larger positive contribution to their overall income and profitability, the additional period of regulatory protection will |

[98] https://www.fiercepharma.com/sales-and-marketing/sanofi-pulls-campath-to-clear-way-for-higher-priced-lemtrada

| Assessment |
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| have a positive impact on estimates of potential income and profitability used in stage-gate assessments. It will also mean payers will have larger costs for the medicine for an additional year.<br>The additional period of protection would improve the competitiveness and investment flows towards EU based originators producing UMN medicines.<br>Increasing developers focus on UMNs may increase their development and regulatory costs, in some limited degree, as applicants would need to meet the UMN criteria.<br>This incentive is expected to focus and possibly increase investments in R&D resulting in a higher number of novel medicines addressing UMNs as compared with the baseline and an increase in treatment options, treatments and improved patient health.<br>The increased flow of medicines for UMNs would have a strongly positive benefit for patients that currently have to live with debilitating conditions with no effective treatment options. The health systems should also benefit from the availability of more effective medicines for these patient groups, making care more cost-effective and reducing costs associated with avoidable hospitalisations.<br>We assume this extension would increase by around 10% the numbers of UMN products being developed, which would amount to 2-4 new authorisations annually. Our modelling work suggests this would generate #320m-€640m in additional protected sales annually, based on the €160m annual EU revenue for the average product. The increasing number of UMNs – with a longer period of RDP – would lead to additional costs for health payers on the order of €163m-€326m, based on the difference between the premium priced product (in the final year of RDP) and the price of the first generics to enter the market (c. 50%). We estimate that the generics industry would see a loss of income on the order of €77m-€154m as a result of the +12-month delay in market entry. |
| **C.1.6. Special incentive bonus: if data package includes comparative trial with standard of care (+6 months)** |
| Same as A.1.4<br>We assume a 6-month extension might lead to the use of comparative trials for an additional 8-10 products a year. We assume the additional costs of a comparative trial design might amount to €10m.<br>With average additional peak income (EU) of €160m, a 6-month extension might secure an additional €80m in income, or €640m-€800m a year in additional protected sales for originators.<br>The bonus would result in a delay in the market entry for generics for these additional products, which might amount to a loss of income of around €154m-€192m a year for the generics industry<br>There would be some additional costs for health payers, which result from the delay in the market entry of generic competition. This may amount to €326m-€408m a year.<br>This should deliver faster access to markets and costs savings thanks to improved reimbursement decisions<br>Moore et al (2020) in a review of 101 new FDA medicines (225 individual clinical trials), found the median cost of an individual clinical trial was around $19m (range = $12m-$33m). They found the Phase 3 development costs almost doubled with second trial (albeit the single biggest cost driver is the number of patients).<br>Moore et al identified 62 (27.5%) of the total set of 225 clinical trials had a comparison group rather than a placebo or uncontrolled trial. |
| C.1.7 Require transparency on public contribution to research and development costs in relation to clinical trials included in the marketing authorisation application (this information would be published) |
| This proposal for increased transparency around public support for R&D in clinical trials, is narrower than the proposal under Policy Option B, where the issue of transparency covers any aspects of public support for medicines development, including various tax reliefs.<br>This option would be simpler to implement as it relates to the direct support of specific clinical trials through publicly funded R&D grants. This information is more likely to be in the public domain already (through online, public grants databases) and does not require a complex financial exercise to link / attribute the public support to a specific trial and resultant application for a new medicine. It is therefore likely to meet with slightly less resistance from industry on the grounds of commercial confidentiality.<br>Greater transparency around public support for R&D may strengthen pricing and reimbursement agencies' position when negotiating with MA holders, helping to place a downward pressure on prices and thereby helping to maintain or improve access to medicines with concomitant benefits to patient health.<br>Administrative costs may increase for firms needing to prepare the required information.<br>Understanding the scale of public contributions to clinical trials research would need to be established over time, from the evidence submitted by applicants. We found no good data on this in the wider literature.<br>The analysis of public support would be reported by applicants in a section of the Common Technical Dossier. This would affect 4,000 clinical trials authorised each year in the EEA. This equals approximately 8,000 clinical-trial applications, with each trial involving two Member States on average.<br>The statistics show that around 60% of clinical trials are coordinated (sponsored) by industry and around 40% by non-commercial organisations, mainly academia. However, these trials do not necessarily relate to new medicinal products that will be submitted to the EMA and where an academic trial does feed into an industry application it is possible that trial would have been partly funded by industry or a research charity with little or no support from public R&D funders. |

| **Assessment** |
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| C.1.8 Give regulators the possibility, in the context of a marketing authorisation, including a conditional marketing authorisation, to impose a **post authorisation obligation** for **additional studies** on the effectiveness compared to the standard of care |
| same as B.1.8<br>Imposing a post-authorisation obligation for MAHs to include new information about the effectiveness of the medicines (i.e comparative clinical trials) may impose additional costs on MA holders, albeit this may be a matter of timing and degree, as many businesses carry out additional research on the cost-effectiveness of their medicines with a conditional approval. The EMA annual reports show that around one third of all medicines that have been granted a CMA since 2006 have gone on to be granted a full marketing authorisation (i.e. sufficient additional evidence has been gathered to confirm effectiveness). As such, it may increase and bring forward costs associated with such studies for tens of businesses. Those costs might amount to €20-€50m for each product.<br>MA holders will have to bear some additional costs and there may be a small increase in the number of medicines that are found to be less cost-effective than had been anticipated. This last point could impact on the ability of individual companies to raise finance or otherwise weaken their competitive position, but there would be no substantive impact – positive or negative – on overall competitiveness, or the functioning of the internal market.<br>This obligation would help to confirm the relative effectiveness of the products in question several years earlier than is the case currently. The EMA annual report (2020) shows that the 30% of CMAs that have been granted full marketing authorisation took an average of 3.5 years post-authorisation to get their products fully authorised. This would allow more timely action in respect to individual medicinal products – e.g. withdrawal or more widespread use – and would indirectly give HTAs and payers greater confidence in the CMA pathway.<br>There would be some additional administrative costs for the EMA and NCA staff working with them following from the increasing numbers of assessments of these additional studies and consideration of the case for granting full authorisation.<br>The improved clarity as regards the relative cost-effectiveness of medicines should increase confidence across health systems in making full use of those products, and thereby benefiting patient health. |
| C.1.9. **Breaking market protection** in case of urgency and insufficient coverage by authorised medicines (compulsory licensing) |
| same as B.1.6<br>There has only been one instance of an EU member state using a Compulsory Licence, as such this is an ultra-low probability event, and the link with the EU general pharmaceutical regulation is about ensuring external coherence.<br>There should be no or minimal direct impact on EU pharma in general, given it would be implemented indirectly and by exception and for a localised and time limited period.<br>It may increase burden on regulators and expand the numbers of government bodies that must become involved in explaining their use of this regulatory exception<br>The time and costs involved in developing safe and effective copies of protected medicines may mean that the policy lacks the speed or certainty to respond with confidence to public health crises |

### Summary assessment of the Incentives for innovation

Policy Option C reduces the current standard period of regulatory protection for new medicines and requires originators to disclose information in their applications regarding the level of public funding of their clinical trials. There is a special bonus available where the data package includes a clinical trial.

Policy Option C does not include any special incentives relating to UMNs, beyond the codification of PRIME in the legislation, which has some relevance to originators working on new medicines targeting UMNs and hoping to benefit from the additional advice that follows from PRIME designation.

MAHs are given increased obligations regarding the conduct of additional studies relating to for example, CMAs.

Policy Option C gives relatively more weight to repurposing, and the overarching objectives of improved access and affordability. It seeks to deliver a significant expansion in the number of extensions of existing medicines to new indications by targeting the under-exploited off-patent and off-label use of older medicines, through a combination of a more inclusive definition of scientific evidence for repurposing, with the simplified obligations for non-commercial entities to become MA holders (possibly through public private partnership) and

the obligation on MA holders to include a new indication when supported by that scientific evidence and assessment.

There is an additional period of data protection available for these repurposed medicines, where the extension is judged to be a major public interest for reasons of public health or innovation.

*Table 52 Option C – Summary assessment of the Incentives for innovation*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.1.1 | + | +/- | + | +/- | +/- | + | - | - | +/- |
| C.1.2 | + | + | +/- | - | ++ | ++ | +/- | + | +/- |
| C.1.3 | + | - | + | + | ++ | +/- | +/- | + | +/- |
| C.1.4 | -- | +/- | -- | -- | - | --- | + | - | +/- |
| C.1.5 | ++ | +/- | - | + | +/- | + | - | + | +/- |
| C.1.6 | + | - | + | +/- | +/- | + | + | + | +/- |
| C.1.7 | - | - | - | +/- | +/- | +/- | + | +/- | +/- |
| C.1.8 | +/- | - | - | +/- | +/- | + | - | + | +/- |
| C.1.9 | - | - | - | - | - | - | - | +/- | +/- |
| Overall impact | ++ | -- | - | - | ++ | ++ | +/- | ++ | +/- |

### Assessment of any synergies and tensions

Within the Innovation Policy Block, the policy elements proposed under Policy Option C are largely complementary to each other, whereby the proposal to reduce the period of regulatory protection for the standard innovative medicines pathway (by 1 year) is mirrored by a policy element to provide a +6 month special bonus for data packs that include comparative trials. The proposed new obligations around the transparency of public funding of clinical trials research may serve to reduce industry's interests in public R&D grants.

Relatively greater weight is given to repurposing under Policy Option C, with a general reduction in the level of support for innovation, at least through the standard EMA regulatory pathways. The ability to impose a requirement on MA holders to carry out additional studies post-authorisation would not reduce the attractiveness of the EMA's various expedited regulatory pathways, but should rebuild support among member states (HTAs, health payers) for conditional marketing authorisations in particular.

### *12.5.2 Policy Block B (C.B): Antimicrobial resistance*

### Assessment of the proposed incentives for innovation and prudent use

Policy Option C is similar to Policy Option B, regarding the proposed measures to encourage more prudent use of antimicrobials. It would reinforce these stewardship measures with the addition of a new requirement for MA holders, whereby developers must prepare an AMR lifecycle plan as part of their marketing authorisation application.

Policy Option C omits the play or pay model in favour of a stronger incentive, a transferrable voucher, similar to that in Policy Option A.

The proposed interventions are assessed in the table below:

*Table 53 Option C – Assessment of the proposed incentives for Innovation and prudent use of antimicrobials*

| **Assessment** |
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| C.2.1 Novel antimicrobials (new active substance, new mechanism of action, first in class) fall in the central procedure's mandatory scope |
| As this policy element formalises what happens in practice already, there would be no additional impact on the development of novel antimicrobials or their more prudent use. |
| C.2.2. PRIME like support scheme, including rolling review |
| Same as B.2.2<br>If the system in place for rolling reviews is easy for SMEs and large companies to navigate and flexible, there is potential for a large positive effect on EU pharma businesses by increasing company-regulator interactions in areas that may not be currently attractive for business to invest in R&D. This could result in a positive impact on innovation rates and overall EU pharma industry output.<br>The targeted survey revealed that industry respondents were broadly in favour of codifying rolling reviews, in particular for new technologies or major innovations in medicinal products. However, the demands on Rapporteurs are high, with significant increase in workload; one NCA interviewed stated that the COVID-19 pandemic rolling review required approximately 50% increase in resources/workload. The demands on companies are also relevant, as the process requires more communication and clarifications (data packages may not be structured, may contain errors, etc). Furthermore, rolling reviews bring uncertainty on the added therapeutic value of medicines and inequity of access is larger for orphan medicines. Considering these reasons, some civil society and public authority respondents were against codifying rolling reviews in a way that would expand the scope of use of this procedure outside exceptional medical conditions and public health emergencies. |
| C.2.3 Require companies to develop AMR lifecycle management plan as part of marketing authorisation to set out coherent strategy for prudent use, stewardship monitoring and reporting (including consideration of optimised package size and rules on disposal) to address the environmental challenges as well). |
| The AMR Product life-cycle management (or PLCM) document would provide an opportunity for continuous development and improvement, a framework for change management to facilitate assimilation of novel control strategies, analytical procedures, and process tools as they become available to the industry.[99] It may involve reassigning some resources from other areas within companies to develop the AMR PLCM document required for antimicrobials.<br>Expanded surveillance would have no direct impact on EU pharmaceutical companies conduct of business. Indirectly, and in the longer term, improved surveillance data may help to accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for industry overall. The legislation and accompanying guidelines would have no direct impact on EU pharmaceutical manufacturers, wholesalers or pharmacies, indirectly it may lead to an expansion in overall sales volumes and income, as pharmacies buy smaller volumes more frequently, prescribers push for smaller pack sizes, and patients a less likely to self-medicate.<br>Even though preparing the AMR PLCM document may take some time, establishing appropriate mechanisms to share information with regulators and possessing records from inspection or assessment activities can mitigate increased burden on the MAH later on. Any implications for enhanced environmental risk assessments could be more challenging for SMEs to carry out / afford.<br>The AMR PLCM document as any PLCM document could provide an opportunity for continuous development and improvement and assimilation of novel control strategies, analytical procedures, and process tools as they become available to the industry.[99]<br>An expanded surveillance system could impact the costs borne by public authorities, both one-off costs associated with system development, capital investment and training and recurrent costs associated with additional data collection and additional data curation and storage costs.<br>Stricter disposal rules would bring additional costs for public authorities, with a substantial one-off cost for EU / MS authorities in developing and championing the roll-out / adoption of the guidelines and additional ongoing costs for national authorities in maintaining / monitoring adherence and for the EMA and its advisory groups in tracking developments and giving ad hoc advice.<br>Stricter disposal rules / smaller pack sizes may increase the unit costs of antimicrobials and stricter management of stocks may also add costs.<br>Patients should see a benefit from a reduction in self-medication using unused and out of date medicines.<br>The AMR PLCM document would cover the whole lifecycle of antimicrobials and help address AMR in the human and animal health and plant protection sectors. |

[99] Schiel and Turner. The NISTmAb Reference Material 8671 lifecycle management and quality plan. Anal Bioanal Chem. 2018.

| **Assessment** |
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| More prudent use and more informed production and disposal of medicines would help reduce the level of human-related active ingredients getting into the environment. |
| **C.2.4. Optimise package size** |
| Same as B.2.3.<br>This policy element would encourage the use of smaller package sizes, thereby increasing manufacturers' costs relating to product packaging and distribution.<br>It may also increase the cost of antimicrobials for health payers (smaller package sizes are more costly), including an increase in average prices for a course of treatment for an individual patient, albeit these price increases should be offset in some small degree by lower levels of consumption.<br>It may have implications for storage costs (more space required) but may ease dispensing and take pressure off pharmacists' local storage requirements.<br>We don't foresee additional extra administrative costs on the side of businesses and authorities.<br>By helping to reduce overall levels of consumption, this policy element may contribute in some small degree to reducing AMR and avoiding AM releases to the environment. The smaller pack sizes will increase packaging waste, which would increase costs associated with waste management and recycling. |
| **C.2.5. Tighten prescription requirements for antimicrobials** |
| Same as B.2.5<br>While prescribing policies are a matter for national authorities in the first instance, the legislation can invite member states to do more to bring practice in line with international standards.<br>These obligations and guidelines do not affect industry directly. Indirectly, and if successful, better prescribing would accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for the pharmaceutical industry overall and particularly those generics companies that supply older, lower-cost, broad-spectrum antimicrobials.<br>Indirectly, there may be a differential impact on the generics industry and particularly that sub-set of pharma businesses that include older, broad-spectrum antimicrobials in their portfolio. There may be a small benefit for MA holders with more specific antimicrobials, if prescribers both reduce overall prescription numbers and switch from cheap, broad-spectrum medicines to more specific (more expensive) antimicrobials.<br>Indirectly, tighter prescription is likely to reduce usage and that may weaken the return on investment for antimicrobials in general, worsening the investment case in an area of medicines research that is already regarded as being uneconomic.<br>Indirectly, health systems may see savings because of better prescription practices and reduced consumption, albeit this may be offset by increased costs associated with diagnostic tests and a switch to more costly antimicrobials. If successful, this policy element should reduce consumption and that in turn should reduce the potential for negative environmental impacts. |
| **C.2.6. Transferable voucher – independent and in addition to data/market protection for antimicrobial products.** |
| Similar to A.2.2<br>The right to be transferred relates to the transfer of the right to extend the data protection by a length to be determined. The assumption/calculation is based on an extension of data protection by 1 year.<br>The antimicrobials that would be applicable to generate this right are all antimicrobials or a subgroup e.g. antibiotics only or their alternatives which either (i) represent a new class and/or new mode of action, addressing new target or absence of known cross-resistance (WHO innovation criteria) or candidates targeting priority pathogens (WHO list for antibiotics) or innovative platform technologies able to confer break-through clinical benefit, (ii) ground-breaking innovation within an existing class.<br>Given the current pipeline, and the scale of the incentives foreseen, we assume the average number of TVs will be one a year (albeit U JAMRAI predicts fewer).<br>Companies may use a TV on existing successful medicines that are still covered by data protection, and which are still at least 2 years (EFPIA proposal) away from the expiry of their data protection period. ,<br>The TV would be most relevant to products where the last defence before generic entry is the regulatory protection. For those where there is a 10+ years patent or SPC protection, the extended data protection does not give any benefit. Hence, only a part of all products could benefit from a TV.<br>In principle the extension would need to be sufficient to provide a substantial incentive to compensate for the development of a new antibiotic, which is estimated to be on the order of €1.2bn. However, the EU market is some 20% of the total pharmaceutical market globally, and so a proportionate contribution to the development cost with the EU voucher may be a sufficient incentive. It would be possible for companies to receive the right to a TV for antimicrobial products that were already in the pipeline ahead of the implementation of the new regulation, to generate additional income / profits within 2-3 years of implementation, and thereby underpin an early expansion in investments in novel antimicrobials.<br>Based on the application of a voucher to an average top-10 product, we estimate an originator would secure an additional €543m in non-contested sales because of the 1-year extension. |

| **Assessment** |
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| There would be a cost to the generics industry of a year's delay on the order of €164m.<br>There would a cost to the health system too, which we estimate at €283m. We further estimate the patient + payer monetised loss would be on the order of €441m<br>Some vouchers may be sold rather than used directly by the developer of the antimicrobial and we have estimated the average sale value of a voucher at €360m.<br>Each year, about 33,000 Europeans die as a consequence of antibiotic-resistant bacteria. On average, a hospitalised patient with antibiotic-resistant infections costs an additional 10,000 to 40,000 USD. The expansion in the development and authorisation of novel anti-microbials should help to manage and even reduce AMR, with fewer hospitalisations and deaths, although it has so far not been possible to estimate the scale of these potential benefits, in order to compare with the social costs of the incentives for taxpayers and health payers. |
| C.2.7. Consider adapted system for authorisation of phages therapies and other alternative products |
| Same as A.2.3.<br>This policy element would support the development of phage therapies potentially increasing the number of companies willing to invest and develop these therapies which will in turn increase competition, reducing prices of these therapies. The use of phage therapies may also reduce healthcare costs/budgets since phages are an inexpensive natural resource present in the environment, and offer immense potential as an alternative when antibiotics are rendered ineffective due to bacterial resistance . Finally, by reducing the use of antibiotics it would help reduce the presence of antibiotics in the environment. |

## Summary assessment of prudent use of antimicrobials policy

Option C would be expected to catalyse an improvement in prescribing practices and stewardship by combining the stewardship measures set out here and under Policy Option B with the addition of an AMR lifecycle action plan.

Option C would provide substantive direct support for innovation, through the introduction of a transferable voucher, which would reinforce the investments of global MNCs active in the development of novel antimicrobials. The adaptation of the system for the authorisation of phage therapies may catalyse increased investment in this emerging and innovative technology.

*Table 54 Option C – Summary assessment of the proposed incentives for prudent use of antimicrobials*

| Policy elements | COB | Admin | SMEs | CTI | Internal Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.2.1 | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| C.2.2. | + | - | + | +/- | +/- | + | - | + | +/- |
| C.2.3 | +/- | - | +/- | +/- | +/- | +/- | - | + | + |
| C.2.4 | - | +/- | +/- | +/- | +/- | +/- | - | + | + |
| C.2.5. | +/- | +/- | +/- | +/- | +/- | +/- | - | + | + |
| C.2.6. | +++ | -/+ | +++ | ++ | -/+ | +++ | --- | + | +/- |
| C.2.7 | + | +/- | +/- | + | + | + | - | + | + |
| Overall impact | +++ | - | +++ | ++ | +/- | +++ | --- | ++ | + |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

*Assessment of synergies and tensions within the Policy Block*

Within the AMR Policy Block, the policy elements proposed under Policy Option C are largely complementary to each other, with the mandating of the use of the Central Procedure dovetailing with the proposal for EMA create a PRIME-like scheme for AM products. The Transferrable Voucher would reward antimicrobial innovators with an additional period of regulatory protection for their other medicines.

The adaptation of the system for the authorisation of phage therapies is a further complementary initiative that recognises the potential for this emerging and innovative technology to make a substantial contribution to combatting AMR. Moreover, the proposals on prescribing practices, package size, and disposal all work well together in supporting more prudent use. The expansion in the scope of the existing surveillance system would also provide an important means by which to track progress in environmental management across the EU. Lastly, the AMR PLCM would provide a framework for the optimal use and good stewardship of individual medicines.

### *12.5.3 Policy Block C (C.C): Future proofing*

Option C is a refinement of the current arrangements, with seven principal interventions that are discussed in the table below.

*Table 55 Option C – Assessment of the proposed measures for Future Proofing*

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| C.3.1. Adapted regulatory framework framework (*e.g. adapted requirements, authorisation procedures, collection of post-authorisation monitoring data*) for certain categories of novel products/technologies (e.g. personalised medicine, medicines combined with self-learning artificial intelligence, medicines that contain or consist of GMOs, platform technologies) or low volume products (hospital preparations) on the basis of well-defined conditions and respecting the principles of quality/safety/efficacy. Such frameworks could be adapted or expanded through delegated acts to set the technical framework that can be adapted to emerging scientific and technical advances (adaptive framework). Where applicable, such delegated acts should be developed in close coordination with other relevant competent authorities such as e.g. medical devices, IVDs or substances of human origin. |
| C.3.1 has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. It would also address the issues of current technological advancements that are not adequately legislated for and provide the legislation with a mechanism of keeping pace with technology through both facilitating adaptation and drawing on the expertise of deeply engaged stakeholders with in-depth technical knowledge of emergent areas. However, there would be an associated increase in administrative burden due to a likely expansion of the number of specific non-legislative (soft law) tools that would require development, maintenance, review etc. and ongoing need for feedback loops, iteration and adopting delegated acts. EMA and the regulators need to stay in control and ensure that the soft law tools are meeting the overall objectives of the legislation since the incentives and alignment of all stakeholders (some of whom have valuable technical expertise that this framework is designed to harness) is not implicit |
| C.3.2 Clinical trials: a risk-based approach is applied to determine when a specific GMO assessment is required. Where required, the assessment of the GMO aspects of investigational medicinal products is performed by EMA, within the maximum timelines defined in the Clinical Trial Regulation (centralised assessment). |
| This is the same as A.3.2<br>Clinical trials for investigational medicinal products (IMPs) for human use that contain or consist of GMOs are subject to both clinical trials and GMO legislations under national competences. This causes delays in clinical trials as the directives are not uniformly interpreted or applied between MSs and is especially problematic for clinical trials that are conducted over multiple MSs. These differences in interpretations also impact on the authorisation of GMO-containing medicinal products that fall under the mandatory scope of the centralised procedure creating complexities for developers as different MSs have different requirements and stakeholders involved, ultimately causing regulatory burdens and delays in market authorisations.<br>A.3.2 has potential to improve the efficiency of GMO assessment and thus accelerate authorisation of GMO-containing medicinal products by focussing regulatory efforts on GMO containing medicines that pose the greatest threat to the environment. A centralised approach to GMO assessment has already been adopted by the United States where the review of medicinal products containing GMOs has been centralised within the FDA to improve efficiency and regulatory agility. |

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| C.3.3 Adapt certain definitions, including that of medicinal product and *delink scope from industrial process* to address technological developments, gaps/borderline questions, taking into consideration the views of regulatory authorities for other relevant legal frameworks (e.g. medical devices and blood, tissue and cells) - linked to scope of the legislation. |
| C.3.3 has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. Delinking scope from industrial process would immediately bring under regulation several potentially excluded products and processes – most notably novel manufacturing such as bedside such as pharmacoprinting. It would be important that upon their being brought in scope the GMP was able to adequately accommodate them or that sufficient alternative tailored guidance was available. Addressing gaps in the legislation would impact positively on patient safety though could cause a (likely short term) reduction or delay in access while adaptations for compliance to greater regulation were made. There would be additional regulatory burden to implement the extended scope of the legislation. However, long term the efficiencies and predictability are anticipated to increase investment and innovation, reduce the time to access and improve patient safety. |
| C.3.4. For specific cell-based (ATMP) medicinal products adapted regulatory requirements under the pharmaceutical legislation to facilitate production in the hospital setting (improved "hospital exemption" mechanism) and respecting the principles of quality/safety/efficacy. [*link with revision of BTC legislation*] |
| ATMPs prepared "on a non-routine basis" for individual patients can by granted a hospital exemption by individual member states and can then be produced in the hospitals, exempt from the legislation scope which would require market authorisation and following GMP. This reflects a large proportion of ATMP development being undertaken by non-commercial entities (hospitals, research institutions, academia etc) for small patient numbers and was anticipated to increase ATMP development, improve timely access to ATMPs at affordable prices. The granting of the exemption has a lower evidence burden (including for safety and efficacy) than market authorisation and production of ATMPs in the hospital setting is not as strictly regulated in terms of batch-batch or patient-patient quality, safety and efficacy consistency.<br><br>Our understanding is that C.3.4 responds to this issue by the legitimising of hospital production increasing regulation such that it is more robust. In the context of ATMPs this would go alongside and require amendments to the hospital exemption which may include increased requirements of efficacy and safety demonstration in order to be granted, EU central oversight to harmonise pharmacovigilance across the same products, increased clarity to minimise differences in interpretation. In the case these were enacted then limitations of the number of patients treated could be removed thus facilitating hospital production under the new legitimate production method.<br><br>Increased patient safety through greater evidence burden for the exemption and then more consistent hospital production<br><br>More hospital production as patient numbers can be increased once this is removed from the exemption – better access and more data though we may expect a short-term reduction in ATMP access as production comes under regulation. Simultaneously as such an increase in production may make the market less attractive for commercial developers there could be a further withdrawal by them and potentially less ATMPs being picked up for MA as spin-offs by more commercial actors. Conversely, we may see commercial actors becoming more involved in development if they are able to access the hospital production route rather than MA – this may support more public-private partnerships.<br><br>There is some risk that research by SMEs, academics, and other non-commercial entities (currently the main stakeholder in ATMP development) reduce their activities as the costs increase through the need to have trial data and GMP manufacturing capability in order to be granted hospital exemption.<br><br>More transparent and predictable which may also encourage investment – by both commercial and non-commercial entities. |
| C.3.5. For specific products (named in annex – e.g. keratocytes etc.) less complex cell-based medicinal products to be defined on the basis of clear risk-based approach criteria - two sub-options could be explored in this regard:<br><br>C.3.5a. adapted requirements <u>within the pharmaceutical legislation</u> and authorisation by pharmaceutical national competent authorities (NCAs);<br><br>C.3.5b. to provide for a mechanism to <u>exclude</u> these medicinal products <u>from the scope</u> of the pharmaceutical legislation (in consultation with relevant authorities) and transfer them under the blood tissue and cells (BTC) legislation with authorisation by BTC NCAs |
| There are significant regulatory hurdles for less complex cell-based products (such as 'legacy products' existing before ATMPs) that are classed as ATMPs and subject to related standards. Many of these products could be produced in hospital settings. Additionally, there are borderline issues between the BTC and ATMP frameworks with some differing interpretation and classification between member states including some delineation reliant on the presence of an industrial process, no definition of which currently exists.<br><br>In theory, C3.5.a and C.3.5b should bring greater clarity around borderline products and simplify legislation for the less complex cell based medicinal products which would bring efficiencies and predictability. However, since both elements involve processes conducted at member state level there exists a potential for heterogenous interpretation and application. Such an outcome could impact negatively on patient safety as well as further exacerbate existing issues around ATMP classification and differentiation from BCT. |

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|---|
| Depending on how C3.5.a and C.3.5b are implemented these measures may represent an increased regulatory burden for NCAs. |
| C.3.6. Introduction of a regulatory sandbox environment, especially in the context of the approval and oversight of complex/cutting-edge products especially those linked to the concept of a 'medicinal product' |
| We understand the purpose of the regulatory sandbox environment is to create an 'agile, evidence-based and resilient framework' which fosters competitiveness, growth, sustainability, and regulatory learning' to accelerate innovation of complex/cutting-edge medicinal products.<br>Sandboxes are increasingly being used in healthcare settings[100]. This has been inspired from the success of first regulatory sandboxes in the FinTech sector, which have helped businesses to attract investment and increase speed to market by 40% compared to the regulator's standard authorisation times[101]. Thus, sandboxes have the potential to facilitate EU patients getting faster access to complex /cutting edge medicinal products. |
| C.3.7. Create a central *classification mechanism* for advice on whether products are medicines or not, building on the current EMA Committee for Advanced Therapies (CAT) mechanism for ATMPs to all medicinal products (borderline products) in close coordination with other concerned authorities in particular in the frameworks of medical devices and substances of human origin. |
| This is the same as B.3.4.<br>Medicines are increasingly being used in combination with a medical device, usually to enable the delivery of the medicine. However, these combinational products have brought regulatory difficulties for NCAs in terms of uncertainty whether they should be classified as a medical product or medical device and what regulatory framework applies.<br>C.3.7. would improve consistency of the classification of borderline products and the resulting choice of the most appropriate pathway through the EMA committee structure. This should harmonise coordination between concerned authorities in particular in the framework of medical devices and substances of human origin, and thereby deliver some small efficiency gains and avoid assessment committees being distracted from their assessment work by definitional questions. It may also improve the overall timeliness of assessments. The creation of a central screening mechanism may be timely as more definition questions arise for example, 1 in 4 centrally approved medicines typically include a medical device component. Success would depend on EMA finding the capacity to deliver relevant advice at speed. |

*Table 56 Option C – Summary assessment of future proofing*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.3.1 | ++ | + | + | ++ | + | ++ | --- | + | +/- |
| C3.2 | + | + | +/- | + | + | ++ | - | + | +/- |
| C.3.3 | + | + | + | + | ++ | + | +/- | ++ | +/- |
| C.3.4 | +/- | - | +/- | +/- | +/- | + | - | + | +/- |
| C3.5a. | + | + | +/- | +/- | +/- | +/- | - | + | +/- |
| C3.5b. | + | + | +/- | +/- | +/- | +/- | +/- | + | +/- |
| C3.6 | + | +/- | ++ | + | + | ++ | --- | + | +/- |
| C3.7 | + | + | + | + | + | + | +/- | + | +/- |

[100] European Commission. (2021). *Proposal for a regulation of the European Parliament and of the Council laying down harmonised rules on artificial intelligence (artificial intelligence act) and amending certain union legislative acts COM/2021/206 final*. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52021PC0206

Leckenby, E., Dawoud, D., Bouvy, J., & Jónsson, P. (2021). The Sandbox Approach and its Potential for Use in Health Technology Assessment: A Literature Review. In *Applied Health Economics and Health Policy* (Vol. 19, Issue 6, pp. 857–869). Adis. https://doi.org/10.1007/s40258-021-00665-1

[101] FCA. (2017). *regulatory-sandbox-lessons-learned-report*; FCA. (2019). *The Impact and Effectiveness of Innovate*.

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Overall impact | + | + | + | + | + | + | - | + | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

### Assessment of any synergies and tensions within the Policy Block

A tension exists in this block between promoting business – particularly around ATMP development by commercial entities – and the recognition that the majority of ATMP development is currently undertaken by academic, research and SMEs who are non-commercial and unsuited to be MAHs but represent the major stakeholder in this area. In this context promoting business, incentives and patent protections for commercial entities does not necessarily go hand in hand in with promoting innovation.

Future proofing elements in this policy options related to reducing regulatory burden to promote innovation and access: Adapted regulatory framework for certain categories of novel products/technologies (C.3.1); adapt definitions, including that of medicinal product and delink scope from industrial process (C3.3); risk-based classification of less complex cell-based medicinal products (C3.5); and creating a central classification mechanism for borderline products (C3.7) will add clarity and streamline existing legislative pathways that complement with horizontal measures such as streamlining of procedures, including avoiding duplicative processes (including GMO requirements, prioritisation of applications, better coordination within the regulatory network; streamline procedures to facilitate efficient interaction and synergies between different but related regulatory frameworks e.g. Medical Device (for certain type of products) and Health Technology Assessments and create an expert group to give advice/guidance on UMN – cross sector involving health technology assessment bodies (via the Coordination Group of HTA bodies set up under the new HTA Regulation), pricing and reimbursement bodies, patients, and academic representatives. There are also synergies and complementary measures around definitions with security of supply measures (definitions of critical medicine, critical shortage, critical medicine) as well as additional measures in manufacturing quality that would also focus on adapting to new manufacturing processes.

Future proofing elements in this policy element related to improved mechanisms/approaches for innovation to promote access to novel medicines: Introduction of regulatory sandboxes (C.3.6) will provide an adaptive mechanism to support novel innovation approaches to develop medicines. Adapted regulatory requirements to improve use of HE mechanism will facilitate production of non-commercial cell based (ATMP) medicinal products. While a risk-based approach for GMO assessments (C3.2) will focus regulatory efforts on assessment of GMOs posing highest risk to the environment. Together these elements will facilitate the development of novel medicines, GMOs (ATMPs) that have high potential to address UMNs. Element C1.2 also has good synergies in the support of non-commercial entities and making more robust hospital-based manufacturing processes.

#### *12.5.4 Policy Block D (C.D): Access*

### Assessment of the key impacts for the policy elements

Option C incorporates two elements that were previously discussed in Options A (facilitating multi-country packs) and B (Requirement to include small markets in MRP/DCP applications) respectively, but also introduces two new elements.

C.4.1. Conditional marketing authorisation: UMN incentives are only granted upon switching to standard MA

This measure introduces a conditionality on the granting of the incentives proposed within Block A. It is assumed that this pertains specifically to the granting of an additional period of data protection for products with a demonstrated ability to address an UMN (elements A.1.3, B.1.5 and C.1.5). As such, this element does not introduce *new* impacts but rather limits the extent to which the expected impacts linked to these elements may materialise. The intent of C.4.1. is to further incentivize the generation of post-authorisation evidence for conditionally approved products and to ensure that their (cost-)effectiveness and safety can be sufficiently established. Thus, introduction of this conditionality may be expected to be beneficial for authorities tasked with this assessment, as well as for health systems and patients who receive greater assurances that incentives are not granted to products not deserving of these.

C.4.2 Facilitate 'multi country packs' with labelling to allow their placing on the market in several Member States with the same packaging and pack sizes

Same as A.4.1

Currently, information on the pack (outside and inside) must be in the official language(s) of the MS where a product will be placed on the market, bar a few exceptions for certain products that are not intended to go directly to a patient. This language requirement, along with other potentially country-specific requirements, means that MAHs must produce packs specifically designed for each market. This increases production costs and may make smaller markets, where these costs cannot sufficiently be offset by revenues, commercially unattractive. Additionally, country-specific requirements can hinder the movement of medicines between different EU markets when products need to be repacked and relabelled, to meet all requirements of the importing country.

Facilitating 'multi-country packs' may result in more products being placed on a greater number of markets, in particular smaller or less economically attractive markets. In addition, medicines can be moved between EU countries more easily to mitigate or resolve shortages. This would improve security of supply and mitigate some of the risks resulting from product unavailability (e.g. treatment interruption, suboptimal treatment with alternatives). It will, however, be important to ensure that use of multi-country packs does not limit the ability of patients and healthcare providers to access information regarding, for instance, the correct use and safety profile of medicines. No studies were identified that detail experiences with multi-country packs as a way to overcome access challenges and that thus could inform an estimation of impact.

In economic terms, it is expected that multi-country packs would result in a cost saving to MAHs by reducing the number of different presentations they need to produce and streamlining production lines. The magnitude of these savings will depend primarily on the number of countries and languages included, whilst the size of the markets reached by multi-country packs will further influence the profit potential for the MAH.

In theory, multi-country packs may have the added benefit of facilitating joint procurement between countries. Several initiatives already exist whereby smaller countries engage in joint procurement to increase their purchasing power. Such initiatives have the potential to negotiate lower prices. A 2020 study for WHO shows that whilst these initiatives hold promise, they often take months or years of cooperation before tangible results are achieved. The study did not specifically look at the role of multi-country packs in facilitating joint procurement.

**C.4.3 If a medicinal product is appropriately and continuously supplied in all MS (unless it is demonstrated that a certain MS does not wish supplies) within a period of 2 years from MA and not later withdrawn before the additional exclusivity kicks in, then the product receives an additional 2 years of data protection**

This pivotal element seeks to encourage developers of innovative medicines to place products on all EU markets by offering a 2-year extension of regulatory data protection in return for doing so within two years of authorisation. To avoid potential abuse of the incentive and simultaneously address problems with access and continuity of supply, the incentive is linked not simply to market entry but to whether the product is appropriately and continuously supplied (subject to MS electing to reimburse / accept the product).

This element will complement the decision to reduce the standard period of regulatory data protection from 8+2 years currently to 6+2 years in future, with most MA holders being in a position to launch their new products in all member states willing to reimburse those medicines. This condition will bring the overall RDP back to the current 10 years (6+2+2) for the great majority of products.

We assume the 10-12 products annually may chose or fail to comply with the condition 'all markets within 2 years' and that these MAHs will see a loss of income (c. 22%; €352m-€422m a year) on those products, as a result of earlier generic entry (from year 8). We assume the cost of servicing say 25 EU markets on average rather than say 15 (more typical currently) would be cost neutral, with the higher sales volumes in the additional 10 smaller markets offsetting the additional marketing, distribution and other costs associated with smaller / marginal markets. EU health systems will also save money from earlier competition (€210m-€270m a year).

There are some practical issues to be tackled in the final detail design of this proposal. The element raises several questions as to how this should be operationalised. The first relates to the clock start. As most innovative medicines are approved via the centralised procedure, the most likely start time would be the date of central approval by the EMA. It has, however, not been specified whether medicines authorised via a national route would also be able to qualify and, if so, which date of authorisation should be considered.

| |
|---|
| Second, it is not clear how the measure would allow for the introduction of 'clock stops' to accommodate variability in the duration of pricing and reimbursement decision-making processes by public authorities. In the annually published results of the W.A.I.T. survey, conducted by EFPIA, it is estimated that the average time for a centrally approved medicine between marketing authorisation and the date at which products gain access to the reimbursement lists, varies from 133 days in Germany to over 800 days in Bulgaria, Poland and Romania.[102] In these results, however, it has not been specified to what extent such differences are due to factors on the site of the MAH and of the public authority respectively. It is thus difficult to predict by how much an incentive for MAHs alone would be able to shorten this period if authorities are unable or unwilling to approve reimbursement within the required timeframes. This issue has not been discussed in consultations with public authorities and therefore it is not possible to indicate whether a two-year window would be sufficient.<br>Questions may also be asked about how to define 'appropriate and continuous' supply and how to apply this concept in determining whether eligibility criteria have been met. The concept exists in Article 81 of Directive 2001/83/EC which requires MAHs and wholesale distributors of a medicine that is placed on the market to ensure "appropriate and continued supplies", within the limits of their responsibility, to cover the needs of patients. This concept has, however, been interpreted differently in different countries and offers limited guidance on how to establish whether an MAH (or wholesaler) has acted appropriately to fulfil its obligations. It is therefore to be expected that similar difficulties will be encountered in its application in the context of the here proposed element, particularly if this assessment needs to be provided by the Member States where the products have been placed on the market. |
| C.4.4. Requirement to MAH applying for MRP/DCP to include small markets (in particular address the post-BREXIT challenges) or possibility for MS to opt-in a pending MRP/DCP procedure |
| Same as B.4.4<br>Most generic medicines are currently approved through the MRP/DCP route . Because of this, these products would not fall within the scope of the requirements imposed by B.4.2 and B.4.3. By also extending greater obligations for inclusion of smaller markets in the application for approval via the MRP/DCP, the Commission aims to increase access to a wider group of products, in particular generic medicines, than would be achieved via marketing obligations on centrally approved medicines alone. It is assumed that the proposed element intends only to require the applicant to include specific countries into the MRP/DCP application, such that there is a valid MA in these markets, but does not require the applicant to directly place products on these markets.<br>Requiring MAHs applying for an authorisation via the MRP/DCP route to include specific markets – or allowing countries to opt-in – will enable these countries to obtain medicines more easily from other EU MS (through parallel distribution), even when the MAH does not place the product directly on the market. This may have the effect of increasing access to medicines that are not within the scope of the CP, especially generic medicines. This, in turn, may be expected to positively affect both health outcomes for patients and the affordability of treatment by increasing access to low-cost generic versions. It will also improve security of supply for included countries by facilitating redistribution in case of shortages. |

## Summary assessment of the principal costs and benefits by impact type

Table 57 presents a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under Option C, by impact type. Whilst the impact of some of the individual elements has been detailed previously under Options A and B, the introduction of new ones, as well as the new combination of elements will have intrinsically different synergies and tensions and thus result in a different assessment of the overall impact.

*Table 57 Option C – Summary assessment of access elements*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.4.1 | +/- | +/- | +/- | +/- | +/- | ++ | ++ | ++ | +/- |
| C.4.2 | ++ | + | +/- | + | ++ | +/- | + | + | +/- |
| C.4.3 | - | - | +/- | -- | + | +/- | ++ | ++ | +/- |
| C.4.4 | --- | -- | - | -- | + | - | ++ | +++ | +/- |
| Overall impact | --- | --- | -- | -- | ++ | +/- | +++ | +++ | +/- |

[102] https://www.efpia.eu/media/636821/efpia-patients-wait-indicator-final.pdf. Last accessed 23 May 2022.

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

- The proposed elements impact different groups of industry stakeholders differently. For innovative medicine developers, the package of measures is skewing positively, by introducing a new incentive for market placement and removing some barriers to operating in smaller markets by facilitating multi-county packs. At best, these elements will enable innovators to increase their operating profits whilst on the other hand there are no new obligations introduced that could cause harm to their cost of business. Generics manufacturers on the other hand are not likely to benefit from the new incentive, as their products are normally not under regulatory protection, yet face a new requirement to include smaller markets in their MRP/DCP applications. Additionally, the incentive offered to innovative developers means a longer exclusion from the market for generic companies. Jointly, these measures thus most likely represent a substantial net negative for generic manufacturers.
- Inclusion of additional countries, in particular smaller MS, in the MRP/DCP application (C.4.4 will facilitate the movement of medicines between markets where the product has been authorised. This measure is substantially synergistic with the measure to facilitate use of multi-country packs (C.4.2). Jointly, these measures may be effective in facilitating the movement of medicines within the EU internal market to countries that are comparatively underserved or where medicines are in shortage.

### Assessment of any synergies and tensions within the Policy Block

As under Options A and B.

### *12.5.5 Policy Block E (C.E): Competition*

### Assessment of the key impacts for the policy elements

Table 58 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements.

*Table 58 Option C – Assessment of the proposed measures for competition*

| **Description** |
|---|
| C.5.1 New simpler regulatory pathway for generics (adapted EMA/CHMP working methods, shorter approval timelines, potentially distinguishing between complex generics/biosimilars – reducing requirements for known biologics) |
| As described for A.5.1.<br>The key impact from a simpler regulatory pathway with shorter approval times will be faster availability of generics to patients. It should create more clarity and potentially less administrative burden for marketing authorisation applicants, encouraging more applications and increased development activity for generics.<br>We assume that generics will be on the market soon after approval and access to generics will be similar in all member states. The latter assumption has been adopted for ease of analysis as generics market penetration varies considerably across member states and would add uncertainties to our assessment. |
| C.5.2 Interchangeability of biosimilars with their reference product will be generally recognised in guidance or e.g. through a recital in the legislation and will be scientifically assessed as part of the product assessment and indicated in the summary of product characteristics (SmPC, product information) to inform healthcare professionals and their patients as well as downstream decisions makers |
| As described for B.5.2.<br>Interchangeability, switching (by prescriber) and substitution (by pharmacy) of a reference medicine by its biosimilar currently fall within the remit of EU Member States. Guidance on interchangeability from one originator (reference) or biosimilar product to another at the EU level would enable all member states to make decisions on |

| Description |
|---|
| whether to allow switching and/or substitution for certain products, especially those countries where the relevant technical capacity is not available. There is potential to pool the best expertise from across the EU if product assessment is done as part of the centralised procedure, reducing burden on individual member state authorities. Inclusion of the guidance in a recital in the legislation and product information (SmPC) would inform prescribers, patients, and decision makers about interchangeability of specific products, potentially increasing uptake of biosimilars. This could improve access to biologics for patients and reduce health system costs if cheaper biologics were switched or substituted for more expensive ones.<br>It is not clear if additional data will be requested for the scientific assessment of interchangeability e.g. switch studies. Our assumption is that no additional data will be required – a study by Kurki et al. (2021) which analysed post-marketing surveillance data suggests that biosimilars approved in the EU are highly similar to and interchangeable with their reference products. A recent qualitative study also shows that European and UK regulatory, legal and policy experts do not see any added value in additional data or switching studies. |
| C.5.3 Broader Bolar exemption – allow additional beneficiaries (companies, producers of active pharmaceutical ingredients (APIs) and non-industry actors) to conduct studies/trials |
| Overall, the broader Bolar exemption is likely to increase legal certainty, access to medicines, cost savings and research activity in the EEA compared with a narrower exemption.[103] |
| C.5.4 Extend Bolar exemption beyond generics – Allow repurposing studies/comparative trials without infringing patent rights |
| Overall, the extended Bolar exemption is likely to increase legal certainty, access to medicines, cost savings and research and innovation activity in the EEA compared to a narrower exemption.[82] |
| C.5.5 Duplicates restricted to cases of intellectual property protection or co-marketing |
| As described for B.5.6b.<br>There will be a reduction in barriers to competition and monopolisation of the market by the first generic/biosimilar of an originator product to receive an MA. Consequently, there will be no delay in the second generic/biosimilar coming onto the market once it receives approval. This will mean greater consumer choice and price competition. |

## Summary assessment of the principal costs and benefits by impact type

Table 59 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block E under Policy Option C and for each impact type.

*Table 59 Option C – Summary assessment of the proposed measures for competition*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.5.1 | + | + | + | + | + | + | + | + | -/+ |
| C.5.2 | -/+ | -/+ | -/+ | + | + | -/+ | ++ | ++ | -/+ |
| C.5.3 | + | + | -/+ | + | + | + | ++ | ++ | -/+ |
| C.5.4 | + | + | -/+ | + | + | + | ++ | ++ | -/+ |
| C.5.5 | -/+ | -/+ | + | + | ++ | + | ++ | + | -/+ |
| Overall impact | + | + | + | + | ++ | + | +++ | +++ | -/+ |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and

[103] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Some of the key expected impacts are as follows:

- Increased international competitiveness through creation of a more favourable regulatory environment for generics/biosimilars (simplified generics pathway) and broader scope of activities and actors covered under the Bolar exemption. The broader Bolar exemption will increase the share of EU-based API producers and API manufacturing jobs and lower costs of supply for European generics.[104] The cost savings would be more pronounced for European generics manufacturers of specialised products e.g. for oncology or central nervous system
- Improved consumer choice and competition through availability of both generics/biosimilars and originators on the market (including guidance on interchangeability), resulting in lower prices and improved access for patients across member states. Modification of the duplicate regime will mean originator companies will not be able to severely undercut the price of potential biosimilar competitors through a duplicate authorisation for an autobiological while allowing the reference originator product to maintain a high price.[105]
- The extended scope of the Bolar exemption will increase returns to innovation and therefore increase incentives to innovate for European R&D based pharmaceutical companies in countries that currently have a narrow Bolar scope. This would increase R&I for generics and biosimilars and can be expected to lead to an increase in the number of skilled jobs[84]
- If the extended Bolar exemption leads to more clinical trials in a country, this will have impacts on access as it has been shown that new medicine adoption is wider in countries where the clinical trial was run[91]
- A very high likelihood of positive impact on patients through making medicines more readily available and reducing costs for health systems (generics represent around 80% cost reduction compared to originators, and entry of a generic also reduces price of the off-patent medicine by 61%[106]; biosimilars are 20% cheaper[107] compared to originator products)

### Assessment of any synergies and tensions within the Policy Block

There is synergy with the horizontal measure of streamlining and harmonisation with making the regulatory pathway for generics simpler. Changes to the Bolar exemption will have synergy with elements introduced to improve access, but may have some negative implications for innovation activity if ROI figures change for originators. Change to the duplicates regime improves background conditions for timely availability of biosimilars on the market and thus access.

[104] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

[105] https://www.biosliceblog.com/2019/11/update-on-eu-duplicate-marketing-authorisations/

[106] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

[107] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilarsv

### *12.5.6 Policy Block F (C.F): Supply Chain Security*

#### Assessment of the key impacts for the policy elements

Table 60 presents our assessment of the key impacts of each of the proposed measures, drawing on our consultations, desk research and targeted literature review.

*Table 60 Option C – Assessment of the proposed measures for Supply Chain Security*

| **Assessment** |
|---|
| C.6.1. Introduce EU definition of a shortage, including a critical shortage and critical medicine |
| The measure has the potential to harmonise numerous definitions of shortages that exist across the EU. The clarification of criticality criteria can further help in making changes in shortage notification to cover shortages for most critical medicines. Overall, many stakeholders, and particularly industry representatives have advocated for the adoption of the concept of 'product criticality' into definitions of shortages and regulatory measures aimed at notification and prevention of shortages. The study of medicines shortages also called for the introduction of criticality criteria and further measures associated with it.[108]<br>The clarification of shortage criticality criteria can further help in making changes in shortage notification to cover the most impactful shortages. |
| C.6.2. a) Increase notification period to 12 months for all withdrawals of products that have been on the market for more than two 2 years<br>b) Notification at least 6 months in advance or as soon as identified for all shortages (non-withdrawal)<br>c) Introduce a common template for reporting withdrawals and shortages including details of root causes, alternatives medicines and impact. |
| This option differentiates between planned (permanent) market withdrawals and temporary supply disruptions, setting different notification timeframes for each. There is more explicit recognition of the fact that not all shortages can be foreseen 6 months in advance. It is uncertain whether this element will result in earlier notification than presently the case, given that most shortage notification are currently made with less than 2 months' notice, citing 'exceptional circumstances'. There is no clear reason why extending the notification period would remedy this situation. Where potential shortages are notified more in advance, these situations often are resolved before they result in an actual shortage. Extending the notification period may thus increase the number of 'false alarms'. There is also a risk that a longer notification period will increase the administrative burden on both MAHs and public authorities without clear benefits.<br>In some countries, parallel distributors also fall under a notification obligation. In consultation, this industry has indicated that a 6-month notification requirement would not be possible to meet since they typically do not hold stocks for more than 2-3 months.<br>Earlier notification of planned withdrawals (element a), however, may be more feasible and provide authorities more time to identify and source alternatives.<br>The obligation to utilise a common reporting template (Element c) is received positively by the stakeholders. Common data collection approaches, particularly if linked to a standardised reporting portal and automatic sharing of information between MS could, in the longer term, result in cost savings for authorities. Greater standardisation of information may also enable a better understanding of the causes of shortages and allow for the development of better-tailored policy approaches to address the issue of shortages. |
| C.6.3. Stockpiling requirements for MAHs for unfinished critical medicines, as appropriate |
| Some further elaboration is needed to determine criteria to establish what constitutes 'as appropriate'. More detailing is also needed about the expected quantity of such stock, what state the product needs to be in (e.g. intermediates or finished but unlabelled/unpacked products), at what level the stock will be held (e.g. EU, national, regional), who has ownership and responsibility for the stock (e.g. MAHs, wholesalers or authorities) and whether stock may be redistributed according to need. All such factors may strongly influence the operational feasibility of this measure and its acceptability to involved stakeholders.<br>Among wholesalers there is a sense that a limited level of additional reserve stockholding (~2-3 weeks) – with reserves dynamically rolled into normal stock – for critical measures may be a cost-effective measure against supply disruptions, holding larger volumes of stock is both unfeasible and unnecessary.<br>It is expected that the costs of increased stock holding will either need to be shared between MAHs and public authorities, or if not, that MAHs will seek to recoup the increased costs by raising prices. For generic manufacturers, whose products are typically under strict price regulations and caps, this may not always be possible. Among generic manufacturers, there is therefore a fear that in the absence of a balanced cost/risk |

[108] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages*

| **Assessment** |
| --- |
| sharing arrangement, companies may be unable to continue operating in markets where these stock obligations apply. |
| C.6.4 (as in A.6.3.) Marketing authorisation offered for transfer to another MAH before a permanent withdrawal |
| Requiring a MAH to offer the MA to another party before allowing it to withdraw the product from a specific market could delay the original MAH's withdrawal decision, as it seeks to avoid enabling its own competitors.<br>Hypothetically, requiring MAHs to offer the MA to another manufacturer could benefit such manufacturers who are enabled to market a product that already has an established patient base. However, as indicated previously, a large proportion of product withdrawals can be traced to low product-level profitability[109]. It is not clear to what extent a MA transfer could effectively address these underlying profitability issues. Such transfers would only be feasible/interesting in case a product remains commercially interesting for the new MAH or if commercial viability is not required for another party to take over the MA (e.g. in case of transfer to a not-for-profit entity).<br>The study team has identified no experiences with similar measures that could inform a (quantitative) estimation of potential impact. Moreover, the EU trade association for the generics industry (Medicines for Europe) has indicated that it considers this proposal unconstitutional and not compliant with the proportionality requirements of EU treaties. It indicates that permanent withdrawals for commercial reasons are often necessitated by national market conditions, such as pricing and reimbursement policies (e.g. price cuts, reference pricing, claw backs and rebates), that are imposed by Member States and over which the MAH has no control. Mandating that the MAH offers the authorisation to another party before allowing it to withdraw is therefore considered a form of regulatory expropriation in violation of Art. 16 of the European Charter of Fundamental Rights. |
| C.6.5. Marketing authorisation holders to have shortage prevention and mitigation plans for all medicines. |
| Early identification of risks to the security of supply and of possible mitigation steps could reduce the occurrence and impact of supply disruptions. Fewer medicine shortages, as well as faster and more effective mitigation of the impact of shortages when these occur, improves patient access to (critical) medicines and leads to better health outcomes. The health system experiences fewer costs associated with dealing with medicine shortages.<br>Depending on the level of detail required and the degree to which risk mitigation steps (e.g. contractual agreements with backup suppliers) are expected, MAHs may make additional costs not only in drawing up the plans but also in implementing the actions therein specified.<br>Industry representatives have indicated that an important condition for the submission of shortage prevention plans would be that the company retains ownership of the plan, and that information remains confidential, as this could be commercially sensitive. In consultations, industry stakeholders have strongly opposed applying this measure to all authorised medicines rather than limiting it to critical medicines and those medicines at high risk of shortage. Amongst these stakeholders the measure is widely viewed as unnecessary, impractical, and burdensome as these plans would need to be regularly updated to remain relevant. It is expected this will create a very significant administrative burden for both regulators and MAHs.<br>There is greater support for this measure should it be limited in scope to critical medicines and products at risk of shortage. Even under these circumstances, however, industry stakeholders note that MAHs may not be able to offer alternatives as this is the responsibility of physicians and prescribers. |
| C.6.6. Monitoring of supply remains at MS level, with information exchange at EU level for critical shortages based on national monitoring, using a common methodology/format to ensure compatibility & exchange at EU level. |
| This policy element is economically advantageous for MAHs and NCA as it builds upon the existing system of national monitoring. The implementation of the element is also feasible: existing initiatives and networks such as SPOC can be used for the purposes of the exchange. However, countries would still need to adopt the definitions of critical medicines in order to make the exchange efficient. |
| C.6.7 Expanded requirements for key suppliers and back-ups to diversify supply chain for critical medicines |
| C.6.7. aims to force MAHs to diversify their supply chains to prevent shortages and thus improve the availability of medicines and overall patient outcomes.<br>Requiring more diverse supply chains most likely will result in increased production costs as MAHs may need to procure goods and services from less economically advantageous suppliers. These costs could be substantial, although no data was collected that would allow this impact to be quantified. There may be additional payments to backup suppliers, to reserve goods and space on production lines, even if not needed.<br>These additional costs occurred by the pharmaceutical industry may result in higher medicine prices and greater costs to health systems and patients. If requirements are introduced by individual MS rather than at the EU level, |

[109] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages* (Issue December).

| Assessment |
|---|
| this could discourage MAHs from operating in markets with such requirements and contribute to inequitable access to medicine.<br>Importantly, the measure may not be feasible to implement for many medicines, for which globally a limited number of API and raw materials manufacturers exist, meaning that it may not be feasible for MAHs to sufficiently diversify their supply chains. Separate measures would be needed to enable this, e.g. economic incentives for industry to increase the manufacturing of APIs and raw materials. |
| C.6.8 Establish a mechanism of exchange of relevant information on supply chains between Member States to identify the supply chains bottlenecks and vulnerabilities |
| It is assumed this refers to sharing of information about the structure of supply chains, including the upstream aspects such as production and sourcing of raw materials and APIs, e.g. identifying the number, location and production capabilities of suppliers. Whilst improved insight into these structures certainly would be beneficial to understand which products may be at higher risk for supply disruptions, it is unclear who would be expected to provide the information or how it would be used. MAHs likely will consider such information commercially sensitive. It is, however, also unlikely that NCAs would be able to collect such information without the input from MAHs and other parties that make up the supply chain. It is thus difficult to understand the foreseen impact pathway and the actions needed to implement these policy elements. Consequently, we are presently not able to predict their potential impacts. |
| C.6.9. (same as B.6.8) Increase transparency of the supply chain, including:<br>1. active supply sites for all medicines,<br>2. volumes supplied, incl. supply quotas and remaining stocks for critical medicines upon request of NCA's/ EMA,<br>3. parallel traders and wholesalers' transactions for critical medicines upon request of NCAs/ EMA. |
| Improved transparency of the supply chain, at least for public authorities, has the potential of improving the security of supply by better matching supply and demand.<br>MAHs and parallel distributors each have a clear commercial interest in keeping (aspects of) information about their transactions confidential and are not generally welcoming of disclosing this to the other. For instance, parallel traders fear that full public disclosure of information about their transactions will render their trade practically impossible by allowing MAHs to throttle their supply to the level where no surplus is created.<br>For these parties to agree to share information with public authorities, it will be essential that strong agreements are made about what information is disclosed, for what purposes, how this will be used and who has access to it. Without this, it is unlikely that industry will cooperate. Mandatory disclosure of commercially sensitive information could furthermore distort competition between MAHs.<br>It may be assumed that regular sharing of information between supply chain actors and authorities – particularly when not done though an automated system – entails substantial administrative costs on all sides. |

## Summary assessment of the principal costs and benefits by impact type

Table 61 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block F under Policy Option B and for each impact type.

*Table 61 Option C – Summary assessment of Policy Block F (Security of Supply)*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.6.1 | +/- | + | +/- | +/- | +/- | +/- | +/- | + | +/- |
| C.6.2 | -- | -- | +/- | +/- | +/- | +/- | +/- | ++ | +/- |
| C.6.3 | -- | -- | +/- | -- | +/- | +/- | - | + | -- |
| C.6.4 | - | - | +/- | - | +/- | +/- | +/- | ++ | +/- |
| C.6.5 | - | -- | +/- | -- | +/- | +/- | + | ++ | +/- |
| C.6.6 | +/- | + | +/- | +/- | +/- | +/- | + | ++ | +/- |
| C.6.7 | --- | --- | -- | -- | - | +/- | +/- | ++ | -- |
| C.6.8 | +/- | +/- | +/- | +/- | +/- | +/- | + | ++ | +/- |
| C.6.9 | +/- | -- | +/- | -- | - | +/- | + | ++ | +/- |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Overall impact | -- | -- | +/- | - | - | +/- | ++ | +++ | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

### Assessment of any synergies and tensions within the Policy Block

Similar to Option B, several policy elements (C6.6. and C.6.7) are dependent on element C.6.1. (Introduce EU definition of a shortage, including a critical shortage and critical medicine). Overall, the elements are synergistic and do not contradict each other.

### *12.5.7 Policy Block G (C.G): Quality and manufacturing*

### Assessment of the key impacts for the policy elements

Table 62 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on desk research and targeted literature review.

*Table 62 Option C – Assessment of the proposed measures for quality and manufacturing*

| **Assessment** |
|---|
| C.7.1. Strengthen the oversight of the sites within a supply chain (including distributors and APIs manufacturing/importing sites) by extending the scope of mandatory inspections and modifying provisions on inspections (frequency, content, triggering points) |
| This measure will strengthen end-to-end oversight of the supply chain and could improve GMP/GDP compliance. However, it would impose significant additional burden on businesses and competent authorities. It would substantially increase the workload of inspectors (because of the extended scope and depending on the modified provisions), which would need to be met with more resources. |
| C.7.2. Stronger EMA role in ensuring proper oversight of the manufacturing sites via adapted IT tool and by increased role in coordination of inspections, including in setting up multinational inspection teams |
| The proposed policy element would have efficiency benefits with regard to oversight of manufacturing sites in the long term through better data management, transparency, resilience, and interoperability. However, this effect would depend on the quality, content and implementation of the IT tool, and would require additional resources in the short term. A stronger role for the EMA and setting up of multinational inspection teams would allow harmonisation of approaches. The latter would promote knowledge exchange and efficiency, benefitting national competent authorities. In the short-term, there may be high costs involved in restructuring capabilities. |
| C.7.3. Reinforcing Member States GMP and good distribution practices (GDP) inspections capacity by setting up a mandatory joint audit scheme |
| Same as B.7.2.<br>This policy element has the potential to increase inspection efficiency through more cooperation and knowledge transfer. This may have a positive effect on manufacturing and distribution practices within the EU and globally, which would ultimately positively impact public health in the long-term. |
| C.7.4. Adaption of legislation/inclusion of specific provision covering new manufacturing methods (decentralised, continuous manufacturing, etc). to ensure levels of quality and safety equivalent to current methods |
| Same as A.7.3<br>The proposed measure has the potential to bring several product categories that are currently excluded from the legislation into the fold and provide regulatory certainty to manufacturers. These include magistral formulae (pharmacy-based preparation for an individual patient), radionuclides in sealed sources, hospital-manufactured medicines, and single-batch medicines. In addition, manufacturing methods such as decentralised manufacturing (where manufacturing occurs at different locations) and 3D printing-based methods could be accommodated.<br>Covering new manufacturing methods in the general pharmaceutical legislation has the main advantage of helping to standardise the methods themselves, quality control of the methods and resultant products and associated regulatory pathways at the EU level. Thus, there is a harmonisation benefit. Moreover, accommodating new technologies sends a positive signal to innovators as well as companies and will encourage more innovation and research activity and adoption of the new methods. There will be further knock- |

| Assessment |
|---|
| on effects on competition, competitiveness, and access to medicine. If greener manufacturing methods are used there will be an impact on environmental sustainability, but the likelihood and extent of that is unclear.<br>With more certainty over the manufacturing methods and the resultant products as well as more medicine developers adopting these methods, we could imagine a very high increase in the number of new therapies in comparison to the baseline. |

### Summary assessment of the principal costs and benefits by impact type

Table 63 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block G under Policy Option C and for each impact type.

*Table 63 Option C – Summary assessment of the proposed measures for quality and manufacturing*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.7.1 | - | - | - | - | - | -/+ | - | +/- | +/- |
| C.7.2 | + | + | +/- | +/- | +/- | +/- | + | +/- | +/- |
| C.7.3 | +/- | +/- | +/- | + | +/- | +/- | + | +/- | +/- |
| C.7.4 | -/+ | -/+ | -/+ | + | + | + | -/+ | + | -/+ |
| Overall impact | -/+ | -/+ | - | + | +/- | + | + | + | -/+ |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Extending the scope and modifying provisions of inspections and expanding oversight to all sites within a supply chain (including distributors and API manufacturers) could create additional transaction, compliance and administrative costs which could put a large burden on SMEs in particular. Moreover, NCAs will need additional inspection capacity and training to accommodate the changes in the scope, provisions and actors. On the other hand, a mandatory joint audit scheme for member states and stronger coordination of inspections by EMA will create efficiencies and savings for NCAs (and to some extent for businesses in the long term).

Adaptation of the legislation or inclusion of specific provisions to accommodate new manufacturing methods will improve international competitiveness, encourage greater research and innovation, and increase choice and competition in the sector. It would also have a direct impact on patients by making more treatments available and require additional transaction, compliance and administrative costs for oversight (both for businesses and NCAs). The measures to improve oversight of manufacturing but the quality standards are already high so there is unlikely to be greater added benefit to public health.

### Assessment of any synergies and tensions within the Policy Block

Policy elements C.7.1, C.7.2 and C.7.3 have synergies with regard to enabling stronger supply chain oversight through different mechanisms.

#### *12.5.8 Policy Block H (C.H): Addressing environmental challenges*

### Assessment of the key impacts for the policy elements

Table 64 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review.

It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

*Table 64 Option C – Assessment of the proposed measures for addressing environmental challenges*

| **Assessment** |
|---|
| C.8.1 Include assessment of the environmental risk of manufacturing into ERA, including main supply chain actors (API, raw materials) |
| This measure represents considerable additional burden for medicine developers and supply chain actors, and public authorities in terms of compliance and administration costs and review costs respectively. On the other hand, it will allow tracking of the environmental risks of manufacturing across the supply chain providing a more comprehensive assessment of the potential environmental impact of a new medicine. For example, if risk associated with active pharmaceutical ingredient discharges from manufacturing sites is included in the ERA, it would increase the relevance of the assessments by including a part of the life cycle of the product responsible for the highest environmental concentrations detected.[110] |
| C.8.2 Strengthen the ERA requirements and conditions of use for medicines, while taking stock of research under the innovative medicines initiative (IMI) |
| The proposed measure should enable robust assessment of the environmental risks of pharmaceuticals as well as promote prudent use, supporting sustainable consumption and helping to minimise the environmental footprint of medicines. However, this may place slight additional burden on public authorities for reviewing ERA submissions (in case of additional data requirements) and monitoring medicine use (if required) as well as on businesses and other stakeholders responsible for complying with said requirements and conditions. |
| C.8.3 Advisory role of EMA on ERA and green manufacturing aspects and quality (e.g. with relation to generics) |
| Constitution of a new advisory body/bodies and ongoing costs of providing advice will be the main drivers of administrative burden for EMA. However, the advice will help companies to better address ERA requirements and adopt green manufacturing practices, which will in turn aid pharmaceutical sector businesses to be more sustainable. |
| C.8.4 Include the AMR aspects into GMP to address the environmental challenges |
| This measure would help minimise amounts of antibiotics entering the environment via manufacturing and thus prevent emergence of AMR from pharmaceutical manufacturing. Recent evidence indicates the presence of a selection pressure for AMR within environments receiving wastewater from antimicrobial manufacturing, as opposed to environments receiving wastewater from municipal sewage treatment plants (containing antibiotics from human use) that do not receive waste from antimicrobial manufacturing.[111]<br>There would be the additional costs for businesses to comply with the AMR requirements in GMP and data requirements and for public authorities for enforcement of the requirements. This could present barriers for smaller actors.<br>The KPI would be amount of an antibiotic in waste and wastewater in µg/l. Suggested annual mean value for an erythromycin environmental quality standard (EQS) is 0.2 µg/l.112<br>For the current impact assessment, we would assume that compliance with the measure will result in levels below the EQS and thus there is a high likelihood of impact on sustainable production (environmental impact). |

## Summary assessment of the principal costs and benefits by impact type

Table 65 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block H under Policy Option C for each impact type.

[110] Eeb. (2018). Policy options for regulating pharmaceuticals in the environment.

[111] WHO Expert Committee. (2020). *Annex 6 Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance*.

[112] UBA – Umweltbundesamt (Hrsg.) (2018) Empfehlungen zur Reduzierung von Mikroverunreinigungen in den Gew ssern,Hintergrund, Februar 2018, Dessau-Ro lau, https://www.umweltbundesamt.de/sites/default/files/medien/1410/publikationen/uba_pos_mikroverunreinigung_final_bf.pdf

*Table 65 Option C – Summary assessment of the proposed measures for addressing environmental challenges*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.8.1. | - | - | - | - | - | +/- | - | + | ++ |
| C.8.2. | +/- | +/- | - | - | - | +/- | +/- | + | ++ |
| C.8.3. | +/- | +/- | +/- | +/- | +/- | +/- | - | + | + |
| C.8.4. | - | - | - | - | +/- | +/- | - | + | + |
| Overall impact | - | - | - | - | - | +/- | - | + | ++ |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

The key impact of the measures to address environmental challenges in Policy Option C are expected to be increased sustainable production and waste management owing to improved ERA, inclusion of AMR in GMP and green manufacturing. This may have an indirect effect on public health local to manufacturing sites due to reduced emissions and the possibility of fewer AMR strains emerging.

There may be additional burden on SMEs to meet the new requirements either in terms of administrative costs or need for specialised expertise with implications on competitiveness and the internal market. Similarly, the EMA and NCAs may require additional capacity or incur greater administrative burden in reviewing and assessing products based on the additional requirements for ERA and GMP.

### Assessment of any synergies and tensions within the Policy Block

There are no major synergies or tensions within this block for Policy Option C. Policy element C.8.1. is in line with elements in other blocks that aim to increase transparency and obligations about supply chain actors, but conflicts with the horizontal measure aimed at simplification. C.8.2. has synergy with the horizontal measure aiming to strengthen and harmonise ERA across member states, while reducing duplication of testing. C.8.4. has complementarities and synergies with measures to restrict and monitor use of antimicrobials, especially B.2.4. (Stricter rules on disposal) and B.2.8 (Establish monitoring system for data collection on human antimicrobial consumption and use and potentially on the emission of APIs to the environment). However, there is a risk of duplication of effort/data in the GMP/environment reporting requirements for companies, which should be covered in the revision.

The additional advisory role of the EMA has potential synergy with the measures to strengthen ERA and modify GMP and could support industry in smooth transition to and harmonised implementation of the new requirements.

## *12.5.9 Policy Block I (C.I): COVID-19 lessons learnt*

### Assessment of the key impacts for the policy elements

Table 66 presents our broad assessment of the likely costs and benefits of the proposed policy element, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

*Table 66 Option C – Assessment of the proposed measures for COVID-19 lessons learnt*

| Assessment |
|---|
| C.9.1. Refusal of immature marketing authorisation applications |
| Same as B.9.1<br>The most significant efficiency gains would be for public authorities, which could save time currently spent on assessing immature applications and resolving internal differences of opinion as regards their evaluability or suitability for processing through the CMA pathway. As per baseline, we assume that there could be 2 to 3 marketing authorisation applications every year that do not initially request a CMA despite not containing enough data for standard marketing authorisation. This would likely lead to 2 to 3 immature marketing authorisation applications refused every year in the first one or two years, possibly increasing to 5 to 10 refused applications every year in the next 3-5 years as the evidentiary threshold is established. Industry would begin to recalibrate the acceptable levels of evidence in parallel and the numbers of weak applications should fall back to some minimum within 5 years, perhaps never quite falling below 2-3 a year over the remaining years through to 2035.<br>Overall, assuming an average annual reduction of 3-5% in the total number of applications for assessment and 100-120 applications annually, which are increasing at 5-10% a year (as per EMA annual report 2020), cutting assessments by 3-5% might result in a reduction of EMA / NCA costs of 2-3% (the work of the EMA committees is a major cost driver).<br>There could be a negative impact on cost for developers that are currently submitting immature marketing authorisation applications for valid reasons. For example, addressing an UMN may be difficult in terms of conducting large clinical trials. This may discourage developers of medicinal products for UMN if it is not combined with other policy elements. On the other hand, less immature data means HTA bodies and P&R authorities would be more able to assess therapeutic value, which could have a positive impact on access and affordability. Thus, the impact on healthcare systems could be negative (less developers working on UMN) and positive (more streamlined and coherent procedure leading to faster market launch). |

### Summary assessment of the principal costs and benefits by impact type

Table 67 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block I under Policy Option C and for each impact type.

*Table 67 Option C – Summary assessment of the proposed policy elements for COVID-19 lessons learnt*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.9.1. | - | +/- | - | - | +/- | +/- | + | +/- | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

## 12.6 Overview of proposed horizontal measures

### *12.6.1 Introduction*

The impact assessment identified the need to improve the flexibility of the regulatory framework, to futureproof the system and ensure its effectiveness over the next 15-20 years.

In response, the EC and the wider regulatory 'family' has developed a long list of proposals for improving efficiency of the regulatory system, which are listed below in Table 68. The impact assessment has explored each of these areas through our consultations and wider desk research, which suggest there may be substantial opportunities for streamlining and reducing regulatory burden.

The initial assessment of this long list is shown below and has been used to identify a series of 10 pivotal horizontal measures, which have been the subject of a more detailed assessment and cost benefit analysis.

*Table 68 Original long list of horizontal measures that have been considered by the IA study*

| **Streamlining proposals** |
|---|
| Abolish the sunset clause for all medicinal products |
| Abolish requirement for renewal of marketing authorisation for all medicinal products |
| Abolish the additional monitoring requirement and accompanying black symbol. |
| Abolish risk management plans for generics, biosimilars, hybrid and informed consent products |
| Certification of active substance master file (ASMF) |
| Shorter timeline for MRP and DCP – what is the impact bearing in mind the market protection period? |
| Repeat use procedure (RUP) – legal basis for administrative zero-day MRP/RUP to prevent or address shortages |
| Establish legal basis for a platform for EMA to facilitate alignment of evidence requirements |
| Building in structured exchanges to ensure that the advice given is taken into account by the other bodies |
| Efficient governance of European Medicines Regulatory Network |
| Digitalisation through electronic submissions, variations to MA (see below) |
| Electronic submission of applications or registrations by companies. |
| Legal basis for Electronic Product Information (i.e. electronic labelling and package leaflet |
| Streamline procedures to facilitate efficient interaction and synergies between different regulatory frameworks |
| Closing potential gaps in Benefits/Risk of combination products where medicinal products have the primary role |
| Introducing joint scientific advice for developers of combination products |
| Data sharing for centrally authorised medicines with downstream decision makers |
| Increase collaboration between MS and trusted strategic partners to ensure better supervision |
| Additional leverage of regulators on summary of product characteristics (SmPC) |
| Increase or optimise the regulatory support to SMEs, academia and public innovators |
| Address availability issues related to radiopharmaceuticals |
| **Empowering new concepts** |
| Strengthen the environmental risk assessment (ERA) |
| Empower regulatory authorities to access raw data |
| Use experts outside national competent authorities to ensure capacity and expertise for assessment |
| Opening certain procedures for third country participation to strengthen global attractiveness |
| Adapt where necessary the regulatory system to support the use of new concepts including real world evidence |
| Information from application dossiers available to authorities |
| Introduce an EU-wide centrally coordinated process for early dialogue |
| Create an expert group to give advice/guidance on UMNs |
| Creation of an emergency use authorisation (EUA) at EU level |

Table 69 presents our light touch assessment of each of these horizontal measures. There are 10-15 specific examples of proposals that would abolish certain current procedures, which have been found to be of limited effectiveness as regards their original objectives (e.g. the sunset clause and medicines shortages) or otherwise largely duplicative (e.g. risk management plans for generics). There are a similar number of proposals to improve the level of coordination, integration and harmonisation of the many working parts of the overall regulatory ecosystem, which are often intertwined with proposals to make fuller use of digital solutions across the system. There are also several measures that relate to growing concerns around new types of products and production processes, which are raising questions about where they fit in the overall regulatory architecture. Challenges are particularly evident around: Advanced therapy medicinal products (ATMPs); Combinational products; Products containing genetic modified organisms (GMOs).

Several concepts overlap with the issues raised through the IA consultations, and these are addressed briefly here and in the main body of the IA report (e.g. the abolition of the need to renew marketing authorisations after 5 years). Most of the individual proposals will only be considered here in this technical annexe.

### *12.6.2 The strengths and weaknesses of the various proposals*

Table 69 presents our qualitative assessment of the 20 or so streamlining measures and Table 70 presents our assessment of a further 10 horizontal measures that relate to new regulatory concepts and structures.

The treatment has included a brief review of what was found in the related evaluation of the EU general pharmaceutical regulation and the Impact Assessment consultation and literature review. Column three provides a synopsis of any advice or feedback from the Impact Assessment stakeholder workshop, and in particular Break Out Group 4, which focused on regulatory burden and flexibility. The final two columns provide qualitative reflections on the likely direction and intensity of future costs and benefits. The study team has sought to identify data and studies that would help to quantify and monetise these impacts, however, the proposals are so particular in their design, that we have been unable to find any relevant data or statistics to support a more granular cost benefit analysis. This absence of data holds even where proposals relate to major development initiatives (e.g. the EMA's digital transformation programme, which is being implemented by around 80 FTEs) or existing legislative activities that have been evaluated (e.g. the EMA's international cooperation programmes and joint inspections have been evaluated, but no attempt was made to quantify costs or benefits).[113]

We have assessed each proposal against the current situation (baseline) using the same 7-point scale used in the assessment of the policy options, however, with such highly particular measures and no or few data, these assessments have had to be more cautious. We have had to be content for the most part in signalling the direction of costs or benefits with a single plus or minus, as there is simply no basis for determining likely real costs or benefits. In two or three instances, we have assigned two pluses or two minuses, where the proposal relates to a process or activity that is extensive and where our evaluation or impact assessment have picked out the issue as a source of substantial additional costs, time delays or other inefficiencies.

Based on our assessment of this long list, the biggest opportunities for efficiency gains appear to relate to the abolition of various redundant procedures (e.g. 5-yearly renewals), increased

[113] https://www.ema.europa.eu/en/documents/other/programme-rationalise-international-good-manufacturing-practice-inspections-active-pharmaceutical/active-substance-manufacturers-terms-reference-procedures-participating-authorities_en.pdf

integration and collaboration among regulators within and beyond the EU and the need to pursue digitisation in a more determined and holistic manner.

Several points emerge from our assessment of this long list of proposals, whereby the feedback from our wider consultations and literature reviews suggests that these proposals may need to be appraised finally based on a more strategic view of the organisation and resourcing of the overall ecosystem. We see a risk in principle that this elemental approach could lead to piecemeal implementation of the easier fixes, and miss the opportunity to achieve more substantive and lasting improvements:

- The overall system is complex and in danger of becoming more so, and that creating new coordination units or advisory structures is likely to add to the costs and the confusion, without bringing any substantive improvements in functional effectiveness. Our consultations revealed widespread criticism by industry as regards the complexity, rigidity and levels of duplication that the experience with the current system. While these stakeholders can offer numerous examples of difficulties experienced or delays in decision making, they were unable to quantify these inefficiencies overall. Their concerns are echoed by the regulators too, who point to the challenges of fragmentation and resourcing that accompany the EU regulatory model, as compared with the more centralised and integrated US system. There are also concerns being expressed publicly by the chair of the CHMP who told the DIA Europe 2022 conference delegates that the EMA struggles to do its job as a result of its limited resources and its reliance on experts from national regulators to carry out a large part of the work of the committees, given these experts have day jobs and may not be available or allowed to invest the time needed. He noted the duplication of regulatory work across the EU, with numerous regulators carrying out their own reviews of the same products, between sectors and across countries, even within the EEA. The concerns about resourcing, complex committee structures and organisational efficiency were underlined in another presentation, by the head of the EMA's regulatory science and innovation task force, noting problems with approval times. He commented on the use of the clock-stop methodology, which was hiding issues with turnaround times. He also cited the study carried out for EFPIA looking into the 67-day decision making process (33-198 days in practice)[114] at the EC for the issuing of a marketing authorisation decision following the CHMP opinion, and whether it could be shortened.
- The many proposals for organisational reform and digitalisation should be considered together, in the round, with a view making a step change in the level of systemic integration, data sharing, collaborative working and the findability of relevant data and information from across the system.
- Many of these proposals have merit and could be taken forward to the benefit of the system overall, however, it is not clear that many should be a matter for the regulation specifically, inasmuch as they have no need to be detailed specifically in the primary legislation and possibly not even in the accompanying technical guidelines and other 'soft law.' Most of the proposals are about the organisational coherence and dynamism of the whole regulatory system and its integration with other contiguous areas of regulator interest in the health, environment, innovation, and industrial policy realms. There is a risk that hardwiring these elements in the legislation will reduce the long-run effectiveness of the overall ecosystem, adding costs rather than adding speed, efficiency, and agility.

[114] https://www.vintura.com/news/every-day-counts-improving-regulatory-timelines-to-improve-time-to-patient-access-across-europe/

*Table 69 Qualitative assessment of proposals for streamlining*

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| Abolish the sunset clause for all medicinal products | Evaluation revealed feedback suggesting this procedure had not been used greatly<br>EMA monitors withdrawals (I think), which relate to all regulatory pathways and can be triggered by EU / MS regulators | Industry sees little added value in this procedure, which would create some small savings<br>National regulators are more positive about having an ability to formally register that a medicine has been withdrawn and thereby close a file | No quantitative data identified<br>No substantive costs expected (+/-) | No quantitative data identified<br>Would reduce costs to a very limited degree for MAHs (+) |
| Abolish requirement for renewal of marketing authorisation for all medicinal products | Evaluation confirmed this was problematic<br>IA feedback | Almost universal support for this proposal<br>The 2-3 environmental groups in the room disagreed | No quantitative data identified<br>No substantive costs expected (+/-) | No quantitative data identified<br>There would be substantial time-related cost savings for regulators and industry (++)<br>(could we use pharmacovigilance fees as a proxy?) |
| Abolish the additional monitoring requirement and accompanying black symbol. | Eval: No feedback<br>IA: not asked<br>The EMA maintains a current list of medicines subject to additional monitoring (c. 375) and black label | The EFPIA delegation suggested they would be supportive of this proposal<br>No other delegates offered any remarks | No quantitative data identified<br>No substantive costs expected (+/-) | No quantitative data identified<br>There would be time-related cost savings for regulators and industry (+)<br>(could we use pharmacovigilance fees as a proxy?) |
| Abolish risk management plans for generics, biosimilars, hybrid and informed consent products, unless the reference medicinal product has requirement for additional risk minimisation measure in its risk management plan or unless specifically requested for generics etc. | Eval: No feedback<br>IA: asked as part of a composite question, which received a very strong positive response from industry (and regulators | RMPs for generics were not discussed in BG4 | No quantitative data identified<br>The introduction of a risk-based approach to the development of RMPs should not create any meaningful additional costs, beyond the initial costs to develop, pilot and refine a robust system (-) | No quantitative data identified<br>The introduction of a risk-based approach to the development of RMPs should deliver cost savings to the generics industry (++) |
| Certification of active substance master file (ASMF) – an independent procedure prior to application for | Eval: No feedback | Medicines for Europe said they support this proposal 'very | No quantitative data identified | No quantitative data identified |

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| marketing authorisation for generics | IA: not asked | strongly,' but it didn't attract wider comments | The design and implementation of this new certification system would create additional one-off / ongoing costs for regulators (-) | A certified file may reduce the need for generics companies to prepare a separate document (+) |
| Shorter timeline for MRP and DCP – what is the impact bearing in mind the market protection period? | Eval: No feedback<br>IA: not asked | Not discussed | No quantitative data identified<br>Shortening timelines implies more resources and or further simplification of procedures by regulators (-) | No quantitative data identified<br>Industry generally benefits from shorter decision-making periods (+) |
| Repeat use procedure (RUP) – legal basis for administrative zero-day MRP/RUP to prevent or address shortages | Eval: No feedback<br>IA: not asked<br>The current RUP arrangements allow member states up to 90 days accept an assessment by the reference member state | Not discussed | No quantitative data identified<br>Creating this exceptional legal basis would require national regulators to develop / agree / implement 'emergency' assessment procedures, which will create additional costs at the design stage and would create additional costs and risks at each time of use (-) | No quantitative data identified<br>Accelerated approval in an EU MS of an alternative medicine(s) authorised in another MS may help to address critical shortages, to the benefit of patients (+) |
| Establish legal basis for a platform for EMA to facilitate alignment of evidence requirements through parallel scientific advice (building on mechanisms introduced by the HTA Regulation) | Eval: No feedback<br>IA: not asked<br>The chair of the CHMP presented a paper on regulatory governance at the DIA 2022 Conference, where he talked about duplication of efforts within EMA and between EMA and other regulators | Not raised as an issue by stakeholders | No quantitative data identified<br>There would be costs – and political challenges – involved in designing, setting up and maintaining a more open and integrated system for obtaining, sharing and reusing scientific advice across regulators (-) | No quantitative data identified<br>There could be substantial efficiency gains – and speed enhancements – across the system (++) |

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| Building in structured exchanges to ensure that the advice given at each step of the development is known and taken into account by the other bodies (e.g. scientific advice given by EMA should be aligned with the authorisation processes of the clinical trials related to this advice). | Eval: No feedback<br>IA: not asked<br>Harald Enzmann chair of the CHMP presented a paper on regulatory governance at the DIA 2022 Conference, where he talked about duplication of efforts within EMA and between EMA and other regulators | Industry delegates cited the work done by their various representative bodies on the biggest opportunities for streamlining, from an industry perspective, which include<br>1. Iterative regulatory advice and agility<br>2. Expedited, flexible and dynamic assessment and decision-making pathways.<br>The top 5 issues were identified through a poll at the DIA 2022 Conference | No quantitative data identified<br>There would be costs – and political challenges – involved in designing, setting up and maintaining a more open and integrated system (-) | No quantitative data identified<br>There could be substantial efficiency gains – and speed – across the system (++) |
| Efficient governance of European Medicines Regulatory Network | Eval: No feedback<br>IA: not asked<br>The European Medicines Regulatory Network strategy to 2025 includes a section on governance, operational excellence and sustainability. But no references to or expected scale of impact.[115] | Not discussed | No quantitative data identified<br>Strengthened coordination would bring some small additional costs (ongoing) for regulators, for secretariat / governing body / individual members (-) | No quantitative data identified<br>Strengthened coordination may deliver more timely / effective / even contributions to the work of the network (+) |
| Digitalisation through electronic submissions, variations to MA (see below) | Eval: industry and regulators argue that the regulatory system had fallen behind on digital<br>IA: all stakeholders are strongly supportive of further digitalisation to improve timeliness, | All stakeholders were supportive of the need for the regulatory system to exploit digitalisation more fully<br>Variations to the MA were noted as being a major source of administrative costs for industry | No quantitative data identified<br>The incremental improvement to the submission of applications and variations may be relatively low cost and could possibly be done without | No quantitative data identified<br>Improved portals for submissions and variations would provide efficiency gains / savings for applicants and MAHs (+++)<br>… and for regulators (+) |

[115] https://www.ema.europa.eu/en/documents/report/european-union-medicines-agencies-network-strategy-2025-protecting-public-health-time-rapid-change_en.pdf

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| | efficiency and consistency<br><br>The EMA is investing heavily in digital transformation, and is closely involved with wider projects on digital health. EMA Digital Business Transformation task force (17 FTE); EMA Data Analytics and Methods Task Force (62 FTEs)[116] | Several contributors signalled a note of caution around digitalisation: there is substantial work in hand already by EMA and others; and there is a need for a wide-ranging and holistic approach to digitalisation that goes far beyond the regulation.<br><br>Digitalisations also needs to be properly planned, funded and overseen | impeding wider ambitions<br><br>There would be some limited one-off costs involved with digitalisation of submissions (-)<br><br>The ongoing costs would be recharged as fees to applicants / MAHs, increasing charges by a small fraction (-) | |
| Electronic submission of applications or registrations by companies. This would cover not only applications for marketing authorisation and variations, but also possibly for manufacturing or wholesale distribution authorisation as well as registrations of manufacturers/importers of active substance and of brokers. | Eval: industry and regulators argue that the regulatory system had fallen behind on digital<br><br>IA: all stakeholders are strongly supportive of further digitalisation to improve timeliness, efficiency and consistency | All stakeholders were supportive of the need for the regulatory system to more fully exploit digitalisation<br><br>Variations to the MA were noted as being a major source of administrative costs for industry<br><br>Several contributors signalled a note of caution around digitalisation: there is substantial work in hand already by EMA and others; and there is a need for a wide-ranging and holistic approach to digitalisation that goes far beyond the regulation.<br><br>Digitalisations also needs to be properly planned, funded and overseen | No quantitative data identified<br><br>The incremental improvement to the submission of applications and variations may be relatively low cost and could possibly be done without impeding wider ambitions<br><br>There would be some limited one-off costs involved with digitalisation of submissions (-)<br><br>The ongoing costs would be recharged as fees to applicants / MAHs, increasing charges by a small fraction (-) | No quantitative data identified<br><br>Improved portals for submissions and variations would provide efficiency gains / savings for applicants and MAHs (++)<br><br>… and for regulators (+) |
| Legal basis for Electronic Product Information (i.e. electronic labelling and package leaflet to replace the paper one for hospital administered products and | Eval: no feedback<br><br>IA: all stakeholders support the move to ePI | All stakeholders support the move to ePI, while noting it may take time and there are issues of digital access / literacy | No quantitative data identified<br><br>The numerous pilot initiatives being run at EU, member state and | No quantitative data identified<br><br>Electronic product information would provide numerous advantages in terms of the ease of |

[116] https://www.ema.europa.eu/en/documents/report/final-programming-document-2022-2024_en.pdf

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| products administered by healthcare professionals). | | People noted there is substantial activity in this space already, that needs to be learned from.[117]<br>The move to digital also creates opportunities for a more diverse / effective means by which to communicate stator information such that patients are more likely to see this information and understand it<br>It was suggested that the legislation should facilitate this trend by considering ePI equivalent to paper leaflets | international levels suggest that while the electronic solution may be relatively simple to put in place, the creation of an integrated / safe system is likely to be costly / challenging (--) | access for the majority of patients with opportunities to improve readability and assistive technologies and to ensure information is kept up to date and in line with the SmPC(++) |
| Streamline procedures to facilitate efficient interaction and synergies between different but related regulatory frameworks e.g. Medical Device (for certain type of products) and Health Technology Assessments. | Eval: No feedback<br>IA: Strongly positive feedback from industry and regulators on this aspect | Delegates flagged the presentations by regulators at the DIA 2022 conference openly calling for reform of structures and processes both within the core medicines regulators (EMA) and between EMA and others | No quantitative data identified<br>Devising and implementing new structures to facilitate improved interaction would bring one-off costs and ongoing costs for regulators seeking to ensure that all actions / decisions are fully joined up with other affected regulators (-) | No quantitative data identified<br>Improved interaction may reduce occasional delays and duplication of effort (+) |
| Closing potential gaps in Benefits/Risk of combination products where medicinal products have the primary role | Eval: no feedback<br>IA: not asked directly<br>Stakeholders were strongly positive about the potential benefits of the introduction of coordination and advisory mechanisms to | Delegates were supportive of the need for a regulatory ecosystem that didn't have gaps and was well-integrated (e.g. combinations with medical devices) and future proof (e.g. AI) | No quantitative data identified<br>The new mechanisms would bring additional costs for the EMA and other regulators (-) | No quantitative data identified<br>Closing gaps would help reduce some unnecessary delays in assessments for applicants (+) |

[117] https://www.eahp.eu/practice-and-policy/ehealth-and-mhealth/ePIsurvey

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| | facilitate the timely / consistent assessment of the growing number of combination products | | | |
| Introducing joint scientific advice for developers of combination products | Eval: no feedback<br>IA: not asked | Not discussed | No quantitative data identified<br>The creation of a mechanism for providing joint scientific advice may create some additional costs for regulators with one-off costs to set up protocols and guidelines such that the structure / process can be implemented as necessary and consistently (-) | No quantitative data identified<br>The creation of a mechanism for providing joint scientific advice may reduce occasional difficulties working across committees and regulators, and thereby create some small efficiency gains for regulators and some time savings for applicants (+) |
| Data sharing for centrally authorised medicines with downstream decision makers in compliance with GDPR, taking into account commercially confidential information and the EHDS proposal | Eval: no feedback<br>IA: not asked | Delegates acknowledged the importance of a holistic approach to ehealth including data sharing | No quantitative data identified<br>Setting up an EU-wide system to facilitate downstream access to authorised medicines data would be challenging and may be quite costly to implement and operate for EMA (fees charged to HTAs) (--) | No quantitative data identified<br>Improved access to data by HTAs etc may facilitate their assessment processes and allow occasional queries to be answered by direct interrogation of those data. However, it is not clear how significant such data are to effective / expeditious decision making (+)<br>In the longer term, it may benefit MA holders through an ability to re-use large parts of a dossier for an HTA assessment from their submissions to the assessment agency (+) |
| Increase collaboration between MS and with trusted strategic partners to ensure a better supervision while saving resources by: developing collaborative | Eval: no feedback<br>IA: not asked | International cooperation was not discussed at length during the workshop, however, there | No quantitative data identified<br>(the EMA has published several reviews | No quantitative data identified<br>The EMA's international collaboration on |

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| inspection programmes and expanding the existing ones on API and sterile product manufacturing sites; increase the reliance on inspection reports from trusted authorities, e.g. US FDA, MHRA (concept paper on this); extra inspection capacity and build more efficient specialised inspector capability (concept paper on this) | There is substantial work ongoing, including for example the EMA-coordinated International Collaboration on GMP inspections, the ICMRA (International Coalition of Medicines Regulatory Authorities), and through the EMA's ad hoc work with non-EU regulators through its thematic topics or 'clusters.'[118] | was an acknowledgement of the potential for reducing burden through greater cooperation internationally | of its international programmes, but none has sought to quantify the costs and benefits)[119]<br><br>The EU pharma legislation may need to explicitly approve the legitimacy of this global collaborative approach. Beyond providing the necessary permission, most of the relevant activities would fall outside the legislation.<br><br>Creating a more substantive international collaboration programme for inspections (etc.) would bring some additional design / set-up costs and would bring costs associated with the EMA's oversight / coordination of EU and EU MS participation in this global programme (-) | inspections states that there are important gains from increased cooperation and collaboration that derive from pooled resources, reduced duplication, greater consistency, and greater scope / reach of inspections.<br><br>There is an expectation that the revisions to the legislation will seek to extend the scope of EU interests in the performance of global supply chains and that the need for collaboration will become more urgent and demand greater reciprocity. This may become more of an international relations issue, however, it should also deliver efficiency and quality benefits for the system overall (+) |
| Additional leverage of regulators on summary of product characteristics (SmPC) based on evidence on safety and efficacy (i.e. to adapt the product information without full consent of the marketing authorisation holder). This adaptation could be during the assessment of the application for marketing | Eval: no feedback<br><br>IA: not asked<br><br>Our consultation did consider the potential benefits of a more harmonised and regular process for updating SmPC linked with older | Not discussed | No quantitative data identified<br><br>The intensification / acceleration of the established process for notifying / updating SmPCs would bring additional costs for industry | No quantitative data identified<br><br>With no view on the nature and extent of the problem, it is not possible to determine what benefits such a change would deliver, even qualitatively or directionally (+/-) |

[118] https://www.ema.europa.eu/en/partners-networks/international-activities/cluster-activities

[119] https://www.ema.europa.eu/en/documents/other/programme-rationalise-international-good-manufacturing-practice-inspections-active-pharmaceutical/active-substance-manufacturers-terms-reference-procedures-participating-authorities_en.pdf

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| authorisation or during post-authorisation procedures. | antimicrobials, which was viewed positively. | | and for regulators (-)<br>The suggestion that regulators – or their agents – would update the product information without the consent of the MAH, even as a last resort, would be resisted by industry (--) | |
| Increase or optimise the regulatory support to SMEs, academia and public innovators to bring their innovative products to market more efficiently. Similar measures for academic and public innovators be introduced as for SMEs, e.g. fee reductions, more advice | Eval: the evaluation found a positive view regarding the support provided to SMEs, in terms of both additional advice and fee reductions<br>IA: this question was not asked specifically | Industry delegates underlined their wish for a much more agile and interactive regulatory system. They noted this dynamic approach was especially important for smaller businesses<br>On a related matter, industry delegates signalled caution about the possible risks of regulators seeking to encourage engagement by non-commercial actors through the creation of less-rigorous pathways<br>The healthcare and academic communities did not offer a view on the needs / solutions for optimising support | No quantitative data identified<br>This would have some limited additional cost and resource implications for the EMA and its partner national regulators, in setting up and delivering additional, on-demand bespoke advice for SMEs, academics and non-commercial organisations (-)<br>Any further fee reductions would also<br>There may be limited additional demand for such services, so the ongoing costs | No quantitative data identified |
| Address availability issues related to radiopharmaceuticals. Better define the scope to avoid overregulation of radiopharmaceuticals as per defined in the evaluation. | Eval: no feedback<br>IA: not asked | Not discussed directly, beyond a short remark about these types of therapies having a potentially high environmental risk and needing to be considered by the pharma legislation based on benefit-risk to patients as well as to the environment | No quantitative data identified | No quantitative data identified |

*Table 70 Assessment of horizontal measures that may support new regulatory concepts and structures*

| Empowering new concepts | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| Strengthen the environmental risk assessment (ERA), as appropriate, and assess whether it should be part of the risk-benefit assessment; assess whether the introduction of risk mitigation measures, where needed, would be enough to address the environmental concerns; ensure no duplication of testing is carried out; aim at the harmonisation in the way ERAs are carried out in all Member States, while assessing what entails to have a common data basis, accessibility and transparency of environmental information for all products. | Stakeholder feedback revealed broad support for doing more with ERA<br><br>Public authorities, CSOs and health services believe this is important<br><br>Industry is slightly positive | Industry is supportive of a strengthened ERA, but suggests the assessment should be risk-based and focus on the APIs rather than product<br><br>Industry supportive of more harmonisation and more transparency (EPARs)<br><br>CSOs noted that there is less work done – and more gaps on older APIs – on pharma substances than in other sectors<br><br>Industry noted that EU-based manufacturers are responsible for a fraction of all releases (2%); perhaps not the case globally<br><br>Industry noted that there is substantial other legislation that address these issues (inclusion in the pharma legislation is less relevant) | No quantitative data identified<br><br>A strengthened ERA would bring additional limited costs for all MA applicants (-)<br><br>A more careful assessment of an expanded ERA and a fuller record of that assessment may bring limited additional costs for regulators (-) | No quantitative data identified<br><br>Greater transparency and reuse would avoid duplication of effort and bring some limited savings for industry and regulatory bodies (+)<br><br>Given the thicket of other applicable EU legislation, this initiative would not add much value from an environmental perspective (+/-) |
| Empower regulatory authorities to access raw data, e.g. in cases where a regulatory submission include only aggregated data or to monitor the effectiveness following post-marketing authorisation. Competent authorities for medicines authorisation to access raw data of applicants or marketing authorisation holders to review/analyse this data themselves. | Eval: no feedback<br><br>IA: not asked | Not discussed directly<br><br>There was general support by industry and regulators and CSOs for the regulatory system to improve its management, re-use and access to regulatory data overall<br><br>Given the likely costs and risks to privacy / confidentiality, industry may object to the proposal that regulators should have the authority to insist on having routine access to raw data to | No quantitative data identified<br><br>Some limited additional costs for industry that would follow a need to curate / archive 'raw data' securely enough to grant regulators managed access (-)<br><br>Some additional costs associated with regulators having to resource these occasional and ad hoc deep dives (-) | No quantitative data identified<br><br>The need to make raw data open to regulators may have a small positive impact on the curation of data and the consistency of the underpinning work processes (+)<br><br>There may be some limited gain for applicants if regulators can clarify at least some technical questions that arise during assessments from direct access to micro-data. However, there is a risk that such open and unguided |

| Empowering new concepts | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| | | support their own assessment work | | access to data would be likely to generate more queries rather than fewer. (+)<br>There may be a timing benefit if queries can be resolved more easily and quickly through direct access. (+) |
| Use under certain conditions experts outside national competent authorities to ensure capacity and expertise for assessment | Eval: no feedback<br>IA: not asked directly<br>EMA / NCA resourcing pressures were raised in the consultation | Not discussed directly<br>Delegates suggested that the EU regulatory model is under pressure and that resourcing issues are causing many delays and disadvantaging EU businesses | No quantitative data identified<br>Regulators would have to fund the creation and management of a large pool of appropriately qualified experts and pay their fees (cf DG RTD's pool of expert evaluators that support the review of calls for proposals (-) | No quantitative data identified<br>A standing college of experts would help to reduce delays in assessments relating to capacity bottlenecks. It is unknown how often capacity is the root cause of significant delays (+)<br>External experts would help to reduce the unevenness of workloads across NCAs, with several EU member states providing a disproportionate share of capacity for scientific assessments (+) |
| Opening certain procedures for third country participation to strengthen global attractiveness | Eval: no feedback<br>IA: not asked | Not raised as an issue | No quantitative data identified<br>The scope or purpose is unclear, however, there would be additional costs to the regulators if this expands enquiries / applications overall (and that expansion tracks back to organisations with limited prior knowledge of the EU regulatory context (-) | No quantitative data identified<br>The scope or purpose is unclear, so benefits cannot be understood beyond the general notion of increased global attractiveness (+/-) |
| Adapt where necessary the regulatory system to support the use of new concepts including real | Eval: no feedback<br>IA: RWE was raised in the consultation | Industry delegates made clear they are advocates of regulators being | No quantitative data identified | No quantitative data identified |

| Empowering new concepts | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| world evidence, health data while keeping the standards of Q/S/E | as being an important trend that will benefit regulatory systems in future<br>The EFPIA study on real-world data and real-world evidence found that companies are making use of RWD (84%) albeit less than half had used these data in regulatory documents[120] | open to new concepts including RWE<br>Regulators / CSOs did not offer a view on this question | Regulators may incur some limited one-off costs associated with the development of new guidelines (-)<br>There may be some inefficiencies / delays initially as committees build experience of using these new concepts and calibrate the value of novel data sources. (-) | Some timing and efficiency gains for MA applicants and MA holders, but impacts may be quite limited in the medium term as these data types are generally used as complements to other data<br>Should result in regulators being able to take more confident / speedier decisions on applications<br>Should improve quality / efficiency of post marketing authorisation activities (+) |
| Information from application dossiers, including for nationally authorised products, as regards the manufacturing sites for finished products and APIs, available to authorities and make data held by regulatory agencies and manufacturers available using the EHDS framework. | Eval: no feedback<br>IA: not asked | Not raised as an issue directly, but as noted above there was general support across stakeholders for enhancing the use of digital solutions to facilitate increased data sharing and re-use<br>There was strong support for developing structures / platforms to facilitate increased worksharing | No quantitative data identified<br>There would be costs associated with such a system for industry, in ensuring its data are held and curated in a manner that would facilitate this more open approach (-)<br>There would be costs associated with the design and implementation of such a system for EMA and NCAs, even if it were inked with the existing EHDS infrastructure (-) | No quantitative data identified<br>This data sharing would be beneficial to post authorisation activities, providing improvements in speed / convenience of access, reuse and supporting collaborative working (+) |
| Introduce an EU-wide centrally coordinated process for early dialogue and more coordination among clinical trial, marketing authorisation, health technology assessment bodies, pricing and reimbursement authorities and payers for integrated medicines development and post-authorisation monitoring, | Eval: no feedback<br>IA: not asked | Industry delegates underlined their wish for a much more agile and interactive regulatory system. They noted this dynamic, interactive approach was especially important for smaller businesses | No quantitative data identified<br>Early dialogue may place additional pressures on EMA finances and resourcing (and the regulatory network)<br>Doing this EU-wide would bring substantial | No quantitative data identified<br>Early dialogue is seen by industry as a major opportunity to improve developers' abilities to deliver mature / comprehensive applications that are more likely to |

[120] https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.2103

| Empowering new concepts | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| pricing and reimbursement. When providing scientific advice to developers, at its scientific discretion EMA can take into account this early dialogue and coordination. | | A delegate suggested that academia and SMEs should have access to early agile and maybe more informal advice (price is prohibitive for academia). They noted that the INTERACT meeting with the FDA is quite efficient for early discussion: a phone call with a simple briefing package allows for early brainstorming and then early directions in regard to potential classification and regulatory considerations | additional costs (--) | be assessed quickly (and positively). Doing it EU wide would be a strongly positive approach (++)<br>A more coordinated approach should result in some savings for national authorities (+) |
| Create an expert group to give advice/guidance on UMN – cross-sector involving health technology assessment bodies (via the Coordination Group of HTA bodies set up under the new HTA Regulation), pricing and reimbursement bodies, patients, and academic representatives. | Eval: no feedback<br>IA: not asked directly | Not discussed | No quantitative data identified<br>Introducing a regulatory incentive specifically for UMNs will require the creation of an agreed set of definitional criteria or lists of UMNs. This will require additional guidance and possibly additional advice for assessment bodies.<br>A cross-sector working group may reduce the operational effectiveness and timeliness of such a body, from the perspective of medicines regulators specifically (-) | No quantitative data identified<br>The creation of a standing group to give advice on UMNs to multiple regulators and pubic bodies may produce some efficiency gains and support a more consistent implementation, with a potential for cost sharing across stakeholders (+) |
| Creation of an emergency use authorisation (EUA) at EU level as an additional tool to support faster use of medicines without a marketing authorisation during pandemic situation | Eval: no feedback<br>IA: not asked directly | Not discussed | No quantitative data identified | No quantitative data identified |

### *12.6.3 Cost benefit analysis for the horizontal measures*

#### 12.6.3.1 Qualitative assessment of costs and benefits relating to the pivotal horizontal measures

Table 71 presents an overview of the 10 pivotal measures and our qualitative assessment of the costs and benefits for each proposal, which we have analysed in Table 72 below.

*Table 71 Overview of the pivotal horizontal measures and their expected costs and benefits*

| Description | Qualitative assessment of costs and benefits |
|---|---|
| **1. Streamlining of procedures**, including avoiding duplicative processes (including GMO requirements, prioritisation of applications, better coordination within the regulatory network; renewal of marketing authorisation, PhV requirements – RMPs for generics + black symbol):<br>– Abolish the sunset clause for all medicinal products<br>– Abolish requirement for renewal of marketing authorisation for all medicinal products<br>– Abolish the additional monitoring requirement and accompanying black symbol.<br>– Abolish risk management plans for generics, biosimilars, hybrid and informed consent products, unless the reference medicinal product has requirement for additional risk minimisation measure in its risk management plan or unless specifically requested for generics etc.<br>– Certification of active substance master file – an independent procedure prior to application for marketing authorisation for generics | Benefits: the various streamlining procedures proposed would deliver direct cost savings to both industry and regulators. Abolition of risk management plans may be the most beneficial to generics companies and national regulators. These various procedures bring occasional costs for most companies at some point in time (++)<br>Costs: the proposed abolition of various duplicative procedures should not result in any meaningful additional costs for any stakeholders. The creation of a certification system for the ASMF would bring one-off costs for the design and implementation of the enhanced procedure, falling on regulators |
| **2.** Enable an **accelerated mutual recognition procedure** (MRP) within the EU, Enable a (more) efficient Repeat Use Procedure, For EU authorities to reduce the administrative and cost burden submission of post approval changes<br>– Shorter timeline for MRP and DCP – what is the impact bearing in mind the market protection period?<br>– Repeat use procedure (RUP) – legal basis for administrative zero-day MRP/RUP to prevent of address shortages | Benefits: as accelerated procedure would benefit the generics industry directly and possibly health payers indirectly, with generic competition being brought forward by a month or so in a proportion of cases. A legal basis for a zero-day MRP may help to address critical shortages to the benefit of patients, where there is an alternative medicine(s) authorised in another MS but not in the MS in question. (++)<br>Costs: the accelerated MRP should be achieved through streamlining and harmonisation of procedures (and various improvements to digital infrastructure, worksharing and pan-EU data services), so should bring few if any additional costs for regulators. The zero-day RUP would require some limited one-off costs for the network / regulators to prepare a detail design and associated procedures that all member states would support. (--) |
| **3.** Efficient governance of European Medicines Regulatory Network: (not for assessment) formalize the structure of the network including role and tasks of Heads of Medicines Agencies; efficient cooperation of EMA committees – simplify processes of EMA committees when several are involved. Strengthen system of inspections to better use resources | Efficient governance<br>Benefits: more efficient governance of the regulatory network should reduce the average elapsed time between initial application and a recommendation, which will benefit developers by creating the potential for earlier market launch and patients indirectly. It should also bring efficiency gains for regulators. Better coordinated cross-border and international inspections should provide efficiency gains for regulators (+++) |

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| – Increase collaboration between MS and with trusted strategic partners to ensure a better supervision while saving resources by :<br>– develop collaborative inspection programmes and expand the existing ones on API and sterile product manufacturing sites<br>– increase the reliance on inspection reports from trusted authorities, e.g. US FDA, MHRA (concept paper on this)<br>– support extra inspection capacity and build more efficient specialized inspector capability (concept paper on this) | Costs: Strengthened governance may bring some small additional costs for regulators associated with an expanded coordination function (-) |
| **4.** Streamline procedures to facilitate **efficient interaction and synergies between different but related regulatory frameworks** e.g. Medical Device (for certain type of products) and Health Technology Assessments.<br>– Closing potential gaps in B/R of combination products where medicinal products have the primary role<br>– Introducing joint scientific advice for developers of combination products<br>– BTC framework could be added as well. | Efficient interaction between related regulatory frameworks<br>Benefits: more efficient interaction across regulatory frameworks should reduce the average elapsed time between initial application and a recommendation for a proportion of applications (e.g. combination products), which will benefit developers by creating the potential for earlier market launch. It should also bring efficiency gains for regulators. (++)<br>Costs: Devising and implementing new structures to facilitate improved interaction among regulators would bring one-off costs associated with the design / implementation of those new structures and ongoing costs for regulators of running those coordination mechanisms seeking to ensure that all actions / decisions are fully joined up with other affected regulators (-) |
| **5.** Legal basis for the network to analyse real world evidence, **create computing capacity, store and manage large data sets and to share the data** with the HTA Coordination Group as set out in Regulation 2021/2282 and Pricing and reimbursement authorities, in compliance with GDPR, taking into account commercially confidentially information and the EHDS proposal. | Real world evidence and a pan-EU data service<br>Benefits: a more inclusive view of allowable data should help regulators with both the assessment of applications and various post-authorisation activities. The creation of an integrated online data service accessible by various types of health regulators should bring major efficiency gains for the system overall. (+++)<br>Costs: The EU and regulators may incur significant one-off costs associated with the creation of a new integrated data infrastructure for the regulatory system overall. There will be additional recurrent costs associated with the operation and maintenance of what would be a large and growing data set. (---) |
| **6.** Legal basis for **Electronic Product Information** (i.e. electronic labelling and package leaflet to replace the paper one for hospital administered products and products administered by healthcare professionals). | ePIL<br>Benefits: having a legal basis for ePIL would anticipate and reinforce a trend. Electronic product information would make it easier for healthcare professionals to access comprehensive and up-to-date information on products within different settings. There would be some small environmental benefit in terms of reduced use of paper and less waste, albeit manufacturers would need to run paper and electronic systems in parallel) (++)<br>Costs: manufacturers would incur one-off costs associated with the upgrading of their electronic publishing capabilities. But should otherwise be well placed to expand ePIL provision. Regulators and healthcare systems would incur one-off costs when negotiating the creation of a 'common' EU-wide infrastructure for ePIL and recurrent costs associated with its operation and maintenance. (---) |

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| **7.** Electronic submission of applications or registrations by companies<br>– This would cover not only applications for marketing authorisation and variations, but also possibly for manufacturing or wholesale distribution authorisation as well as registrations of manufacturers/importers of active substance and of brokers. | Electronic submission<br>Benefits: manufacturers would see efficiency gains from the introduction of a fully digital submission platform. Regulators would similarly see efficiency gains from a move to digital submissions supporting the re-use of data across functions and committees and for example eliminating the need for committee members to work with large paper files. There would be an environmental benefit too from the reduction in the use of paper. This would provide a small but lasting benefit to the whole industry and to all regulators (++)<br>Costs: manufacturers may incur some very limited one-off costs associated with harmonisation of their data systems with any new templates. The regulators would incur one off costs in creating the new submission system and recurrent costs associated with its operation and maintenance. There is already substantial use of online submissions and digital solutions, so while there would be costs for all actors these should be relatively modest (-) |
| **8.** Increase or **optimise the regulatory support** to SMEs, academia and public innovators to bring their innovative products to market more efficiently | Optimise regulatory support SMEs and non-commercial<br>Benefits: SMEs would benefit from additional support / scientific advice tailored to smaller developers, which may help them to develop applications with more confidence and with a greater likelihood of a successful opinion. Non-commercial organisations would also benefit from tailored support, as they are likely to have even less experience and internal support when it comes to regulatory matters. Given the growing importance of small biopharma, this expansion in regulatory support could be highly beneficial to startups and innovative therapies. (++)<br>According to the latest EMA annual report, requests for scientific advice has been increasing at 5-10% year over the past five years (787 requests in 2020). In 2020, 25% of all requests for scientific advice came from SMEs. The EMA's review of SME support (2020) obtained feedback from 553 SMEs and found the very great majority (80%) judged themselves to be well appraised of the support on offer (fees and advice) and more than 90% judged the support / services to be relevant. The primary requests for improvements related to additional financial discounts and simplified applications<br>Costs: the EMA would incur additional costs associated with this expanded and tailored support. The numbers of users may not be especially high, which would contain costs, however, the amount of support required for an average request may be proportionately much greater than would be the case for most developers (-) |
| **9.** Adapt where necessary the regulatory system to **support the use of new concepts** including real world evidence, health data while keeping the standards of Q/S/E | Adapting the system to use new concepts<br>Benefits: this would deliver greater regulatory alignment with important developments, improving the speed of decision making and reducing regulatory costs. It would reward developers for using new and emerging types of data within their applications (++)<br>Costs: the EMA would incur additional one-off costs associated with the creation of new or expanded guidelines and working methods to tackle new concepts with confidence and consistently. (--) |
| **10.** Introduce an **EU-wide centrally coordinated process for early dialogue** and more coordination among clinical trial, marketing authorisation, health technology assessment bodies, pricing and reimbursement authorities and payers for | Early dialogue with developers and across regulators<br>Benefits: early, iterative regulatory advice and dynamic assessment came out as the top two items on an industry poll (DIA Europe 2022 conference) as regards the areas where they would like to see improvements in regulatory performance. Early dialogue and more coordination |

| | | |
|---|---|---|
| | integrated medicines development and post-authorisation monitoring, pricing and reimbursement. When providing scientific advice to developers, at its scientific discretion EMA can take into account this early dialogue and coordination. | should deliver efficiency gains for industry and regulators as well as faster decision making overall (+++)<br><br>Costs: the EMA may incur substantial additional one-off and recurrent costs associated with the move to a more centrally coordinated and dynamic assessment system, covering both the CP and distributed procedures and leading on coordination with other agencies (---) |

Lastly, in Table 72, we have summarised this preceding tabular presentation in a more visual, qualitative assessment of the benefits of each of the 10 pivotal horizontal measures, by key stakeholder group. From this perspective, the most promising horizontal measures – overall, for all stakeholder groups – are the proposals to improve the governance of the European medicines regulatory network, the development of an integrated, pan-EU data architecture for the regulatory system and an EU-wide, centrally coordinated process for early dialogue.

*Table 72 Qualitative assessment of the benefits of pivotal horizontal measures, by key stakeholder group*

| | Business | EMA | NCAs | SMEs | Health Systems | Environmental |
|---|---|---|---|---|---|---|
| **Streamlining and de-duplication** | | | | | | |
| #1 Streamlining of procedures | H | M | M | H | L | L |
| #2 Accelerated MRP and more efficient RUP | H | L | H | L | M | L |
| #3 Efficient governance of the European Medicines Regulatory Network | H | H | H | H | M | L |
| #4 Facilitate more efficient interaction across regulatory frameworks | M | H | M | M | M | L |
| **Digitalisation** | | | | | | |
| #5 Legal basis to allow network to create an integrated, pan-EU health regulatory data service | M | M | H | H | H | M |
| #6 Legal basis for setting up ePIL system for healthcare professionals | L | M | M | L | M | M |
| #7 Electronic submission of applications | H | H | M | H | L | M |
| **Enhanced support and regulatory flexibility** | | | | | | |
| #8 Optimise regulatory support to SMEs and non-commercial organisation | L | M | L | H | H | L |
| #9 Adaptation of the regulatory system to support the use of new concepts | H | M | M | H | M | L |
| #10 EU-wide centrally coordinated process for early dialogue | H | M | H | H | M | L |

### 12.6.3.2 Overview of costs and benefits

Table 73 presents an overview of the costs and benefits associated with the three major categories of horizontal measures identified through the impact assessment. This has been prepared in line with the better regulation guidelines, with the costs presented in line with the standard cost model.

It shows estimated total costs for the pivotal streamlining measures combined fall in the range €1.1bn to €2.5bn. We estimate the total benefits will fall somewhere in the range €2.8bn-€5.8bn. The benefits significantly outweigh the costs for both the lower and upper bound estimates.

The analysis suggests that the proposed streamlining measures are likely to deliver the greatest quantum of benefits, falling in the range €1.5bn-€3.1bn. By contrast the digitalisation measures are likely to be the costliest to implement, albeit with substantial benefits to the efficiency of the regulatory system overall. The analysis suggests the enhanced support measures are likely to be the most affordable (€72m-€108m), and while they will yield a lower overall benefit (€214m-€428m), it is the highest rate of return proportionately.

*Table 73 Overview of the costs and benefits associated with the horizontal measures*

| | **Businesses** | **Businesses** | **EMA** | **EMA** | **NCAs** | **NCAs** | **Totals** | **Totals** | **Totals** |
|---|---|---|---|---|---|---|---|---|---|
| | **one-off** | **recurrent** | **one-off** | **recurrent** | **one-off** | **recurrent** | **one-off** | **recurrent** | **15 years** |
| **Streamlining costs** | | | | | | | | | |
| Direct | | | | | | | | | |
| Enforcement | | | €1.8m - €3.6m | €3.5m-€7.5m | €15m-€30m | €30m-€60m | €16.8m - €33.6m | €33.5m-€67.5m | |
| Indirect | | | | | | | | | |
| Totals | | | | | | | **€16.8m - €33.6m** | **€33.5m-€67.5m** | **€519.3m-€1,046.1m** |
| **Streamlining benefits** | | | | | | | | | |
| Direct | | €15m-€30m | | €3.5m-€7m | | €30m-€60m | | €48.5m-€97m | |
| Indirect | | €55m-€110m | | | | | | €55m-€110m | |
| Totals | | | | | | | | **€103.5m -€207m** | **€1,552.5m -€3,105m** |
| | | | | | | | | | |

| | Businesses | Businesses | EMA | EMA | NCAs | NCAs | Totals | Totals | Totals |
|---|---|---|---|---|---|---|---|---|---|
| | **one-off** | **recurrent** | **one-off** | **recurrent** | **one-off** | **recurrent** | **one-off** | **recurrent** | **15 years** |
| **Digitalisation costs** | | | | | | | | | |
| Direct | | | | | | | | | |
| Enforcement | | | €20m-€50m | €4m-€10m | €100m - €300m | €20m-€60m | €120m-€350m | €24m-€70m | |
| Indirect | | | | | | | | | |
| Totals | | | | | | | €120m-€350m | €24m-€70m | **€480m-€1,400m** |
| **Digitalisation benefits** | | | | | | | | | |
| Direct | | €7.5m-€15m | | €7m-€14m | | €60m-€120m | | €75m-€149m | |
| Indirect | | | | | | | | | |
| Totals | | | | | | | | | **€1,117.5m -€2,235m** |
| | | | | | | | | | |
| **Enhanced support costs** | | | | | | | | | |
| Direct | | €1.6m-€2.4m | | | | | | €1.6m-€2.4m | |
| Enforcement | | | | €4.8m-€7.2m | | | | €4.8m-€7.2m | |
| Indirect | | | | | | | | | |
| Totals | | | | | | | | | **€72m-€108m** |
| **Enhanced support benefits** | | | | | | | | | |
| Direct | | €7.5m-€15m | | €1.75m-€3.5m | | | | €9.25m-€18.5m | |
| Indirect | | €5m-€10m | | | | | | €5m-€10m | |

| | Businesses | Businesses | EMA | EMA | NCAs | NCAs | Totals | Totals | Totals |
|---|---|---|---|---|---|---|---|---|---|
| | one-off | recurrent | one-off | recurrent | one-off | recurrent | one-off | recurrent | 15 years |
| Totals | | | | | | | | | €214m-€428m |

Our overall estimates are likely to be understated slightly, as there are likely to be further indirect benefits associated with these measures, and in particular the likelihood of shortening average times for the assessment of applications, which should flow through to marginally earlier access to new medicines and generic competitors for large numbers of EU citizens and patients. We were unable to push these estimates to the point where we were able to quantify the likely benefits to patients, which are likely to be relatively limited in depth but wide-ranging.

Given the scope and diversity of the proposed initiatives and the large numbers of actors that would be involved, we have had to rely on assumptions drawn from the wider literature, to make our monetary estimates. Given the many uncertainties involved with this process, we have used ranges throughout. Our logic and assumptions are detailed in Table 74.

*Table 74 Descriptive overview of the costs and benefits and assumptions associated with the horizontal measures*

| | Description of types of costs and benefits | Assumptions made in quantification | Notes on sources |
|---|---|---|---|
| Streamlining costs | | | |
| Direct | There should be few if any direct costs associated with the various streamlining measures, which would deliver efficiency gains to businesses | | |
| Enforcement | There should be few if any enforcement costs associated with the various streamlining measures, as the principal regulatory measures relate to the abolition of procedures that are duplicated elsewhere in the system | We have assumed the one-off indirect costs might amount to 0.5-1% of EMA annual expenditure (€365m in 2020) and NCA annual expenditure (€3bn), spread over 2-3 years. We have assumed recurrent annual costs would be slightly higher, 1-2%. | We have found no quantitative estimates of the likely costs of these proposed measures through our consultations or literature reviews, and have had to make assumptions about likely level of effort and multiplied this by EMA / NCA budgets |
| Indirect | There will be no substantive indirect costs from the proposed streamlining measures | | |
| Streamlining benefits | | | |
| Direct | There should be direct cost savings to businesses and | We have assumed that these refinements may save businesses 1-2% of their | We have found no quantitative estimates of the likely benefits of these |

| | Description of types of costs and benefits | Assumptions made in quantification | Notes on sources |
|---|---|---|---|
| | regulators from the streamlining measures | regulatory costs annually (15m-30m: c. €1.5bn based on McKinsey estimate of Regulatory Costs being c. 4.1% of BERD); EMA 1-2% and NCAs 1-2% | proposed measures through our consultations or literature reviews, and have had to make assumptions based on estimates of overall regulatory costs. |
| Indirect | There may be some limited indirect benefits in terms of accelerated procedures meaning applications are authorised several weeks earlier (CP / DCP), which may facilitate at least some new medicines being approved for sale earlier and some generics entering the market earlier. | We assume the average period taken to assess applications may be reduced by 2-4 weeks, albeit the bigger impact may be on outliers and enabling a greater proportion of all assessments to be carried out closer to the median time taken. We based this 10-20 day improvement on the fact that the EMA part of the assessment process is taking around 200 days on average (EMA annual report 2020) and the accelerated assessment takes around 140 days. If we assume 50% of the EMA positive opinions are approved and manage to come to market 2-4 weeks early, and we assume an average annual EU income for a medicine at 50m (c. €1m a week), that would amount to income of around €100m-€200m being brought forward. The market would be competed away 2-4 weeks earlier, so the total income may not change. But there could be first mover advantages as well as the time value of money, and so we might suggest that businesses will benefit by 5% of the value of this earlier cashflow (5m-10m). This accelerated process would apply to generics also, and given the relative scale of assessments (CP v DCP), the benefits for this group of businesses may be an order of magnitude higher (50m-100m) | We have found no quantitative estimates of the likely impact of these proposed measures, and have no good basis for approximating the nature and extent of the possible indirect benefits. We have therefore used a large range for our assumptions. |
| Digitalisation costs | | | |
| Direct | There should be few if any direct costs associated with the various digitisation measures, which would deliver efficiency gains to businesses | | |
| Enforcement | There will be additional one-off costs for the EMA and other regulators in designing and implementing these various | We have assumed the proposed online application system may cost a few millions to implement (c. €2m-€3m, the | We have no quantitative data on costs of benefits relating to the proposed digital measures, so have |

| | Description of types of costs and benefits | Assumptions made in quantification | Notes on sources |
|---|---|---|---|
| | enhanced digitalisation measures | ePIL system may cost an order of magnitude more (c. €10m-€30m) and the integrated regulatory data system will be the most demanding and costly to design and implement and could cost several hundred millions across all regulators (€100m-€300m), perhaps €120m-€350m in total. We have assumed a split between the EMA (€20m-€50m) and NCAs (€100m-€300m). We have assumed these will be one-off costs - spread over several years - and may be associated with recurrent costs (operation, maintenance, depreciation) on the order of 25% of the one-off costs | had to look at past activities for guidance. According to the EMA final-programming-document-2022-2024, the EMA Digital Business Transformation Task Force will have access to 17 staff to deliver its various digital projects, working across 7 areas, including ePIFs and electronic submissions. Annex 19 to the EMA annual report 2020 shows that the agency invested around €7m in Business-Related IT in 2019 and will spend around €20m in 2020. Annual IT spend has fluctuated substantially however, in line with various business development programmes. |
| Indirect | There will be no substantive indirect costs from the proposed digitalisation measures, as they will retain some aspects of paper-based systems (product leaflets) to minimise risks of digital exclusion (not all citizens have or wish to use digital platforms) | | |
| Digitalisation benefits | | | |
| Direct | The various digital initiatives proposed will save time and cost for both businesses and regulators | We have assumed that these refinements may deliver efficiency gains to industry equivalent to 0.5-1% of their regulatory costs. We have assumed an annual efficiency gain of 1-2% for both the EMA and the NCAs | We have found no quantitative estimates of the likely benefits of these proposed measures through our consultations or literature reviews, and have had to make assumptions based on the wider literature on digitalisation and productivity. An OECD review suggests that productivity gains for businesses from digitalisation range from 1-4% on average. Greater use of e-government - as proposed here - is seen to deliver benefits on the order of 1%. The OECD is careful to point out that these figures can differ markedly across sectors and countries, we have therefore used a range of 0.5-1%. These digitalisation proposals will impact to a greater extent on the efficiency of the regulatory system. |

| | Description of types of costs and benefits | Assumptions made in quantification | Notes on sources |
|---|---|---|---|
| Indirect | There may be some limited indirect benefits in terms of accelerated procedures meaning applications are authorised several weeks earlier, which may facilitate at least some new medicines being approved for sale earlier and some generics entering the market earlier. | | We have found no quantitative estimates of the likely impact of these proposed measures, and have no good basis for approximating the nature and extent of the possible indirect benefits |
| | | | |
| Enhanced support costs | | | |
| Direct | There may be some limited additional costs to businesses from greater use of advice or increased dialogue more generally | We assume this might cost business an additional €1.6m-€2.4m. The EMA is currently receiving around 800 requests for scientific advice and protocol-assistance. We have no data on the intensity of work involved in preparing the request or answering it, but no doubt a proportion will be formulated in hours while others may take several staff days to respond to. We have assumed an average of 1 staff day to prepare a request and 3 staff days to process the request (with a market value of c. €1k / staff day). We have further assumed that a more interactive approach to dialogue - and greater support for SMEs non-commercial organisations - may double of treble this level of activity, for industry and regulators. For business: 1.6m=800*1*1000*2 or 2.4m = 800*1*1000*2; For EMA: €4.8m=800*3*1000*2 or €7.2m=800*3*1000*3 | We have found no quantitative estimates of the likely costs of these proposed measures through our consultations or literature reviews, and have had to make assumptions about the likely level of effort based on EMA activity statistics. |
| Enforcement | There will be additional costs for regulators associated with the enhanced and extended support measures | We assume this might cost the EMA an additional €4.8m-€7.2m. The EMA is currently receiving around 800 requests for scientific advice and protocol-assistance. We have no data on the intensity of work involved in preparing the request or answering it, but no doubt a proportion will be formulated in hours while others may take several staff days to respond to. We have assumed an average of 1 staff day to prepare a request and 3 staff days to process the request (with a market value of c. €1k / | We have found no quantitative estimates of the likely costs of these proposed measures through our consultations or literature reviews, and have had to make assumptions about the likely level of effort based on EMA activity statistics. |

| | Description of types of costs and benefits | Assumptions made in quantification | Notes on sources |
|---|---|---|---|
| | | staff day). We have further assumed that a more interactive approach to dialogue - and greater support for SMEs non-commercial organisations - may double of treble this level of activity, for industry and regulators. For business: 1.6m=800*1*1000*2 or 2.4m = 800*1*1000*2; For EMA: €4.8m=800*3*1000*2 or €7.2m=800*3*1000*3 | |
| Indirect | There will be no substantive indirect costs of these enhanced support measures | | |
| Enhanced support benefits | | | |
| Direct | Industry - and SMEs in particular - should benefit from better and more dynamic advice avoiding queries on applications (delay) and rework to the same (cost); regulators should benefit from more mature applications that can be assessed more easily and quickly | We have assumed that these refinements may save businesses 0.5-1% of their regulatory costs annually (7.5m-15m: c. €1.5bn based on McKinsey estimate of Regulatory Costs being c. 4.1% of BERD); EMA 0.5-1%. We have assumed these measures will be of less benefit to NCAs than the more general streamlining and digitalisation measures, and so have not included a value for a benefit. | We have found no quantitative estimates of the likely direct benefits of these proposed measures |
| Indirect | There may be some limited indirect benefits, whereby faster assessments, on average, may facilitate at least some new medicines being approved for sale earlier and some generics entering the market earlier. | We assume the average period taken to assess applications may be reduced by 2-4 weeks. We based this 10-20 day improvement on the fact that the industry part of the assessment process is taking around 160 days on average (EMA annual report 2020) and 200 days for SMEs. If we assume 50% of the EMA positive opinions are approved and manage to come to market 2-4 weeks early, and we assume an average annual EU income for a medicine at 50m (c. €1m a week), that will amount to income of around €100m-€200m being brought forward. The market would be competed away 2-4 weeks earlier, so the total income may not change. But there could be first mover advantages as well as the time value of money, and so we suggest that businesses will benefit by 5% of | We have found no quantitative estimates of the likely indirect benefits of these proposed measures |

| | Description of types of costs and benefits | Assumptions made in quantification | Notes on sources |
|---|---|---|---|
| | | the value of this earlier cashflow (5m-10m). | |

#### 12.6.3.3 Overview of costs and benefits relating to simplification and burden reduction

This annex deals with horizontal measures, which are primarily designed to simplify the regulatory system and reduce burden on industry and regulators alike. This is done for reasons of good governance but also in part to create the financial headroom to introduce new legislative actions and procedures that will bring additional costs, in line with the one in one out principle. As such, the preceding sub-sections deal extensively with simplification and burden reduction.

Table 75 represents these data for the wo horizontal measures that relate most directly to simplification and burden reduction, specifically streamlining and digitalisation measures. The table summarises the balance of costs and benefits, and suggests that the measures as proposed may deliver a reduction in compliance costs and burden in the range of €1.2bn-€2.4bn for industry. More specifically:

- The proposed streamlining procedures will yield useful cost savings for European pharmaceutical businesses, with estimated cost savings falling in the range of €1bn-2.1bn over the next 15-years
- The streamlining procedures are estimated to be cost neutral for the EMA, with investments in additional coordination structures and the development of new protocols and procedures being mirrored by broadly equivalent savings, with the balance of costs and benefits estimated to fall in the range €-4m to €2m over the next 15 years
- The streamlining procedures are estimated to be slightly positive in efficiency / monetary terms, for the national competent authorities, with investments in additional coordination and new procedures being outweighed by savings, with the balance of costs and benefits estimated to fall in the range €15m to €30m over the next 15 years
- The proposed digitalisation measures will provide relatively modest financial savings to industry, given the primary focus is on the integration of regulatory systems and platforms across the EU and support for the re-use of data (e.g. the 'Once Only' principle of the EU digital strategy). Electronic submission will deliver industry cost savings. These are estimated at €112m-€225m over 15 years
- The proposed digitalisation measures will provide similarly modest financial savings to the EMA, given the substantial costs involved in the design and development of the new systems. The savings are estimated at €65m-€70m over 15 years
- The proposed digitalisation measures will provide relatively greater financial savings for NCAs, with the EMA shouldering more of the substantial costs involved in the design and development of the new systems. The savings across the whole EU regulatory network are estimated at €700m-€1,200m over 15 years

*Table 75 Overview of the costs and benefits associated with the horizontal measures related to simplification and burden reduction*

| | Businesses | Businesses | EMA | EMA | NCAs | NCAs |
|---|---|---|---|---|---|---|
| | **one-off** | **recurrent** | **one-off** | **recurrent** | **one-off** | **recurrent** |
| **Streamlining costs** | | | | | | |
| Enforcement | | | €1.8m-€3.6m | €3.5m-€7.5m | €15m-€30m | €30m-€60m |
| Indirect | | | | | | |
| **Streamlining benefits** | | | | | | |
| Direct | | €15m-€30m | | €3.5m-€7m | | €30m-€60m |
| Indirect | | €55m-€110m | | | | |
| Total savings | | €1,050m-€2,100m | | €-3.9m to €1.8m | | €15m-€30m |
| **Digitalisation costs** | | | | | | |
| Direct | | | | | | |
| Enforcement | | | €20m-€50m | €4m-€10m | €100m-€300m | €20m-€60m |
| Indirect | | | | | | |
| **Digitalisation benefits** | | | | | | |
| Direct | | €7.5m-€15m | | €7m-€14m | | €60m-€120m |
| Indirect | | | | | | |
| Total savings | | €112m-€225m | | €65m-€70m | | €700m-€1,200m |

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# Contents

## ANNEX 1: PROCEDURAL INFORMATION

– *Lead DG, Decide reference and Work Programme reference.*

The Directorate General for Health and Food Safety (DG SANTE) is the lead DG on the initiative for the Pharmaceutical Strategy for Europe.

The initiative is in the European Commission's Work Programme for 2022, COM(2021)645 final, under the heading "Promoting our European Way of Life". The initiative has received the validation in the Agenda Planning on 25 March 2021 (reference PLAN/2021/10601) and the Inception Impact Assessment was published on 7 April 2021.

– *Organisation and timing.*

An inter-service steering group (ISSG) for the implementation of the Pharmaceutical Strategy for Europe was established. The ISSG specifically discussed matters relating to the evaluation and impact assessment of the general pharmaceutical legislation to ensure that they met the necessary standards for quality, impartiality and usefulness and written consultations on draft key documents took place; the comments of the ISSG were carefully considered in the development of the evaluation and impact assessment.

Along with the Secretariat-General and Legal Service, the following Commission services took part in the ISSG: DG Health and Food Safety (SANTE) DG Employment (EMPL); DG Communications Networks, Content and Technology (CONNECT); DG Internal Market, Industry, Entrepreneurship and SMEs (GROW); DG for Research and Innovation (RTD); Joint Research Centre (JRC); DG Trade (TRADE), DG International Partnerships (INTPA); DG Eurostat – European statistics (ESTAT); DG Environment (ENV); DG Energy (ENER); DG Economical and Financial Affairs (ECFIN); DG Competition (COMP), DG Climate Action (CLIMA) and DG European Health Emergency Preparedness and Response Authority (HERA).

– *Consultation of the Regulatory Scrutiny Board.*

The file benefitted from an upstream meeting with the Regulatory Scrutiny Board (RSB) on 26 January 2022. A first version of this Impact Assessment Report – with the Evaluation Report annexed – was submitted to the RSB on 22 June 2022, the meeting took place on 19 July and the RSB written report was received on 22 July 2022. The Board's overall opinion was negative and it issued the following findings:

(1) The report is not sufficiently precise about the key factors that cause unequal access to medicines and their affordability, and what exactly determines the observed differences between Member States. It is not clear if the revision will have a direct impact on access and affordability of medicines or it provides only an enabling framework to reach these objectives.
(2) The report does not clearly demonstrate the effectiveness of new incentive measures. It is not clear how the market launch conditionality and the transferable exclusivity voucher for AMR products will work. Possible counter-effects affecting the access-affordability trade-off are not sufficiently assessed.

(3) The report is not sufficiently clear on the impacts of options on innovation and competitiveness for the EU pharmaceutical ecosystem, including SMEs, and how this will affect access to and affordability of medicines for patients.
(4) The report does not sufficiently demonstrate the EU-added value, nor the proportionality of the preferred option.

The table below lists the changes in response to the recommendations of the RSB in its opinion. In addition, targeted corrections and amendments have been included in the new version of the impact assessment report to address the technical comments provided by the RSB to DG SANTE.

| **Recommendations of the RSB** | **Modifications in the impact assessment report in response to these recommendations** |
|---|---|
| (1) The report should analyse and present, in greater detail, the multiplicity of factors (and relative determinants) that lead to accessible, affordable and quality medicinal products while separating more clearly the issues caused by business decisions from those resulting from divergent public policy decisions of Member States' authorities. It should discuss the influence of decisions taken at Member State level and how these decisions emerge from different public policy approaches and procedures in Member States (e.g. assessment of the relative effectiveness of new medicines, their therapeutic added value or different political spending policies, timing of new launches, etc). The report should clearly present and substantiate with evidence the mix of problem drivers that are causing underperformance on the ground and clearly indicate where this revision can realistically improve the situation, also taking into account related initiatives. | In sections 2.1 and 2.2, expanded respectively problem definition, drivers on access and affordability and added a new Annex 14 to describe further factors for access and business decision and different pricing policies in Member States.<br><br>Furthermore, throughout the report clarified the general pharmaceutical legislation as enabling framework for these two objectives, including in section 2, and elaborated on related initiatives such as the SPC revision, e.g. in sections 7.1 and 7.3.<br><br>In the analysis of the options (section 6), especially dealing with measures to improve market access, those factors are taken into account. |
| (2) The report should describe the available information about the current negotiation dynamics between Member States and industry, e.g. to what extent industry already reflects different purchasing power levels in their pricing decisions. On that basis, it should analyse how the new incentives and obligations for placing a medicines on the market in all Member States within two years will change these dynamics in terms of negotiating power and tactics and what the projected impact would be on Member States' health care systems. The stakeholder views from both industry and Member States should be clearly presented throughout the | The new Annex 14 describes industry's sequencing of market launch in view of referencing pricing as an example of the role of different purchasing power levels of the Member States.<br><br>In sections 6.1.1.3 and 6.1.4, increased negotiation power of Member States from the market launch measure and impact on compliance and practical details is taken into account.<br><br>Views of industry and Member States elaborated |

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| report. The report should outline possible trade-offs (in terms of manufacturers' incentives) between expanding access to and improve affordability of new medicines. | in e.g. sections 6.1.1.3 and 6.2.<br><br>In section 6.1.4, clarified that for health systems, the market launch measure is a win-win in terms of access and affordability, rather than a trade-off. |
| (3) The impact of legal uncertainty for companies as regards materialising the additional regulatory protection period should be discussed in depth and should be substantiated with evidence given that the conditional extra years are dependent on factors outside of their control, in particular Member States' behaviour. The report should assess the impacts of this legal uncertainty, including on the launch of new innovation and future pricing decisions. It should assess whether shortening the standard regulatory protection period from eight to six years is likely to lead to higher average prices for health systems during the protection period, including by learning from third countries' experience of such shorter regulatory protection. The report should discuss more thoroughly how legal certainty for innovative businesses can be adequately ensured. It should describe how the Transparency Directive affects and influences Member States' and companies' behaviour and explain how possible non-cooperative behaviour from Member States' authorities can be avoided. Additionally, the report should ensure consistency and clarity when describing the different regulatory protection options when using concepts as standard and baseline protection periods. | In section 6.1.1.3, includes now a more detailed elaboration on the market launch measure including practical details that are taken to ensure legal certainty for innovators on the regulatory protection periods and a good faith approach. Moreover, the role of the Transparency Directive (also described in new Annex 14), national judicial control for abusive behaviour and a new subsection describing impact on prices of medicines has been added.<br><br>The impact on price levels of this modulation is assessed in section 6.1.1.3.<br><br>Reviewed and clarified use of standard and baseline protection periods throughout the report, where relevant. |
| (4) For the transferable exclusivity voucher proposed for AMR products, the report should clearly outline and analyse the key design parameters that affect its effectiveness and efficiency and the supporting evidence and benefit-cost analysis that will be necessary to trigger its practical application. Where trade-offs exist, these should be transparently presented. The report should clarify to what extent the transferable exclusivity voucher is expected to trigger the development of new medicines (not already having entered the development pipeline). It should better assess the impact on competition and prices on the relevant market of | In section 5.2.4, elaborated on transferable exclusivity voucher and its key design parameters.<br><br>In section 6.1.1.4, clarified the impacts of the voucher, including the impact on generic/biosimilar competition from the use of the voucher, and elaborated on the benefit-cost analysis.<br><br>In section 6.2, clarified that the transferable exclusivity voucher should encourage additional research to what is already in the pipeline. |

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| the existing product chosen to benefit from the application of the voucher. | |
| (5) The report should be clear on who will benefit from the new measures and who will bear the costs and what the distributional impacts are for medicine developers, the pharma industry (including generics), SMEs, health care systems and patients. | In section 7.2, narrative adapted and tables added to clarify who benefits and who will bear cost from the measures and distributional impacts. |
| (6) The report should more thoroughly assess the overall impact of the measures promoting innovation and competitiveness of the EU pharmaceutical ecosystem, including SMEs. It should better assess how the reduced standard regulatory protection period will affect the long-term ecosystem innovation capacity. It should analyse how the measures will impact competition between companies (big pharma and SMEs), prices and affordability. It should anticipate unintended consequences on innovation and competitiveness and discuss the risk that the expected benefits will not materialise. | In sections 6.1.2-4 and 7.1, elaborated the impacts on competitiveness and SMEs.<br><br>In section 6.1.1.2, added a subsection on RP reduction and impact on EU competitiveness.<br><br>In section 7.5, addressed the limitations including the risk that the expected benefits will not materialise. |
| (7) The report should better compare the options, based on overall cost-benefit estimates for each option and each affected key group (including their presentation in consolidated comparison tables). It should be clear if a net positive benefit is expected as the preferred option shows a very low benefit-cost ratio. | In sections 7.2 and 8.1, tables added for clearer comparison of the options. The summary tables in these sections together with Annex 3 support the general finding that there is a positive benefit-cost ratio of the preferred option. |

A revised version of the Impact Assessment Report was submitted to the RSB on 28 October 2022 for a final opinion. The table below lists the changes in response to the recommendations of the RSB.

| **Recommendations of the RSB** | **Modifications in the impact assessment report in response to these recommendations** |
|---|---|
| The exact criteria and conditions of the voucher system to address antimicrobial resistance remain vague. | In section 5.2.4. (Policy Option C) on p.36 the paragraphs describing the "transferable exclusivity vouchers and restrictions on their granting and use" have been complemented with the exact award criteria to obtain a voucher. |
| The report is not sufficiently clear on the | Section 6.1.1.3 and notably the subsections |

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| content, functioning and effectiveness of the envisaged safeguards which allows industry complying with the two year medicine launch requirement in all EU markets to benefit from extra-protection. | "*Practical details and impact of modulation of data protection for market launch (option C)"* and *"Would a decreased protection translate into price increase?" (p. 45-46)* have been revised and made clearer. We clarified that:<br>• Non-action of the MS will be considered as tacit approval of the market launch conditions<br>• SMEs and not-for-profit entities would receive a longer, 3-year period to comply<br>• Comparison of international empirical data does not suggest a correlation between prices and data protection periods in different jurisdictions |
| The report should better assess the impacts of reduced regulatory protection periods on the sectors capacity to finance future innovations and international competitiveness. | A dedicated subsection on competitiveness and future innovation is added to section 8.1, on p. 68. |

– *Evidence used together with sources and any issues regarding its quality*

The impact assessment and the accompanying evaluation have been built on:

- Evaluation of general pharmaceutical legislation (for the impact assessment)
- Participatory workshops bringing stakeholders together to inform respectively the evaluation and the impact assessment (see Annex 2: Stakeholder Consultation)
- In a back-to-back exercise, two studies were commissioned to a consortium led by Technopolis Group; an evaluation study and an impact assessment study. These studies are not publicly available and are annexed to this impact assessment as Annexes 12 and 13.

Extensive stakeholder consultations were organised, with input gathered through a public consultation, targeted surveys, an interview programme and workshops, for more information, see Annex 2: Stakeholder Consultation.

Evidence on costs were particularly difficult to gather. Public authorities and pharmaceutical industry provided very little information.

## ANNEX 2: STAKEHOLDER CONSULTATION (SYNOPSIS REPORT)

### 1. Introduction

This report provides an overview of the stakeholder consultation activities carried out as part of the 'back-to-back' evaluation and impact assessment for the revision of the general pharmaceutical legislation (Directive 2001/83/EC and Regulation (EC) No 726/2004). A single consultation strategy was prepared for this exercise, including consultation activities looking backward and forward. It aimed to collect inputs and perspectives of all stakeholder groups both on the evaluation of the legislation and on potential future policy options.

Information was collected through consultations that took place between 30 March 2021 and 25 April 2022 and consisted of: feedback on the Commission combined evaluation roadmap/inception impact assessment (30 March-27 April 2021); Commission online public consultation (PC) (28 September-21 December 2021); targeted stakeholder surveys (survey) (16 November 2021-14 January 2022); interviews (2 December 2021-31 January 2022); a validation workshop on the evaluation findings (workshop 1), on 19 January 2022; and a validation workshop on the impact assessment findings (workshop 2), on 25 April 2022.

The following key stakeholder groups were identified as priority groups in the consultation strategy for the evaluation and revision of the legislation: Citizens; Organisations representing patients, consumers and civil society active in public health and social issues (CSOs); Healthcare professionals and healthcare providers; Researchers, academia and learned societies (academics); Environmental organisations; The pharmaceutical industry and their representatives.

As part of the internal policy work process supporting the revision, the Commission collaborated with the European Medicines Agency (EMA) and the National Medicines Authorities. Both actors play a pivotal role in the implementation of the pharmaceutical legislation. The Commission also worked with Member States, EEA countries (Iceland, Liechtenstein and Norway) and public authorities in the framework of the Pharmaceutical Committee[1]. Other national authorities were consulted to receive the point of view of payers or pricing and reimbursement (P&R) bodies in the meetings of the national authorities on Pricing, Reimbursement and Public Healthcare payers. The results of the consultation activities conducted for the Pharmaceutical strategy for Europe[2] were also considered as valuable inputs to the revision.

### 2. Methodology of the consultation activities

*a) Feedback mechanism on Commission combined evaluation roadmap/inception impact assessment*

The roadmap was published on the Commission *Have your Say*[3] website. 173 responses[4] were submitted by eleven types of stakeholders from 25 different countries. The largest number of submissions came from Belgium (34%), France (12%), Germany (8%) and the United States (7%). The large majority of submissions came from individual businesses (26%), CSOs (25,5%) and business associations (22,5%). All 173 entries were analysed in Excel and Word, recording the main

[1] Pharmaceutical Committee, Veterinary Pharmaceutical Committee and Expert groups (europa.eu)
[2] Pharmaceuticals – safe and affordable medicines (new EU strategy) (europa.eu)
[3] Revision of the EU general pharmaceuticals legislation (europa.eu)
[4] The full set of contributions received are published on the Commission website and can be found here: Revision of the EU general pharmaceuticals legislation (europa.eu).

topics, sub-topics and the type of stakeholder. No duplicates were found, but one campaign was identified from developers of innovative medicines.

*b) Public consultation (PC)*

The PC was published on the Commission *Have your Say*[5] website. There were 478 responses[6]. Most of the answers were submitted by respondents from Germany (18.2%), Belgium (16.7%), and France (9.2%). Contributions from non-EU countries mainly came from the United States (23%), United Kingdom (15%) and Switzerland (9%). With respect to the type of stakeholder groups, most respondents were from the pharmaceutical industry (28.4%), followed by patient or consumer organisations (13.8%), healthcare provider organisation (9.8%) and healthcare professionals (7.9%). 158 respondents (33.1%) attached 183 separate position documents and 19 (4%) did not provide any response to closed questions. The questionnaire was structured into two main sections, backward-looking questions (Questions 1 and 2) exploring how the legislation performed and which issues should be addressed by the revision of the legislation and forward-looking questions (Questions 3 to 15) addressing possible solutions to the problems identified. Closed questions were quantitatively analysed using Excel and STATA, while open questions were manually checked and opinions and themes were summarised for each stakeholder group. Campaigns were identified using combination of statistical analysis and manual checking in Excel.

**Summary of campaigns:**

**Campaign 1** (Nuclear medicine practitioners – 23 answers) – main message: to adapt the legislation to facilitate production and marketing authorisation of radiopharmaceuticals and to simplify regulations for dispensing of radioactive medicinal products.

**Campaign 2** (Wholesalers – 16 answers) – main message: to identify the causes of medicines shortages and address them; to revise the wholesale distribution licensing system and the distinction between pharmaceutical full-line wholesalers and other wholesalers; to recognise the role of pharmaceutical full-line wholesalers to address shortages and strengthen supply.

**Campaign 3** (Innovative pharmaceutical industry – 12 answers) – main message: to consider the importance of a future-proof, predictable and stable legal framework and the importance of maintaining a good level of reimbursement and of regulatory protection periods.

**Campaign 4** (Generic companies – 11 answers) – main message: to give incentives and facilitate the uptake of off-patent products, such as creating new regulatory pathways for value added medicines innovation.

**Campaign 5** (Rare disease patient associations – 10 answers) – main message: to have better genetic testing for approval of oncology therapies; to ensure equal access to medicines and consider local capacity perspectives (i.e. hospital pharmacies); to use real-world evidence to generate information on access, patient needs and response to treatments.

[5] Revision of the EU general pharmaceuticals legislation (europa.eu)

[6] The full set of contributions received are published on the Commission and a report summarising the stakeholders' replies to the PC can also be found at: Revision of the EU general pharmaceuticals legislation (europa.eu)

**Campaign 6** (Microbiome-based product developers – 10 answers) – main message: To integrate microbiome science in the legislation, including standards, methods and definitions.

*c) Targeted stakeholder surveys (survey)*

Surveys tailored for each stakeholder group were developed and implemented in the form of online questionnaires using the survey tool 'Survey Monkey'. It consisted of both closed (scored from 1 to 5) and open questions. Invitations to complete the survey were sent to 220 participants across all stakeholder groups. 90 of these organisations were asked to further disseminate the invitation through their networks. In total, 440 responses were received and 209 remained after cleaning and checking exercises. Representation amongst the different groups was not as anticipated with industry particularly over-represented (55.1%) and CSOs underrepresented (5,8%). Inputs were received from public authorities (26.4%), academic (8.2%) and health services (4.8%). Organisations from Western Europe (45.5%) mainly answered but contributions also came from Southern (19.7%), Eastern (16.3%) and Northern Europe (12.5%) and from non-EEA countries (6.3%). Data was downloaded and quantitatively analysed in STATA. Open-ended questions were analysed qualitatively in Excel. Eight campaigns were identified using a combination of statistical analysis and manual checking in Excel, but only three of them were considered for further analysis because they received more than ten responses.

**Summary of campaigns:**

**Campaign 1** (Industry associations, parallel traders – 20 answers) – main message: support supply obligation for the marketing authorisation holder (MAH) at EU level to enable better competition of on-patent medicines, current legislation does not ensure sufficient stocks to enable a competitive parallel trade market to deliver on affordability; support increased move towards central authorisation for all medicines.

**Campaign 2** (generic companies – 16 answers) – main message: burdensome regulatory requirements and inconsistency with other legal frameworks (medical device regulation, transparency directive…); support regulatory flexibility to accelerate access and avoid shortages; support stimulating the uptake of off-patent medicines and better dialogue between P&R authorities to improve access.

**Campaign 3** (industry associations, wholesalers – 14 answers) – main message: current squeezes on margin/ remuneration for distribution endangers access to all medicines; support the regulatory flexibility applied during COVID-19 and the implementation of '*Green lanes'*.

*d) Interviews*

Semi-structured interviews of about one and an half hour were organised remotely via Zoom or Teams. They were based on an interview guide and individual questions were tailored to each interviewee. The guide had two parts covering the evaluation criteria and later discussing the problem analysis, possible policy measures and their comparison. A total of 138 individuals across all the identified stakeholder groups were interviewed including 57 representatives of the industry, 45 health service providers, 20 representatives of civil society organisations, 10 representatives of the public authorities and 6 academics. Summary notes were imported into Nvivo and coded thematically according to the objectives of the ongoing revision and abstracts were exported for synthesis into the reports.

*e) Validation workshops*

Two online stakeholder workshops were conducted with participants from all stakeholder groups. Both workshops followed the same structure: half-day event hosted via Zoom, with a plenary presentation and interactive polls, breakout sessions and plenary presentation of the breakout discussions. Ahead of the workshop, participants were able to choose two preferred breakout sessions and invitations included a discussion paper for contextualising the emerging findings. For both workshops, over 80% of participants were retained at the final plenary.

*Validation workshop 1 on the evaluation findings*

Out of the 246 invitations sent, 208 participants joined the workshop. The industry was the most represented group (86), followed by public authorities (61), civil society organisations (53), academics (23) and healthcare services (23). Five breakout rooms were created and grouped about 50 participants covering the five stakeholder groups: 1. Safeguarding Public Health; 2. Europe's regulatory Attractiveness; 3. Accommodating advances in science and technology; 4. Ensuring access to medicines; 5. Functioning of the EU market for medicines.

*Validation workshop 2 on the impact assessment findings*

Out of the 339 invitations sent, 199 participants joined the workshop. Public authorities was the most represented group (82), followed by the industry (68), academics (17), civil society organisations (16), and healthcare services (11). Four breakout rooms were created and grouped about 50 participants covering the five stakeholder groups: 1. Enabling innovation including for UMN; 2. Ensuring Access to Affordable Medicines for Patients; 3. Enhancing the security of supply of medicines and addressing shortages; 4. Reducing the regulatory burden and providing a flexible regulatory framework.

## 3. Overview of responses

A summary of the main themes and views provided by each stakeholder group in during the consultation activities is presented below. With regards to the numerous consultation activities conducted, which covered simultaneously the evaluation and the impact assessment, it seemed natural to present the results according to topics and sub-topics.

*a) Evaluation*

*Effectiveness*

Overall, the stakeholders were positive about the effectiveness of the legislation and its revision in meeting its objectives, i.e. safeguarding public health in Europe and supporting innovation of new medicines, providing an attractive and robust authorisation system for medicines and ensuring quality and safety of medicines. The interviews also stressed the positive impact of the centralised procedure to achieve the objectives of the legislation. On innovation, the legislation delivers a good framework for biosimilar medicines and the PRIME scheme[7] has supported access to innovative products.

In some areas, the legislation was less effective; interviews with public authorities and healthcare professionals highlighted shortcomings in terms of ensuring access to medicines as reimbursement remains a Member State responsibility. Workshop 1 also identified the issue of access, affordability

[7] For details regarding the Priority Medicines Scheme, see EMA's website on PRIME

and innovation as areas where gaps remain to be addressed in the legislation. On access, several participants noted the lack of continuity in processes from marketing authorisation to patient access, with some products gaining marketing authorisation but not moving forward fast enough with the Member States' reimbursement decision. It was also suggested by some participants that regulatory protection can affect access by maintaining high prices for innovative medicines. In the scored questions of the survey, stakeholders indicated areas where the legislation has been effective to a lesser extent: *enabling access to affordable medicines for patients and health systems* (assessed as "moderate" by 33% CSOs, 15% public authorities and 24% academia), *minimising inefficiencies and administrative burden of regulatory procedures* (assessed as '*small'* by 30% industry and health services, 16% public authorities[8]), *enhancing security of supply of medicines and address shortages* (assessed as '*small*' by 24% industry, 42% CSOs, 16% public authorities and 23% health services), '*ensuring a competitive EU market for medicines'* (assessed as '*moderate*' by 24% industry, 8% CSOs and 35% public authorities), '*reducing the environmental footprint of medicines'* (assessed as '*very small*' by 16% industry, 25% CSOs, 20% public authorities).

In their answers to open questions to the PC, academics expressed concerns on the evidence requirements for certain innovative cancer medicines. HTA bodies, healthcare payer organisations and a regional authority were also concerned about quantification of benefits based on early efficacy assessment for their cost-effectiveness assessment. In the context of the functioning of the EU market, patient or consumer organisations, healthcare payers and generic/biosimilar companies indicated that the legislation did not facilitate generic entry sufficiently; a campaign by the latter group was identified. However, chemical industry respondents and innovative medicine companies opposed this position. Industry associations also shared the view that the current incentives of the legislation promote the development of traditional product types (e.g. small molecules), while members of the public authorities and CSOs noted the need for more incentives for medicines for rare diseases and new antimicrobials. Another issue raised in the PC and the interviews was the lack of flexibility to accommodate scientific advances, such as advanced therapy medicines (ATMPs) and real-world data; a view that was shared by academic, patient or consumer organisations, healthcare professionals and industry respondents.

Finally, during workshop 1 the environmental impact of pharmaceuticals and the environmental risk assessment (ERA) was debated. CSOs opposed industry stakeholders and shared concerns over the low priority of ERA in marketing authorisation decisions. The workshop also raised issues over genetically modified organisms (GMO) requirements, which do not fit with the legislation; complex innovative products lacking streamlined regulatory pathway; the lack of financial model for antimicrobials; the lack of incentives for repurposing and value-added medicines. Medicine shortages and security of supply were considered a high priority among participants and participants noted that lessons learned from the COVID-19 pandemic could prevent future shortages.

*Efficiency*

While 31% of the respondents to the survey indicated that the costs incurred by the legislation by all stakeholders impacted by it (industry and society including health systems and patients) were proportionate to its benefits to a moderate extent (46% industry, 8% CSOs, 15% public authorities, 18% academics and 30% health services), most stakeholders interviewed could not provide specific quantitative estimates of the costs and benefits associated with implementing the legislation. Interviews with industry stakeholders (41% of total interviews) noted the major drivers of costs were the additional data requirements related with the regulatory dossier and post-marketing authorisation

[8] For targeted surveys not all questions were asked to all stakeholders, e.g. this question was only answered by industry, public authorities and health services.

requirements. Both innovative and generic medicine companies stated that abolition of the recurrent 5-year renewal cycle reduced regulatory burden. Yet, several pharmaceutical industry respondents in the PC and in workshop 1 explained the impact of duplicative processes causes costly regulatory burden, hinders innovation, in particular for SMEs, and causes delays across the life cycle of medicines. Despite the challenges to provide accurate monetary costs, a few industry respondents to the survey provided one-off adjustment costs, related to upgrading IT systems, as well as ongoing regulatory costs. Public authorities noted in interviews and in the open questions of the PC that they had increased workload and resources, including staff numbers, due to the revised legislation.

*Relevance*

Interviews, workshop 1 and results from the survey showed a general consensus that the objectives of the legislation are still relevant, but that the legislation should be amended to address new technological developments, to provide more clarity over unmet medical needs (UMN) and to ensure access to affordable products. In interviews, stakeholders provided further details on the areas the legislation needs to medicines. Academics and CSOs raised issues related to the lack of robust evidence to allow reimbursement, CSOs and public authorities were also looking for more equitable access to medicines, CSOs and healthcare professionals stressed the need for incentives to address antimicrobial resistance (AMR) (for novel antimicrobials and environmental impact of antibiotics); CSOs, public authorities and healthcare professionals were looking for more initiatives to ensure security of supplies. These results were echoed by the survey, where these topics were all ranked as least relevant in the current legislation. In the survey, 24% of respondents assessed the legislation as '*very*' relevant to maintain the security of supply of medicines in the EU, 36% said it was '*moderately*' relevant to maintain resilience and responsiveness of health systems during health crises. For industry interviewees, the legislation needs to be flexible to allow for technological developments and borderline products, and expertise in areas such as gene therapy, healthcare digitisation and use of real-world evidence is important to be built in regulatory agencies. This view was also noted by public authority interviewees, though it was highlighted that resources are needed to continue to expand capacity and expertise.

*Coherence*

All consultation activities indicated there was no major issues concerning the internal coherence of the legislation. However, it was highlighted that coherence with other specialised legislation and wider EU policies (such as ATMPs, medical devices, GDPR and Blood, Tissue and Cells - BTC) could be improved. The lack of clarity of borderline products (e.g. medical devices containing medicines) was mentioned several times in interviews and in the PC by all stakeholders, noting that there is uncertainty over the legislation regulating the area of BTC and also concerns of excessive exclusivity given due to the interplay the legislation and the Orphan Regulation. The survey confirmed the same coherence problems but also highlighted the need to complement health-related legislations on GMOs (assessed as '*not at all'* coherent by 15% of stakeholders including 21% of industry and 5% of public authorities); to complement other EU legislations and policies on data protection (assessed as '*not at all'* coherent by 12% of stakeholders); on environmental requirements (assessed as '*slightly'* coherent by 12% of stakeholders including 12% of industry and 16% of public).

*EU–added value*

The EU-added value of the legislation was clearly supported among stakeholders interviewed compared to what can be achieved at the Member State level, in particular the benefit of the centralised authorisation procedure was noted as very valuable for small countries. This view was confirmed in workshop 1. The harmonisation of good manufacturing practices (GMP) and the regime of inspection was mentioned as another benefit of EU level action in workshop 1.

Participants noted, however, the tensions to maintain requirements for high safety and efficacy of medicines and to improve the speed of authorisation. All stakeholder groups interviewed agreed that EU level action was important to tackle the COVID-19 pandemic in a quicker and more coordinated way. This view was supported, in the survey, to a large or a very large extent. Overall, stakeholders agreed that EU level action has improved Member States ability to put in place appropriate measures. The results of the survey indicated that, without EU level action, Member States would have had no more than a '*very small*' (16% of respondents including 20% industry, 25% CSOs, 13% public authorities and 10% health services) to '*small' or 'moderate'* (24% of respondents including 26% industry, 33% CSOs, 18% public authorities and academics, 30% health services) ability to put in place appropriate measures.

*b) Impact Assessment*

The consultations indicated several areas of the legislation in which future policy measures may be needed. The following areas were discussed in details.

*Incentives for innovation, including unmet medical needs and repurposing*

The PC presented seven possible policy measures to support innovation, including for UMNs and repurposing. In the open-ended questions to the PC as well as in the survey, there was no consensus across stakeholder groups on the most appropriate types of incentives and regulatory schemes to support innovation. Industry stakeholders called for a robust, stable and predictable intellectual property and regulatory protection system to support innovation but there were internal disagreements within this group. A campaign led by innovative medicine companies to maintain current level of incentives and exploring new types of push and pull incentives. Another campaign led by generic/biosimilar companies stated that extending data/market protection for any medicine will have a significant negative impact on affordability and competitiveness. These opposing views were also echoed during interviews. Several industry respondents to the PC and interviewed also expressed a wish to increasing the current 1-year data protection for over-the-counter (OTC) switches to 3 years. Regional public authorities noted that an assessment for better definition of '*innovative medicines'* is needed, with transparency of research and development (R&D) costs as requirement for incentives, a view that was also supported by several CSOs in the PC. However, in interviews and workshop 2, industry stakeholders noted that transparency of R&D costs is not feasible as the methodology to calculate them would vary enormously and would contain sensitive information. Other regional public authorities stated that incentives for early market launch of generics and biosimilars could negatively impact medicine development and noted that strengthening the reward systems for innovative biotechnological medicines would be beneficial for UMN. Academics indicated a need for more incentives to engage universities, hospitals and other non-profit organisations to work in areas of low commercial interest.

The possibility to incentivise the provision of comparative data at the marketing authorisation stage was discussed in workshop 2. There was no consensus on whether there is a need or not for the provision of comparative data, with some noting that this data is already being provided where possible and also that, for some products, this would not be feasible (e.g. ATMPs).

There was broad agreement among stakeholders for the need to define UMN in a clear and transparent way including a multi-stakeholder approach to ensure consistency across different regulatory frameworks and along the medicine life cycle. The PC indicated the most important criteria to define UMN were the '*absence of satisfactory treatment authorised in the EU'* (scored as very important by 63% of all respondents) and the '*seriousness of a disease'* (scored as very important by 50% of all respondents). Similar positions were shared in workshop 2 with industry

stakeholders emphasising that the lack of a definition of UMN could lead to legal unpredictability and impact investment decisions. In the survey, CSOs and academics rated as favourable the option to '*reduce the regulatory protection period for new products that do not address an UMN*', while for industry, the most important measures were additional regulatory protection for repurposing and codification of the PRIME scheme. The majority of stakeholders, but the industry, were supportive of a measure to permit breaking of regulatory protection under exceptional circumstances and the simplification of the obligations for not-for-profit/non-commercial entities to become marketing authorisation holders (MAH). According to the industry this is because regulatory protection is crucial to incentivise the significant investment needed to develop medicines. Other concerns among workshop participants were raised about '*indication slicing'* to meet UMN and the inefficiency of the regulatory protection system due to the patent protection and supplementary protection certificates. In the PC, there was strong consensus across all stakeholder groups that '*early scientific support and faster review/authorisation of a new promising medicine for an UMN'* was a very important (50% of all answers)/ important measure (25% of all answers), and more so for SMEs. However, public authorities and healthcare professionals highlighted that expedited regulatory frameworks should include robust pharmacovigilance and post-marketing authorisation studies to address uncertainties, proposing that sanctions should be in place in case of non-compliance. During the interviews, public authorities confirmed the view that expedited authorisation is important but also cautioned that it should not compromise safety and efficacy of medicines. The PC also showed overall positive views across stakeholder groups on repurposing. Healthcare provider organisations and public authorities noted in the PC and in the interviews more efforts could be done to collect evidence of off-label use and using real-world evidence to identify repurposing studies. CSOs and learned societies suggested in interviews and the PC the creation of a database for repurposed medicine. Most respondents also supported the provision of financial rewards or incentives to stimulate repurposing, in particular for SMEs. Yet, HTA bodies cautioned in the PC that more regulatory or intellectual property protection would not have a positive result for patients, and fair pricing mechanisms should be used instead. This aspect was supported by several health service stakeholders in interviews. Despite this, industry stakeholders and especially generic and biosimilar companies interviewed noted that the current protection of the commercial value of repurposing efforts is a key limiting factor to progress in this area. Several interviewees noted that public investment could also play a role in repurposing as the research is often led by academics, hospital and other publicly funded institutions.

*Antimicrobial resistance (AMR)*

The survey presented ten possible policy measures to address AMR with the highest ranking measure being the '*introduction of a "pay or play" model'* mostly supported by CSOs and opposed by the industry as being unfair for companies with no expertise in AMR. The second highest ranking measure was '*additional market protection period for companies that hold MA for a novel antimicrobial'* mostly supported by the industry. However, there was low inter-stakeholder agreement for both measures. In the open-ended questions of the PC, there was similarly no clear consensus of opinions across stakeholder groups regarding the best types of regulatory incentives for the development of new antimicrobials. Several CSOs, public authorities, healthcare professionals and citizens cited small milestone rewards or longer data protection periods and novel incentives as potential positive measures facilitate development. Feedback from workshop 2 indicated stakeholders had mixed views on TEV. While large industry and SMEs see TEVs as an effective approach to meet the scale of the investment needed for sustainable R&D, the generic industry raised concerns about the high level of investment needed and the potential increase costs for the health system by delaying generic entry. Healthcare payers supported this last point. Interviews with public authorities highlighted that market exclusivity will not solve the problem, as the sale volumes

will remain too low to incentivise the required investment. Instead, they favoured direct financial incentives (e.g. market entry rewards). CSOs concurred that companies would profit from the TEV but recognised the system could be fine-tuned to meet the needs of the public.

*Future-proofing: adapted, agile and predictable regulatory framework for novel products*

In the PC, there was a consensus among stakeholders that *'creating adaptive regulatory frameworks for certain novel types of medicines or low volume products (hospital preparations) in coherence with other legal frameworks'* and *'making use of the possibility for 'regulatory sandboxes' in legislation to pilot certain categories of novel products/technologies'* are the most important measures to consider to create an adapted, agile and predictable regulatory framework for novel medicines, Both measures were ranked as '*very important*' by respectively 43% and 34% of all respondents. These results were also supported in the survey and in interviews, where stakeholders highlighted that regulatory sandbox could increase innovation, competition, and speed to market for complex /cutting edge medicinal products. However, CSOs were concerned that regulatory sandboxes have the potential to lead to undesirable consequences such as '*carve-outs'* and a '*two-tiered'* regulatory framework.

The majority of stakeholder groups also rated as '*very important*' (43% of all answers) or '*important*' (19% of all answers) the measure to '*introduce an EU-wide centrally coordinated process for early dialogue and more coordination among clinical trial, marketing authorisation, health technology assessment bodies, P&R authorities and payers for integrated medicines development and post-authorisation monitoring*'. While this view was supported in the survey across all stakeholder groups but academics, it should be noted that in the PC, the industry expressed split views with 28% of them considering this measure as '*not important'* and 37% as '*very important'*. Workshop 2 highlighted that a centralised classification mechanism would need to involve close stakeholder engagement and have good balance between the competence and expertise of the advisory bodies responsible under each legal framework.

In the survey, out of the three possible policy measures explored to assess the future-proofing aspects of the legislation; the measure to '*adapt the regulatory framework for certain categories of novel products and technologies, including personalised medicines, medicines that contain or consist of a GMOs, platform technologies, or combined with artificial intelligence*' scored consistently highest as having a positive or very positive impact by all stakeholders. The survey also proposed three policy measures related to scope and definitions of cell-based medicinal products. Overall, the measure '*adaptation of regulatory requirements for specific cell-based medicinal products (ATMPs) to facilitate production in the hospital setting while ensuring safety, quality and efficacy*' scored consistently highest as having a positive impact by stakeholders, except industry. The overall lowest ranked measure by the stakeholder groups was to '*provide a mechanism to exclude less complex cell-based medicinal products from the scope of the Pharmaceutical legislation and transfer to the BTC legislation*'. Workshop 2 highlighted that any changes to definitions require an integrated approach in consideration with other relevant legislations. Concerns were also raised about creating new classifications/categories for less-complex ATMPs and different regulatory routes for the different categories with the risk of causing confusion and jeopardise safety requirements for these products. Possible policy measures were also presented to harmonise requirements for GMOs Environmental Risk Assessment (ERA) where the measure to '*adapt a risk-based approach to determine when a specific ERA is required'* consistently scored highest. Interviews highlighted that this measure could increase the efficiency of authorisation of GMO-containing medicines and the competitiveness of the EU in this field.

*Rewards and obligations related to improved access to medicines*

In the PC, there was a shared view among all stakeholders that harmonisation of HTA and greater transparency on P&R is needed at the EU level to improve patient access to medicines. This view was confirmed during interviews and workshop 2. Stakeholders acknowledged that national policies on payment and reimbursement and reference price systems are outside the remit of the legislation and national competence. Among the eight measures explored to improve access in the PC, there was consensus among respondent on the least and most important measures to improve access. '*Maintain the current rules which provide no obligation to market medicines in all EU countries*' was scored as not important by 35% of the respondents, while '*introduce harmonised rules for multi-country packages of medicines*' scored as very important by 41% of all respondents with the strongest support coming from the industry (69%). Results from the survey confirm this view. The second highest rated measure was '*introduction of electronic product information (ePI)'* (scored very important by 27% of respondents). While the industry considered this measure as very important (47%), healthcare professionals, public authorities and citizens were relatively less supportive of this measure (13%). Workshop 2, dominated by industry stakeholders, also confirm this result. Participants explained that marketing authorisation could be complemented by ePI and multi-country packs to address the access issues related to national language requirements on leaflets and packaging. Healthcare professionals, CSOs and public authorities were concerned for citizens with no access to computers.

Regarding obligations to improve access, most consultation activities considered the *'requirement for companies to place – within a certain period after authorisation – a medicine on the market in the majority of Member States (including small markets)*' as a very important policy measure. Industry stakeholders were largely unsupportive of this measure and raised concerns about regulatory penalties to ensure medicine are available on the market. In their view, there are 'multifactorial' issues that may not be in their control, including differences in national regulatory requirements; speed of P&R negotiations; possibly of needing to conduct further research; and unforeseen manufacturing delays. These views were echoed in the interviews and the workshop 2. Results from the survey highlighted that the majority of stakeholders but industry were supportive of the '*requirement to MAH applying for mutual recognition procedure/decentralised procedure (MRP/DCP) to include small markets'*. The workshop 2 also discussed the obligation to place a centrally authorised medicine on the market in the majority of EU Member States. In general, participants found that the obligation could bring benefits depending on its implementation. It was suggested that the obligation could focus on facilitating access to early generic entry in countries where the obligation is not being met.

In the PC, there was consensus across most stakeholders groups that there should be new incentives for swift market launch of medicines across the EU: CSOs and academic/research institutes were most in favour (37% and 33%), with industry split between '*slightly important'* (27%, innovative pharmaceutical companies) and '*very important*' (31%, wholesalers). Results from the PC also indicated the measure to '*allow early introduction of generics in case of delayed market launch of medicines across the EU while respecting intellectual property rights'* was scored as '*very important'* by 30% of stakeholders to improve patient access to medicines. Workshop 2 also explored incentivising product launch in all EU Member States but participants were broadly of the view that the incentive will not necessarily ensure access but it could provide a financial incentive to launch in smaller markets. In the PC, there was a shared view among academics, healthcare professionals and CSOs for the introduction of a '*solidarity pricing'* whereby wealthy Member States contribute to create an '*EU based fund'* to finance access to medicines.

*Enhance the competitive functioning of the market to ensure affordable medicines*

The survey explored measures to enhance the competitive functioning of the market, including measures to support early market entry for off-patent medicines, to facilitate market entry of generics/biosimilars and to address 'duplicates' of centrally authorised medicines. Overall, the measures '*certification procedures to include outcomes that could be used for multiple products to avoid duplicative assessment*' and '*introduce new simpler regulatory pathway for generics and biosimilars to reduce assessment time by authorities*' were the most consistently highly scored by all stakeholder groups. The measure to '*establish the legal basis for EMA committee to provide advice on interchangeability of specific biologics*' was also highly scored by most stakeholder groups (29% of respondents assessed it as having a '*positive impact'*) but the industry. This group was split with 10% of respondents scoring the measure as '*strongly negative'*, 14% as having '*little or no impact'* and 12% with '*strongly positive impact*'.

The '*broadening of the scope of "Bolar exemption" beyond generics by allowing repurposing studies/comparative trials without infringing patent rights*' was assessed as having a '*positive impact*' by CSOs (25%), public authorities (31%) and academics (18%), The industry was relatively less supportive of this measure with 25% of respondents scoring it as having '*little or no impact*' and only 11% of respondents viewing is as having *'strong positive impact'*. Workshop 2, participants confirmed support for this measure in terms of broadening it to more actors and extending it to other purposes (e.g. repurposing studies or comparative studies). But there were mixed views about what aspects this measure should cover. The generic industry was supportive of extending the Bolar exemption. It was noted that the Bolar exemption needs to be considered along with the research exemption and that the activities exempted from patent infringement should be precisely defined. The generics industry noted that proposed changes do not cover all activities needed to get Day 1 launch.

One of the lowest ranked policy measure in the survey was '*introduce specific incentives for a limited number of first biosimilars for a shared market protection*', in particular by industry and public authorities. In workshop 2, it was discussed that this incentive is unlikely to increase uptake in smaller populations. Concerns were raised about giving only one product priority as this would limit competition and thus increase prices of medicines. Moreover, workshop participants indicated the bottleneck is the uptake rather than market entry of biosimilars. The industry shared in interviews concerns over the incompatibility of shared market protection with EU regulatory system because of patent linkage issues. While CSOs (49%), citizens (39%), academics (33%) and public authorities (22%) considered this measure as very important, 26% of the industry ranked it as '*not important'*. In interviews, innovative medicine companies indicated their concerns that increasing incentives for generic entry to the market could discourage innovation in EU.

*Security and supply of medicines*

The PC presented ten possible policy measures to ensure security of supply of medicines in the EU. Overall, stakeholders scored the measure '*companies to have shortage prevention plans'* (46%) and '*introduce a shortage monitoring system at EU level'* (43%) as very important. In contrast, '*maintaining the current rules*' (15%) and '*introducing penalties for non-compliance by companies with proposed new obligations*' (18%) were scored as the least important. CSOs (34%) and public authorities (30%) ranked as very important the requirement for companies to diversify their supply chains, while 34% of industry considered this as not important. 41% of stakeholders ranked as very important '*monitoring and reporting of medicines shortages coordinated at the EU level*' as another measure to ensure security of supply. This view was confirmed in the survey, where the highest

ranked policy measure was the '*introduction of an EU information exchange on critical shortages based on national supply-demand monitoring data'*.

In workshop 2, stakeholders explained that diversification of the supply chain is challenging and not always feasible due to the difficulty to find alternative suppliers upstream in the supply chain. It was pointed out that having a more diverse and sustainable supply chain would likely increase the cost of medicines due to increased compliance costs.

On the possibility to increase shortage notification requirements for all medicines from 2 to 6 months, workshop participants suggested having a definition for critical shortage rather than increasing the notification period. The industry consistently supported this view in interviews and in the PC. In the workshop, concerns were also raised that earlier notification of potential shortages could lead to real shortages by triggering stockpiling and hoarding in Member States. In the PC and in interviews, several public authorities explained that the current notification requirements are appropriate, but compliance needs to be improved. According to academics a requirement for safety stocks should not result in significant price rises. In the survey, most stakeholders, but wholesalers and the developers, thought the measure to '*require MAH to notify authorities of impending shortages 6 months in advance*' would positively impact the security of supply. This split view was also confirmed in the PC.

The issue of stockpiling measures, requirements (or reserve requirements) for MAHs and wholesalers for critical medicines was discussed at the workshop. It was assessed by most participants as an effective approach to temporarily alleviate the effects of shortages. However, such measure would need to happen at the EU level in the form of unfinished product, and for critical medicines only. When considering EU-wide vs national level stockpiling, it was suggested that implementation at a national level would require an obligation for stock-sharing and special flexibility to facilitate easy movement of products between Member States. On the duration of stockpiling, there was a consensus that this could not be a permanent solution but only helpful for the first 2-3 weeks of shortages. Participants highlighted warehousing requirements for stockpiling would be challenging for certain types of products that need to be produced on site or cannot be stored for long periods of time (e.g. plasma-derived products or personalised medicines).

*Quality and manufacturing*

Several policy options were discussed in the consultation activities including harmonising a system of sanctions on GMP, increase sustainability performance in relation to AMR, ensure the legislation is adapted to regulate new manufacturing methods and, lastly, the modification of inspections regime and supply chain oversight. In the survey, only public authorities and industry stakeholders contributed to these aspects. Public authorities viewed all policies, on average, as having potential for positive or large positive impact. Industry stakeholders were in support of reinforcing Member States' GMP and good distribution practices (GDP) inspection capacity by setting up a joint audit scheme to reinforce and strengthen the quality of inspections; strengthening the role of the EMA in supporting the robust oversight of manufacturing sites and in the coordination of all inspections; and to adapt the terms of the legislation to accommodate new and emerging manufacturing methods. They were less in favour of introducing a harmonised system of sanctions related to GMP and GDP; of extending the scope of mandatory inspections to encompass supply chains; of increasing the responsibilities of MAH vis-a-vis the quality of the supply of APIs and raw materials and clarify responsibilities of business operators over the entire supply chain; of adapting GMP procedures to environmental and antimicrobials challenges. Interviews confirmed the support for the policies mentioned above, but also highlighted some tensions. National competent authorities noted the need for more resources to train inspectors (e.g. in the area of antimicrobial resistance) and to cope with

an increased regime of inspections. Industry stakeholders noted that the system of sanctions and the increased regime of inspection and supply chain oversight would present barriers for SMEs. They also stressed the existence of other legislations regulating antimicrobials and thus on the risk for duplication. The PC confirmed the overall positive view on the need to adapt new manufacturing rules and methods. In open questions, CSOs, academics, health services and citizens highlighted the importance to increase the transparency of the supply chain through more oversight. Regional public authorities suggested to increase cooperation for supply chain monitoring within and outside the EU; to clarify the documentation necessary for active substances production; to promote EU manufacturing of essential vaccines and medicines. Both pharmaceutical industry and pharmaceuticals traders/wholesalers emphasised the need for more resources for GMP inspections in less regulated third countries to ensure a level playing field.

*Environmental challenges*

The PC showed general consensus on the importance of strengthening efforts to reduce the environmental impact of medicines, but opinions varied on the urgency and appropriate measures. Citizens were concerned about the pollution of waters, the environmental impact of packaging and disposal of medicines. Environmental organisations expressed that the ERA should be a requirement and part of the risk-benefit analysis for all medicines and through the whole life cycle of the product, including assessment for AMR. This position was also expressed during workshop 1, where CSOs opposed industry stakeholders and shared concerns over the low priority of ERA in marketing authorisation decisions. Several public authorities, healthcare professionals and CSOs suggested the inclusion of environmental impact in the decision-making criteria to award incentives to developers and reduce the environmental impact of medicines. Pharmaceutical industry noted in the PC and in interviews that most APIs do not have a significant risk for the environment and that ERA for off-patent medicines are duplicative and unnecessary. The chemicals industry noted that the current system for tendering does not reward environmentally sound manufacturing practices, and instead focus on low prices. In their view, environmental standards could benefit from more international regulatory alignment. Industry respondents suggested the creation of a fund for investment in greener manufacturing practices in the EU to help SMEs and improve security of supply. Several environmental organisations, healthcare professionals, civils society organisations and citizens noted in the PC the need for clearer guidelines for procurement of medicines, which should include greener manufacturing practices, and more MAH responsibility over all supply chain actors.

Of the three possible policy measures presented in the survey, the option '*to strengthen the environmental risk assessment (ERA) requirements and conditions of use for medicines*' was rated positively by most public authorities, healthcare professionals and CSOs, while the industry was divided with answers ranging from strong negative to strong positive impact. There was no consensus within academics on this option. The option '*to introduce a requirement to include information on the environmental risk of manufacturing medicines, including supply chain actors, in ERA / application dossiers'* was mostly rated as negative by industry stakeholders while all other stakeholder groups viewed this option bringing a positive impact. The last option of the survey '*to establish an advisory role for EMA with regard to ERA and green manufacturing aspects and quality of medicines*' was seen as a having potential positive impact for all stakeholder groups, with only industry average response closer to '*little to no impact*'.

Interviews with industry stakeholders noted that higher manufacturing standards to reduce environmental impact comes with associated costs. In this regard, EU companies should be supported to remain competitive with other regions. Public authorities also highlighted the double challenge to ensure environmental sustainability and to bring manufacturing back to Europe. This will require a multifactorial approach beyond the legislation. They also confirmed an overall support

for strengthening the ERA as long as it does not impact access to patients. CSOs stressed the need for transparency over environmental impact of medicines and suggested to make use of the best practices already implemented across Member States. Workshop 2 confirmed the general view that there is a tension between the need to reduce regulatory burden while expanding environmental considerations. There was a general consensus that the legislation should be linked to environmental legislations. Participants raised several issues, e.g. inspectorates lacking adequate background or mandate over environmental matters, environmental parameters not fit for purpose for GMP and environmental risks related to manufacturing can be site specific and difficult to standardise.

*COVID-19 lessons learnt*

Participants of workshop 1 highlighted that medicine shortages and security of supply was a high priority and noted that lessons learned from the COVID-19 pandemic could prevent future shortages. Out of the four possible policy measures of the survey, the '*possibility of introducing a codified system of rolling reviews for products addressing UMN'* did not gain stakeholders consensus, with industry and public authorities rating this option more favourable than health services and academics. In interviews, all stakeholders recognised that the rolling reviews were successful to address the pandemic. Some public authorities noted the benefit of more developer-regulator interaction but others also highlighted the unsustainability of that system for national authorities. CSOs and healthcare services also noted that if P&R authorities are not able to assess therapeutic value (due to lack of relevant data), the medicine will not reach patients. In the PC, this view was confirmed by academics, healthcare payers and CSOs respondents. Yet, several pharmaceutical industry respondents argued that real-world evidence can support data provision and rolling reviews can play an important role for certain products (e.g. plasma-derived medicinal products). Similar exchanges took place during workshop 1. Academics interviewed noted that the EMA pandemic taskforce was a key enabler in allowing coordinated response and CSOs, healthcare professionals and public authorities discussed the importance of the EU joint procurement of vaccines for speedy and efficient action for access. Industry stakeholders interviewed noted that the virtual audits and inspections could be implemented post-pandemic to save resources, and they highlighted the need for more alignment in clinical trials during pandemics to ensure speed and appropriate designs. It was also noted that the GMO exemption for COVID-19 vaccine could be applied to other areas, such as low risk ATMPs. Public authorities also noted that transparency measures were implemented as a response to the pandemic, as well as strengthening of the network (national competent authorities, EMA and the Commission) through regular meetings, which brought positive outcomes.

The second measure of the survey, '*the possibility of allowing regulators to reject immature marketing authorisation applications'* (when data is insufficient to conduct full assessment to support a decision) was rated as having strong positive impact by public authorities, while industry rated it more negatively. The third measure *to establish an EU emergency use authorisation (EUA) of medicines* received an overall positive score by all stakeholders as currently, there is only national emergency authorisation. The last and similar measure, '*to establish an EUA that would still leave Member States to decide but it would be based on EU level scientific advice'* was also positively viewed by all stakeholder groups, except for academics who ranked it as having little or no impact. Neither the third, nor the fourth measure were discussed in the PC, apart from two pharmaceutical industry respondents expressing a positive view on an EU EUA.

## ANNEX 3: WHO IS AFFECTED AND HOW?

### 1. Practical implications of the initiative

The proposed revisions have substantial positive implications for EU patients, companies and national health systems.

For **patients**, there are many improvements foreseen in all areas of importance: improving the flow of cutting-edge treatments available for conditions for which there are no effective treatment options currently (UMNs), reversing the decline in investment in antimicrobial research and encircling the issues driving AMR, incentivising access in all Member States, a broader repurposing, and the generic and biosimilar entry. A more robust ERA will also support environmental goals. Measures on security of supply will moreover improve access to medicines.

For **companies,** the proposed revisions seek to strike a balance between ensuring a strongly positive environment for research-intensive pharma industry to continue to develop its cutting-edge products within the EU and the need to ensure all EU member states and citizens have access to a broader array of treatment options. Therefore, the modulated incentive scheme provides attractive incentives for innovation and placing on the market. The future proofing of the regulatory framework will also embrace technological change. New obligations for shortages prevention and environmental protection will result in additional costs for businesses. However, simplification and long term benefits from digitalisation are likely to offset any new costs and result in earlier authorisations.

For **health systems**, public health budgets would also benefit from the modulated incentive scheme since more EU citizens will have access to treatments, which results in savings due to more effective treatment and reduced hospitalisations. They will also benefit from stronger competition and transparency measures around public funding for clinical trials. There would be additional societal benefits for families and carers too, in terms of both quality of life / independence and earning potential. Overall, the new incentives will come with costs for healthcare budgets but the public health benefits should outweigh those.

For **regulators**, the effects of the proposed changes would be overall positive especially due to various horizontal measures, which will allow to better coordinate, simplify and accelerate regulatory processes to the benefit of industry and launch new digitalisation programmes to improve the integration and efficiency of the regulatory system overall (as well as its interfaces with other regulatory systems).

### 2. Summary of costs and benefits

Table I presents an overview of the estimated benefits for the pivotal measures under the preferred option, and Table II presents an overview of the main estimated costs associated with those measures.

The estimate of benefits is an **underestimate as there will be many indirect benefits for health systems and patients from improved access to new medicines for UMNs, new classes of antimicrobials and extended market access**. However, while we expect many tens of thousands of individual citizens to benefit in some degree from these revisions, it has not been possible to establish quantify and monetise these many and various social impacts. Likewise, the estimate of costs is also an underestimate as several costs could not be quantified.

For the market access, the overviews include benefits and costs for only the variant of the market launch measure with one year of conditional protection for launch in all Member States within 2 years.

## Benefits

For **patients**, the principal benefit would be access to new medicines. The measures proposed would provide access to new medicines to 67 million more (as compared to today) EU citizens, should they need them.

For **companies**, the principal direct benefits relate to the gross profits for originators and generic/biosimilar companies associated with additional flow of protected sales that will result from the various incentives foreseen (e.g. a year one extension to the overall period of regulatory data protection for medicines addressing an unmet medical need).

For **health systems**, the main indirect benefits relate to the lower prices for health payers associated with those medicines where MA holders do not place their product in all Members States and where, as a consequence, generic competition will emerge two or one years earlier.

There are also savings expected from the various horizontal measures, which will allow benefits for both companies and **regulators**. They will allow to better coordinate, simplify and accelerate regulatory processes to the benefit of industry and launch new digitalisation programmes to improve the integration and efficiency of the regulatory system overall (as well as its interfaces with other regulatory systems). Quantified benefits from the horizontal measure are for companies in the range of €35-70m annually and for regulators €102.3-204m.

| **I. Overview of Benefits (total for all provisions) – Preferred Option** | | |
|---|---|---|
| ***Description*** | ***Amount*** | ***Comments*** |
| ***Direct benefits*** | | |
| Medicines for unmet medical needs (UMNs) | On average, additional **3 new medicines annually** relevant to UMNs (c. 45 new medicines over 15 years). This would result in **originators** securing an additional **€282m** gross profit sales annually (15 years: €4.23bn). | +12 months extension of RDP for innovation, particularly around unmet medical needs (UMNs) would result in a higher proportion of UMNs within all newly authorised medicines.<br>While 1-2 additional UMN medicines are expected annually, the extension of the RDP is expected to apply to 3 UMN medicines annually. |
| Novel antimicrobials | An additional **1 novel antimicrobial annually** (c. 15 over 15 years). This would result in **originators** securing an additional **€387m** gross profit annually (15 years: €5.8bn). | The transferable voucher, if approved, would provide strong support for innovation in novel antimicrobials. The additional income may be secured by the developer of the novel antimicrobial where they use a voucher with another high value medicine in their portfolio or split between the developer of the antimicrobial and another originator that has purchased the (transferable) voucher. We have estimated the purchase value at €360m (assuming one voucher a year). With more breakthroughs a more vouchers the average sale price would fall. |
| Comparative trials | A small number of EMA medicines applications will be able to implement more robust trials and take advantage of the incentive (**8 a** | +6 months extension of RDP for medicines applications that include |

| I. Overview of Benefits (total for all provisions) – Preferred Option | | |
|---|---|---|
| ***Description*** | ***Amount*** | ***Comments*** |
| | **year**). This would result in **originators** securing an additional **€378m** gross profit annually (15 years: €5.7bn). | the findings of comparative trials. |
| Market access | The great majority of new medicines will be able to comply with the market access conditions.<br>**8 medicines annually** (120 over 15 years) may fail to meet the conditions, and in these cases the RDP will lapse at 6+2 years (not 6+2+1).<br>For this sub-set of products where the RDP is the last line of defence, there will be a **€384m** gain each year (€5.7bn over 15 years) to the **EU health system and patients**, because of lower prices from earlier competition by generics.<br><br>**Generic companies** would secure an additional **€51m** annually in gross profits (€765m over 15 years). | +1 years protection conditional on launch in all EU markets in 2 years (the variant). |
| 1 year general reduction of the RP | The reduced protection would allow earlier generic entry and price competition, and also the lower prices would increase patients' access to medicines.<br><br>**Health system and patients** will gain **€1,008m** a year (€15.1bn over 15 years), and **generic companies** would secure an additional **€113m** per year (€2bn over 15 years). | |
| ***Indirect benefits*** | | |
| Patients benefit from effective medicines (UMNs) | Thousands of EU citizens will have access to treatments that help recover them from or manage their debilitating conditions, improving their quality of life and life expectancy.<br><br>There may also be indirect benefits / savings for health systems from more effective treatment and reduced hospitalisations.<br><br>There would be benefits for families and carers too, in terms of both quality of life / independence and earning potential. | It is not possible to quantify / monetise (indirect) patient benefits given the diversity of UMNs (certain neurological conditions, cancers, muscular dystrophy, etc.). These conditions may affect hundreds of citizens or millions in the case of Alzheimer. |
| Patients have access to new classes of antimicrobials that help to contain AMR | It is estimated that each year about 670,000 infections occur, and that 33,000 Europeans die as a consequence of antibiotic-resistant bacteria with the burden being highest in the elderly and infants.<br>It is also estimated that AMR costs the EU €1.5bn per year in healthcare costs and productivity losses.<br>Even a 1% improvement in our management of AMR could save several hundred lives annually and save health systems hundreds of millions too. | It was not possible to quantify / monetise the (indirect) patient benefits that might result from new classes of antimicrobials. |
| Improved decision making for HTAs / Reimbursement bodies | More robust evidence from comparative trials should facilitate HTA decision making, leading to improved reimbursement decisions and faster decisions / access where medicines are approved for reimbursement. | It was not possible to quantify / monetise the (indirect) HTA and patient benefits that might result from the greater use of more robust trials. |
| All EU member states (inc smaller countries) have improved access to new medicines | On average, new medicines will be available to patients in 22-25 markets compared with the current situation (12-15), reaching 80% of the population compared with the current situation (c. 65%).<br>The access to all new medicines in 5-10 additional markets will mean that hundreds of thousands of EU citizens will have better treatment options, with accompanying improvements in health equality and possibly public health. | It was not possible to quantify / monetise the (indirect) patient benefits that might result from the systematic extension of market access |
| Improved management of shortages | Most EU countries report increasing numbers of medicine shortages, with the great majority having recorded shortages for 200 or more medicines in the year.<br>Fewer shortages may benefit tens of thousands of patients, with access to the more appropriate medicines.<br>According to the Pharmaceutical Group of the EU, eliminating shortages might save healthcare systems 5-10% of their pharmacy-related staff costs as well as time wasted by frontline staff. | Fewer shortages would mean more patients have access to the medicines they need.<br>Healthcare systems would see cost savings from avoiding time wasted deciding / finding appropriate alternative medicines. |
| Improved environmental performance of pharma industry | This may make a positive difference to 40-50 new medicines a year (600-750 in 15 years).<br>This should result in a reduction in the intrinsic environmental risks of | New medicines would be subject to a more rigorous assessment, which should feed forward to more |

| I. Overview of Benefits (total for all provisions) – Preferred Option | | |
|---|---|---|
| ***Description*** | ***Amount*** | ***Comments*** |
| | a proportion of medicines, a lowering of the levels of active ingredients getting into the environment through excretion and a lowering of the level and number of accidental releases to the environment by manufacturers (mostly non-EU). | informed selection of APIs, encourage green pharma and select for higher standards across global supply chains. |
| ***Administrative cost savings related to the 'one in, one out' approach**** | | |
| Streamlining, acceleration of processes and coordination of network | **Businesses** should realise savings in the range **€15m-€30m annually** (€225m-€450m over 15 years).<br><br>European and national **regulators** should see savings in the range **€33.5m-€67m annually** (€502.5m-€1005m over 15 years).<br><br>Overall savings should represent on average **€72.75m annually** (€1.09bn over 15 years). | Businesses will benefit from various simplification and governance enhancements producing administrative cost savings.<br>European and national regulators should see a reduction in duplication of effort across committees and among regulators, producing savings in enforcement costs |
| Digitalisation | Digitalisation savings for **businesses** in the range **€7.5m-€15m annually** (€112.5m-€225m over 15 years).<br>Digitalisation savings for **regulators** in the range **€67m-€134m annually** (€1,005m-€2,010m over 15 years).<br><br>Overall savings of on average **€112m annually** (€1.68bn over 15 years) | The various digital initiatives proposed will save time and administrative costs for businesses and deliver substantial efficiencies / reductions in enforcement costs for regulators. |
| Adaptations to new concepts and support SMEs and non-commercial organisations | Enhancement savings for **businesses** in the range **€7.5m-€15m annually** (€112.5m-€225m over 15 years).<br>Enhancement indirect benefits for **businesses** in the range **€5m-€10m annually** (€75m-€150m over 15 years).<br>Enhancement savings for **regulators** in the range **€1.75m-€3.5m annually** (€26.25m-€52.5m over 15 years).<br><br>Overall savings of on average **€21m annually** (€321mn over 15 years). | Industry - and SMEs in particular - should benefit from better and more dynamic advice avoiding queries on applications (delay) and rework to the same (cost); regulators should benefit from more mature applications that can be assessed more easily and quickly.<br>There may be some limited indirect benefits, whereby faster assessments, on average, may facilitate at least some new medicines being approved for sale earlier and some generics entering the market earlier. |

*(1) Estimates are gross values relative to the baseline for the preferred option as a whole (i.e. the impact of individual actions/obligations of the preferred option are aggregated together); (2) We indicate which stakeholder group is the main recipient of the benefit in the comment section;(3) For reductions in regulatory costs, we describe how the saving arises (e.g. reductions in administrative costs, regulatory charges, enforcement costs, etc.;)*

## Costs

For **patients**, the principal costs (indirect) will relate to reduced access to treatments associated with the additional delays in generic entry for new medicines that have benefitted from extensions.

The principal costs for **industry** are associated with the reduced general RP protection, implementation of market access conditions and conduct of comparative clinical trials. In addition costs for industry in relation to reporting on shortages and environmental risks and enhanced support in the range of €31.6m-47.4m annually.

The principal costs for **health systems** relate to the additional period in which they will need to pay a premium price for medicines benefiting from any extensions to the period of regulatory data protection.

For **regulators**, they would bear some costs relating to the design and implementation of the wide-ranging proposals for streamlining and digitalisation as well as shortages, strengthened

environmental risk assessment and enhanced support. Their costs would be in the range of €92.3-189.7m annually plus one-off costs of €136.8-383.6m.

| **II. Overview of costs – Preferred option** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | **Citizens/Consumers** | | **Businesses** | | **Administrations** | |
| | | **One-off** | **Recurrent** | **One-off** | **Recurrent** | **One-off** | **Recurrent** |
| UMNs | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | |
| | Indirect costs | | Costs for 'unserved' patients €246m a year<br><br>€3.69bn over 15 years | | Lost gross profits for generics €39m a year<br><br>€585m over 15 years | | Additional costs for payers €162m a year<br><br>€2.43bn over 15 years |
| AMR | Direct adjustment costs | | | | E.g. industry would incur costs for the development of AMR lifecycle monitoring plans; these cost could not be quantified. | | E.g. regulators would incur costs to examine the AMR lifecycle monitoring plans; these costs could not be quantified. |
| | Direct administrative costs | | | | | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | |
| | Indirect costs | | Costs for 'unserved' patients €158m a year<br><br>€2.37bn over 15 years | | Lost gross profits for generics €54m a year<br><br>€360m over 15 years | | Additional costs for payers €283m a year<br><br>€4.2bn over 15 years |
| Comparative trials | Direct adjustment costs | | | | Comparative trials conducted by originator €280m a year<br><br>€4.2bn over 15 years | | |
| | Direct administrative costs | | | | | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | |
| | Indirect costs | | Costs for | | Lost gross | | Additional |

| II. Overview of costs – Preferred option | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Citizens/Consumers | | Businesses | | Administrations | |
| | | One-off | Recurrent | One-off | Recurrent | One-off | Recurrent |
| | | | 'unserved' patients €112m a year<br><br>€1.68bn over 15 years | | profits for generics €52m a year<br><br>€780m over 15 years | | costs for payers €218m a year<br><br>€3.27bn over 15 years |
| Market access (variant with one year protection) | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | Requesting confirmations of supply to obtain extension of RP; costs not quantified. More applications for P&R; costs not quantified. | | Confirmation of supply by MS; costs not quantified. |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | |
| | Indirect costs | | | | Lost gross profits originators €378m a year<br><br>€5.6bn over 15 years | | P&R bodies to decide on more applications; costs not quantified. |
| 1 year general reduction of RP | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | |
| | Indirect costs | | | | €991m gross profit reduction for originators<br><br>€14.9bn over 15 years | | |
| Shortages | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | Additional costs for industry €10m-€20m a year (ave €15m)<br><br>€150m-€300m over 15 years (ave €225m) | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | Additional costs for |

| II. Overview of costs – Preferred option | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Citizens/Consumers | | Businesses | | Administrations | |
| | | One-off | Recurrent | One-off | Recurrent | One-off | Recurrent |
| | | | | | | | regulators €10m-€20m a year (ave €15m)<br><br>€150m-€300m over 15 years (ave €225m) |
| | Indirect costs | | | | | | |
| Environment | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | Additional costs for industry €20m-€25m a year (ave €22.5m)<br><br>€300m-€375m over 15 years (ave €337.5m) | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | Additional costs for regulators €20m-€25m a year (ave €22.5m)<br><br>€300m-€375m over 15 years (ave €337.5m) |
| | Indirect costs | | | | | | |
| Streamlining | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | Additional one-off costs for regulators €16.8m-€33.6m (ave €25.2m) | Additional costs for regulators €33.5m-€67.5m a year (ave €50.5m)<br><br>€502.5m-€1.01bn over 15 years (ave €757.5m) |
| | Indirect costs | | | | | | |
| Digitalisation | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | | | |

| II. Overview of costs – Preferred option | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | **Citizens/Consumers** | | **Businesses** | | **Administrations** | |
| | | **One-off** | **Recurrent** | **One-off** | **Recurrent** | **One-off** | **Recurrent** |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | Additional one-off costs for regulators €120m-€350m (ave €235m) | Additional costs for regulators €24m-€70m a year (ave €47m)<br><br>€360m-€1.05bn over 15 years (ave €705m) |
| | Indirect costs | | | | | | |
| Enhanced support | Direct adjustment costs | | | | | | |
| | Direct administrative costs | | | | | | |
| | Direct regulatory fees and charges | | | | | | |
| | Direct enforcement costs | | | | | | Additional costs for regulators €4.8m-€7.2m a year (ave €6m)<br><br>€72m-€108m over 15 years (ave €90m) |
| | Indirect costs | | | | Additional costs for industry for engaging with regulators €1.6m-€2.4m a year (ave €2m)<br><br>€24m-€36m over 15 years (ave €30m) | | |
| ***Costs related to the 'one in, one out' approach*** | | | | | | | |
| **Total** | Direct adjustment costs | | | | | | |
| | Indirect adjustment costs | | | | | | |
| | Administrative costs (for offsetting) | | | | Administrative costs to businesses €37.5m a year<br><br>€562.5m over 15 years | | |

*(1) Estimates (gross values) to be provided with respect to the baseline; (2) costs are provided for each identifiable action/obligation of the preferred option otherwise for all retained options when no preferred option is specified; (3) If relevant and available, please present information on costs according to the standard typology of costs (adjustment costs, administrative costs, regulatory charges, enforcement costs, indirect costs;). (4) Administrative costs for offsetting as explained in Tool #58 and #59 of the 'better regulation' toolbox. The total adjustment costs should equal the sum of*

*the adjustment costs presented in the upper part of the table (whenever they are quantifiable and/or can be monetised). Measures taken with a view to compensate adjustment costs to the greatest extent possible are presented in the section of the impact assessment report presenting the preferred option.*

## 3. Relevant sustainable development goals

| III. Overview of relevant Sustainable Development Goals – Preferred Option(s) | | |
|---|---|---|
| **Relevant SDG** | **Expected progress towards the Goal** | **Comments** |
| SDG 3: Good Health and Well-Being for people<br><br>Highly relevant | The revision will help futureproof the legislation, continuing to safeguard public health.<br><br>The revisions will increase the proportion of new medicines that address unmet medical needs (UMN), thereby creating the potential for millions of people across the EU and internationally to access effective treatments for their debilitating conditions.<br><br>The revisions will introduce new incentives for innovative with the potential to tackle disease resistant pathogens and contribute to managing antimicrobials resistance (AMR). | The expected progress towards SDG 3 and SDG 9 are closely interlinked and complementary.<br><br>By improving the innovation capacity of the EU pharmaceutical industry, the revision will contribute to improve the access to all treatment for all Europeans and therefore to ensure good health and well-being to European citizens. |
| SDG 9: Industry, Innovation, and Infrastructure.<br><br>Highly relevant | The revision sought to simultaneously support the EU pharmaceutical industry and patients. The introduction of substantial additional incentives for major medicines innovations in the areas of UMNs, AMRs and other therapeutic areas where there is an evident social need and a demonstrable market failure (e.g. difficult / costly science and small, volatile markets).<br><br>The revision should strengthen the EU industry's global competitiveness in those areas most directly related to UMNs.<br><br>The revisions is expected to lead to a refocus of the R&D industry on European territory attracted by streamlined and harmonised regulatory environments. Thus, the revision should also contribute to the strengthening of EU's attractiveness as a place for carrying out medicines research globally, through the implementation of new incentives for innovation, new definitions, various streamlining and digitalisation measures.<br><br>The revision is expected to strengthen the EU generic industry's competitiveness by incentivising the industry stakeholder to retain their manufacturing capacity within the EU.<br><br>The support ensured to the overall pharmaceutical industry and the related impact is expected to be extended to SMEs as well. However measures such as the transferable vouchers may provide a good opportunity for small biotech firms working on novel antimicrobials to secure substantial additional funding for research through the sale of vouchers or the raising of new finance or acquisition. The proposals to make the regulatory and scientific advice more dynamic and interactive is likely to be valuable to SMEs. | The revision will support progress towards SDG 9 by creating a future-proof environment supporting the pharmaceutical industry.<br><br>Measures addressing the inefficiencies of the regulatory system such as the streamlining of administrative and regulatory activities; the adaptation to innovation and digitalisation will largely contribute to enhance support of the industry.<br>Those measures are expected to ease innovation and day-to-day activities for all industry stakeholders, all along the lifecycle of medicines. |
| SDG 10: Reduced Inequalities<br><br>Relevant | The revision will support improvements in health equality through improved market access, increasing the number and speed at which new medicines are launched on the great majority of EU markets.<br><br>The revision will also support improvements in the management of medicines shortages across the EU, thus helping to contain the upward trend in shortages and increasing the likelihood that patients receive the most suitable medicines. Finally, the increase in the proportion of medicines addressing unmet medical needs will provide those patients with treatment options where that is not the case currently.<br><br>Moreover, it should be noted that:<br>- The revision of general pharmaceutical legislation aligns with the pharmaceutical strategy for Europe, which emphasises the need to ensure access to safe, high quality and effective medicines as a key element of social well-being, including for persons from disadvantaged, vulnerable groups, such as people with disabilities, people with a minority ethnic or racial background and older people.<br>- The revision of the general pharmaceutical legislation aligns with the revision of the orphan and paediatric legislation focusing on reducing health inequalities for these specific population. | Progresses towards SDG 10 echoed the ones of SDG 3.<br><br>Measures such as innovation in the areas of UMNs, AMR and the improvement of market access conditions are expected to contribute to the reduction of inequalities within the entire European population. |

## ANNEX 4: ANALYTICAL METHODS

### Methodology and models for the Impact Assessment

*1. Data sources*

There have been multiple data sources and related analytical methods applied to provide evidence for the impact assessment of the policy elements and options in this study.

**Literature and document review:** we have carried out a targeted literature and document review of academic and grey literature, using specific topics of each policy option, such as access to medicines, to guide our searches. There is a growing body of published literature and analysis reports that studied specific phenomena relevant to aspects of the pharmaceutical legislation. These provide a direct source of facts and figures that we used in our assessments and referenced across the report. Wider literature relevant to newer challenges for the pharmaceutical industry were also reviewed in order to identify future proofing challenges, resilience of supply chains, new manufacturing methods, combination products, digitalisation, new evidence requirements by regulatory authorities and environmental protection.

Our search strategy followed a heuristic approach, using the objectives of the revision to focus our efforts, but building out from our existing view of matters, based on our and others' recent studies, but also the Commission's own recommendations. Our searches covered peer-reviewed and grey literature using keywords in English, Dutch, French, German and Spanish across Pubmed, Scopus, EU institutions, agencies and regulator websites, Google Scholar and international organisations such as WHO and OECD. We have also identified sources from stakeholders such as industry organisations and patient associations.

**Comparative legal analysis:** we explored pharmaceutical legislation of third country jurisdictions in areas where a revision was proposed in the EU. These were based on desk research complemented as needed by targeted interviews with national experts. The following seven countries were selected: USA, Canada, Australia, South Korea, China, Japan, Israel – covering a mix of major developed global markets and smaller ones where regulatory innovation was expected. We have used a standard country report template as data gathering and reporting tool. Sources for those reports included legal research on the third country legal systems but also literature review both in English and respective national languages on the workability and outcome of these legal systems and interviews with relevant actors in these countries (i.e. competent authorities and experts).

**Country reports** were completed by national experts with good understandings of the national context and relevant language skills. The preparation of country reports involved the creation of a guidance document to the country report; a webinar with national experts to discuss aim, context and methodology; interview with regulatory authorities; quality assurance to ensure comparative analysis of indicators, which were based on the objectives of the review of the legislation, such as incentives innovation and future proofing of the legislation.

**Secondary data analysis:** quantitative data collected along the medicinal product lifecycle was analysed to derive a set of indicators and feed quantitative modelling of various policy scenarios. For problem analysis and baseline, we used data where available for the period of 2005-2020 from the IQVIA MIDAS dataset, Informa Datamonitor and Pharmaprojects, EMA's central Marketing Authorisation Application dataset (prepared by Utrecht University), MRI decentralized / mutual recognition procedures database, EudraGMP, and an EU shortages dataset collected from National

Competent Authorities for a bespoke European Commission study by Technopolis Group. The results of this are available in a separate Analytical report.

**Case studies:** seven areas were identified where a deeper analysis of a particular problem would be beneficial to support the impact assessment. These aimed at exploring the nature and evolution of the problem and link those to the proposed policy elements and their potential impacts. The analytical approach relied on document review, secondary data analysis and key stakeholder interviews. Selected case studies were: 1. Incentives for developing new antimicrobials. 2. Agile and adaptive regulatory systems. 3. Regulatory support for SMEs. 4. Improved access to medicines. 5. Generic competition and affordable medicines. 6. Regulatory barriers for emerging manufacturing technologies. 7. Criteria for unmet medical needs.

**Stakeholder consultations:** a number of different approaches were used in gathering evidence and views of stakeholders, which are summarized in a separate Synopsis report. These included a feedback to roadmap and a public consultation (both through the 'Have Your Say' EC website), a targeted survey, semi-structured interviews and two dedicated stakeholder workshops with civil society organisations, academic researchers, public authorities, healthcare professionals and industry.

**Key challenges:** All methods applied to our research encountered a varying degree of difficulty in relation to lack of quantitative data available in the databases and sources examined. Despite a growing body of literature and evidence in several relevant areas (e.g. AMR), we did not find enough data to quantify all relevant impacts of every policy measure discussed in the policy options for the future of the legislation. Whenever possible, we have made reasonable assumptions to assess the impacts, but this lack of quantitative data is a key limitation to our analysis.

*2. Identifying and selecting significant impact types*

We carried out an initial screening of the 35 impact types set out in the Better Regulation toolbox to identify the impacts the study will be reviewing more in depth for each policy block with each policy option. We used findings from the various analytical strands and data sources to identify all potentially important impacts, considering both positive/negative, direct/indirect, intended/unintended as well as short-/long-term effects. Specifically, our screening was based on the principle of proportionate analysis and considered the following factors.

- The relevance of the impact within the intervention logic
- The absolute magnitude of the expected impacts
- The relative size of the impacts for specific stakeholders
- The importance of the impacts for the EC's horizontal objectives and policies
- Any sensitivities or diverging views

This screening identified 10 of the 35 impact types as being of most significance for this impact assessment and therefore a deeper assessment was appropriate for the following key impact types:

- Conduct of business
- Administrative costs on businesses
- Position of SMEs
- Sectoral competitiveness and trade

- Functioning of the internal market and competition
- Innovation and research
- Public authorities
- Resilience and technological sovereignty
- Public health & safety and health systems
- Sustainable consumption and production

*3. Multi-criteria analysis*

Evidence from all data sources was structured along each impact type for each policy element within policy blocks in each of the policy options. This exercise involved a triangulation of qualitative and where available quantitative data explored in the study. Where data gaps were evident, these were clearly noted and best judgement was used by study team members in the following scoring process.

A 7-point scale was adopted to quantify the scale of the impact and likely balance of costs or benefits with a grading system between -3 (significant negative impact expected for the specific impact type) through 0 (no impact is expected from applying a specific policy elements) to +3 (significant positive impact expected for the specific impact type), as compared with the baseline. In most cases, the directionality of impacts for stakeholders was gathered via stakeholder consultation and the extent of impact (performance) was assessed by the study team. Initial scores were given for policy elements in a policy block by study team members responsible for data triangulation for a specific policy block. Scoring across all policy blocks was then reviewed by a panel of three senior members of the study team to ensure consistency.

Multiple policy elements may act in concert or partially against one another when looking through the lens of specific impact types and so internal synergies and tension within a block were considered when overall scores were given. Note that weightings for all impact types were assumed to be 1. Synergies across policy blocks were more challenging to adequately quantify as in any multi-body problem the effects are not additive. Therefore, we provide a qualitative assessment of identified synergies and trade-offs in case specific policy options are simultaneously implemented in a policy option.

This approach allows for a rapid overview and ranking of policy options, for policy elements in a policy block, and suggest which scenario is expected to meet the specific policy objective with the significant positive impact.

*4. Modelling changes in regulatory data and market protection system*

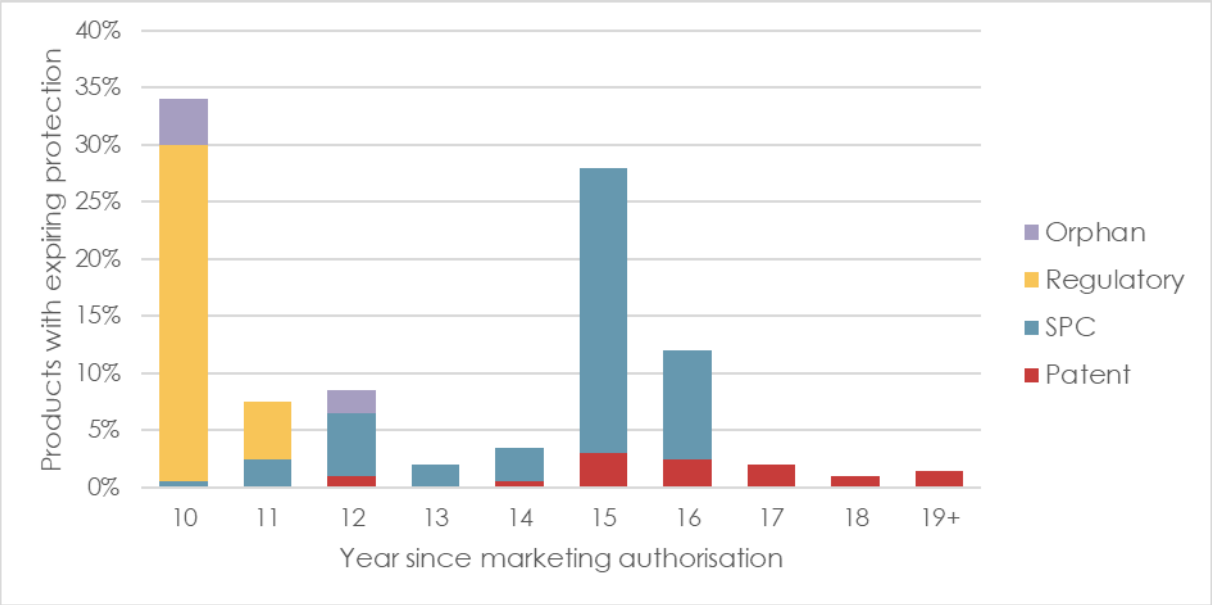
*a. Protection types and length in a sample of medicines*

A basket of 217 products was selected based on IQVIA Ark Patent Intelligence data where the loss of protection (LOP) date was between 2016-2024 in four countries: France, Germany, Italy, and Spain. We chose this sample in earlier years and other countries the regulatory protection system was not fully harmonised due to the legacy of the pre-2005 system. This sample has an additional benefit of having a prospective feature, in that it shows, based on empirical data, the composition of the most recent and also the expected future protection expiries of medicinal products.

Of the 200 products that are on the market (not withdrawn), 69 products had currently regulatory data and market protection (RP) as last measure of protection. This means that 35% of the products in this sample would in principle experience reduced protection under a shortened standard regulatory protection system. Note however, that nine of these products had 24 months or less between RP and patent/SPC expiry and consequently, these products will be affected to a smaller extent by a two-year reduction of the standard RP period. We therefore estimate that 30% of all new medicines will be affected by a two-year reduction of the standard RP period.

The figure below shows that after 10 years from marketing authorisation date, 30% of products have RP expiry and 5% of products have RP expiry in year 11 (due to the additional year of regulatory protection for a new therapeutic indication of significant benefit). Close to half of the products have an SPC expiring as the last measure of protection, predominantly 15 years after marketing authorisation (the maximum value for the combined patent and SPC protection period from marketing authorisation), with a smaller fraction having additional paediatric SPC extension.

**Figure 1 Distribution of protection expiry dates per type**




Note however that while RP-protected products comprise about one third of the product basket, their share in total sales is only 23% of the total. The largest share of the total sales comes from SPC-protected product; when normalised per product, peak sales of SPC-protected products are 2.3 times higher than that of RP-protected products.

**Table 1 Share and average peak sales of products under different protection types**

| Protection type | Share of total products | Average peak sales |
|---|---|---|
| Orphan | 6% | €42m |
| Regulatory | 34.5% | €158m |
| SPC | 48% | €358m |
| Patent | 11.5% | €257m |

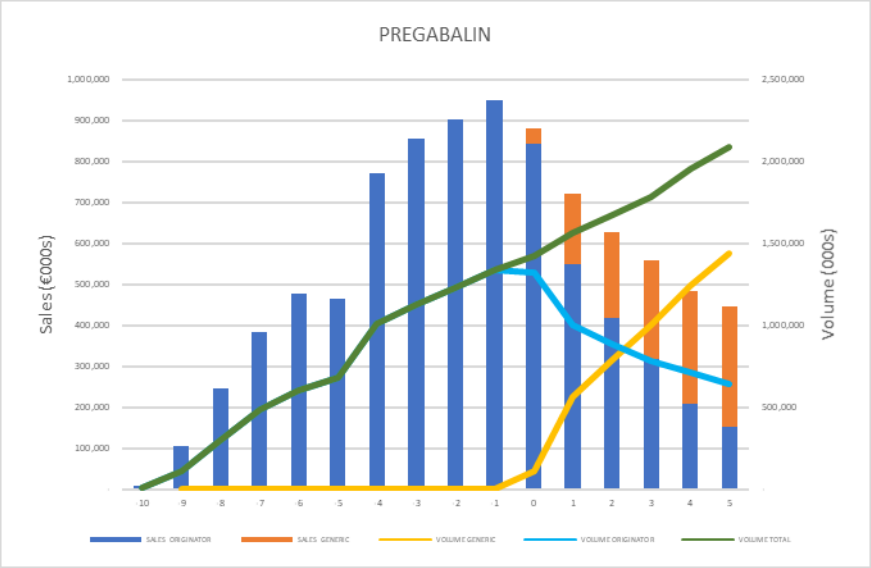
*b. Developing an 'analogue' representing an innovative medicinal product lifecycle*

We aim to generate an average sales revenue-volume graph that capture the lifecycle of innovative products over the protected RP period and that contested by generic/biosimilar medicines in the post RP expiry period. Since this requires a minimum of 16 years of consistent longitudinal data for a product, we used a cohort of medicines approved between 2004 and 2011, where RP is the last measure of protection. For practical reasons the cohort was split into two parts.

The first part included 20 products[9] (involving 2 biologic molecule) that have RP expiry dates between 2016-2021 and for these annual sales were calculated over a 10-year period pre-expiry. The second part included 16 products[10] (involving 1 biologic molecule) that have RP expiry dates between 2014-2016 and for these products annual sales were calculated over 5 years post expiry, along with annual sales data for their generic competitors. Note that 2 products were not contested after RP expiry but included in the cohort to allow for observing systemic effects. For example, the RP period for the biologic Cetuximab expired in 2014 and no biosimilar entered the market to date.

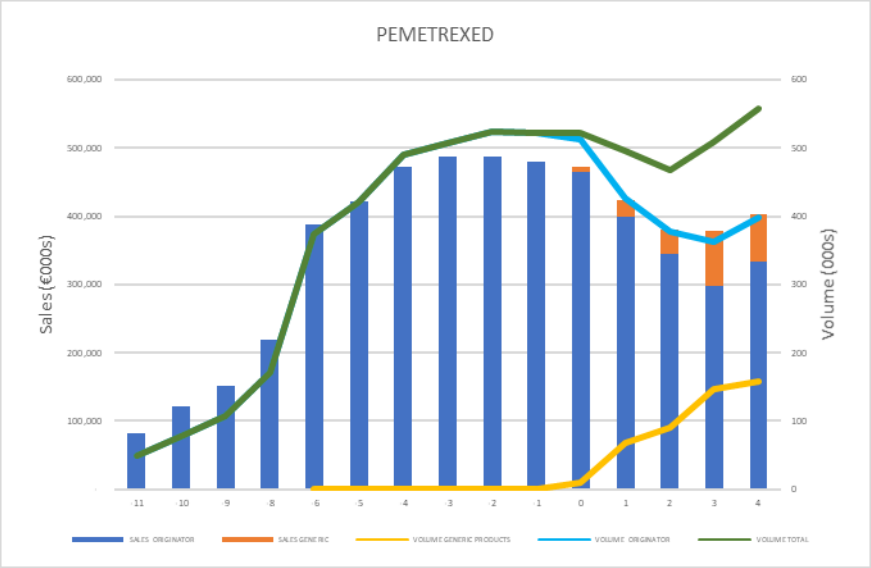
There is significant variation of the sales revenue-volume graphs across individual products, in some cases rapid generics entry erode the market value of the originator product, in other cases the originator maintains their market share, dependent on the level of sales generated by the originator. For two examples, please see the figure below:

**Figure 2 Sales and volume data for two products from the 2014-16 cohort**




[9] Products included: AGOMELATINE, AMLODIPINE!HYDROCHLOROTHIAZIDE!OLMESARTAN MEDOXOMIL, AMLODIPINE!HYDROCHLOROTHIAZIDE!VALSARTAN, AMLODIPINE!OLMESARTAN MEDOXOMIL, ANAGRELIDE, AZACITIDINE, CABAZITAXEL, CLEVIDIPINE, CLOFARABINE, DRONEDARONE, FEBUXOSTAT, GEFITINIB, *MIFAMURTIDE*, NELARABINE, PALIPERIDONE, PRASUGREL, ROFLUMILAST, SILODOSIN, ULIPRISTAL ACETATE, *VELAGLUCERASE ALFA*

[10] Products included: ALENDRONIC ACID!COLECALCIFEROL, ANAGRELIDE, CEFDITOREN PIVOXIL, *CETUXIMAB*, CLOFARABINE, DULOXETINE, EPLERENONE, FULVESTRANT, HYDROCHLOROTHIAZIDE!OLMESARTAN MEDOXOMIL, METFORMIN!PIOGLITAZONE, PEMETREXED, PREGABALIN, RASAGILINE, TIMOLOL!TRAVOPROST, TREPROSTINIL, ZONISAMIDE




We noted that very few biologics were found to be in the cohort for our analysis, however the biologics pipeline is growing (especially antibody modality, see Analytical report Table IEC1.3 and recent IQVIA report on biosimilar competition in Europe[11]) and expected to make a larger share of future product baskets. Biologics and biosimilars may have unique market dynamics because of differences in related development timeline and cost-profile. A comparative analysis of medicinal products launched between 1996-2014 shows that biologics are introduced faster and in more countries than non-biologic medicinal products[12] as it may be more profitable for developers compared to small-molecules. Switching from originator to biosimilars may also have different considerations, and recently launched biosimilars achieved over 50% uptake in their market within two years.[4] Examples of blockbusters (e.g. Humira, Herceptin and Enbrel) show that biologics are often protected by SPCs beyond RP expiry and biosimilars enter soon after expiry. In the RP cohort, we noted however another blockbuster example Xolair (Omalizumab) where RP as the last measure of protection expired in 2015 yet no biosimilar entry has taken place. While there is no current SPC on the product, there is a formulation patent until 2024 in force that may be constraining. In summary, it is not clear what share new biosimilars will have in future RP product cohorts where policy elements under considerations will be of effect. If the share of biologics substantially increases, it is likely that the general product sales/volumes model employed below will be less predictive.

In order for sales revenues (euros) and volumes (standard units) across the pre-expiry and post-expiry cohorts and periods can be joined up and compared, aggregate absolute values were normalised so that the originator products' total sales and volume become equal to 100 at one year before protection expiry (Y-1).

A particular challenge is that sales revenues do not give the full picture of company benefits. The driver of businesses economic activity is not the revenue but the profit. Gross profit appears the most adequate and comparable measure, it is the cost of sales deducted from the revenues. The gross profit only includes the variable costs of manufacturing and distribution, but not the fixed costs, such

[11] The Impact of Biosimilar Competition in Europe (2021) IQVIA. Available at: https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/iqvia-impact-on-biosimilar-competition.pdf

[12] Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018) Copenhagen Economics. Available at: https://data.europa.eu/doi/10.2873/886648

as R&D and investment in infrastructure. In our model we distinguish three categories of revenues, each with a different margin of gross profits.

- **Protected originator sales**: this is the most profitable category during the protected period of new medicines. Based on a sample of reports from publicly listed companies we apply a 80% gross profit margin on the revenues (20% cost of sales)

- **Contested originator sales**: once generics enter the market, originator products are forced into price competition. Still, originator products can maintain a price premium compared to generics albeit reduced thanks to brand loyalty and strong sales force. We assume a 50% gross profit margin in this category.

-

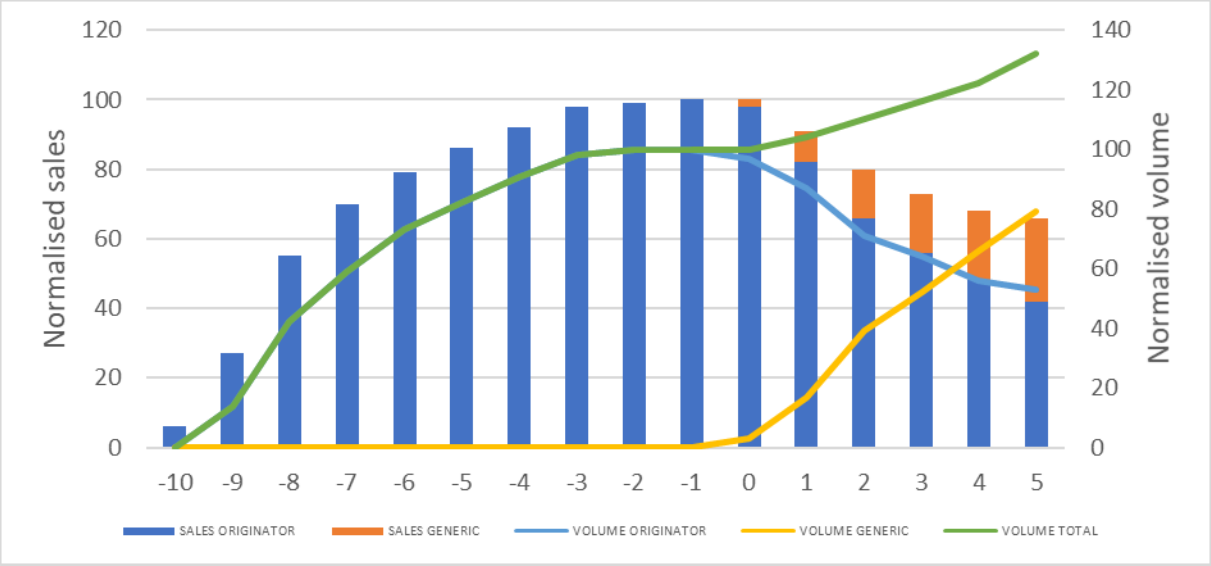
- **Generic sales**: generic industry operates on a high volume, low margin basis. With low product development risk, a lower profit margin can be sustainable. We apply a 33% gross profit margin on generic revenues.

The resulting table and corresponding figure are shown below:

**Table 2 Normalised sales, volume, gross profit and price for products with RP as last measure of protection**

| Year from expiry | -10 | -9 | -8 | -7 | -6 | -5 | -4 | -3 | -2 | -1 | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Originator sales | 6 | 27 | 55 | 70 | 79 | 86 | 92 | 98 | 99 | 100 | 98 | 82 | 66 | 56 | 48 | 42 |
| Generic sales | | | | | | | | | | | 2 | 9 | 14 | 17 | 20 | 24 |
| **Total sales** | **6** | **27** | **55** | **70** | **79** | **86** | **92** | **98** | **99** | **100** | **100** | **91** | **80** | **73** | **68** | **66** |
| Originator volume | 0 | 14 | 42 | 59 | 73 | 82 | 91 | 98 | 100 | 100 | 97 | 87 | 71 | 64 | 56 | 53 |
| Generic volume | | | | | | | | | | | 3 | 17 | 39 | 52 | 66 | 79 |
| **Total volume** | **0** | **14** | **42** | **59** | **73** | **82** | **91** | **98** | **100** | **100** | **100** | **104** | **110** | **116** | **122** | **132** |
| Originator profit | 4.8 | 21.6 | 44 | 56 | 63.2 | 68.8 | 73.6 | 78.4 | 79.2 | 80 | 49 | 41 | 33 | 28 | 24 | 21 |
| Generic profit | | | | | | | | | | | 0.66 | 2.97 | 4.62 | 5.61 | 6.6 | 7.92 |
| Originator price | | 1.93 | 1.31 | 1.19 | 1.08 | 1.05 | 1.01 | 1.00 | 0.99 | 1.00 | 1.00 | 0.94 | 0.93 | 0.88 | 0.86 | 0.79 |
| Generic price | | | | | | | | | | | 0.67 | 0.53 | 0.36 | 0.33 | 0.30 | 0.30 |
| **Average price** | | 1.93 | 1.31 | 1.19 | 1.08 | 1.05 | 1.01 | 1.00 | 0.99 | 1.00 | 1.00 | 0.88 | 0.73 | 0.63 | 0.56 | 0.50 |

**Figure 3 Normalised sales and volume for products with 8+2 years of RP protection (baseline)**




It is evident from the graph that sales revenue and volume grow year-on-year over the 10-year RP period as (i) the product is taken up by the health system and make it accessible to increasingly more patients; and (ii) product is launched in increasingly more member states. It should be noted that health systems may require a number of years before the product becomes accepted by health professionals and routinely prescribed. However, these effects are expected to reach a plateau within a couple of years of introducing the product in a market, and indeed the figure shows that by Y-3 sales figures are close to peaking. The last year before expiry therefore accounts for 14% of total protected sales; while the final two years account for 28% of total protected sales.

The baseline is the current standard regulatory protection (for all medicinal products) of 8 years of data exclusivity plus extra 2 years of market protection, and in cases of additional indication with significant benefit +1 year of market protection.

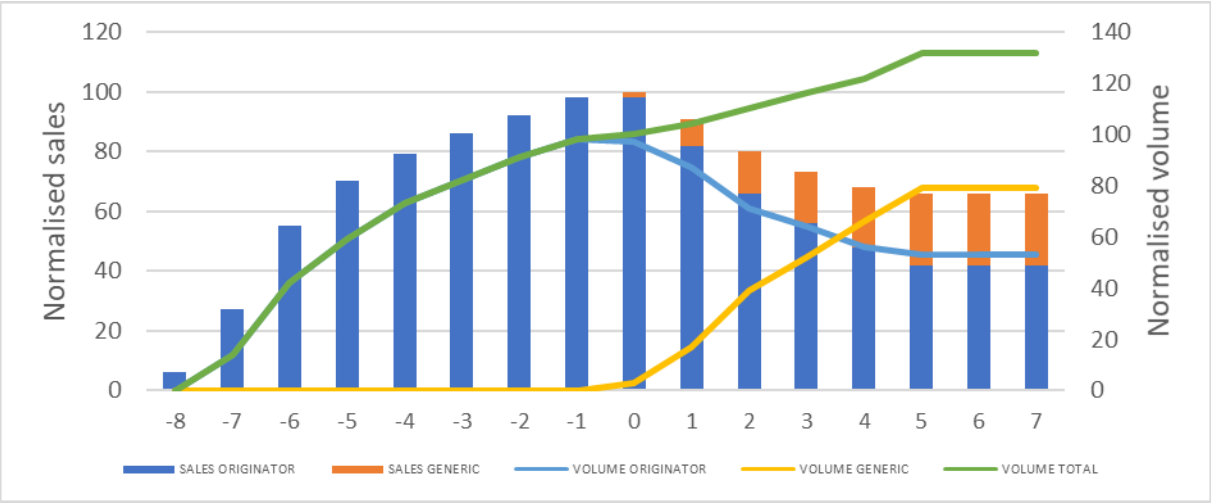
*c. Modelling the economic impact of decreasing regulatory protection*

We assume that after 5 full years of generic competition an equilibrium value of annual sales and volume of product sold are established and thus we can use Y5 data for originator and generic products as long-term level to calculate the value of RP loss over the product lifetime. It

should be noted again that this basket of products is dominated by small-molecule medicinal products; the lifecycle of biologics may be more extended given the absence of automatic substitution rules.

We also assume that the pre-expiry sales trajectory is not changed by company behaviour and thus the baseline Y-1 and Y-2 sales are lost under the new standard RP regime. In the figure below thus the original Y-1 and Y-2 values are removed and Y6 and Y7 values are added at equilibrium level. In addition, we assume that the market dynamics of generic competition (between Y0 and Y5) in the new standard RP regime will not change compared with the RP period of 8+2 years.

**Figure 4 Normalised volume and sales data for products with 6+2 years of RP period**




| | Baseline | RDP 6+2 | change | change % |
|---|---|---|---|---|
| Originator protected sales | 712 | 513 | -199 | -28% |
| Originator contested sales | 392 | 476 | 84 | 21% |
| Originator profit | 765.6 | 648.4 | -117 | -15% |
| Generic sales | 86 | 134 | 48 | 56% |
| Generic profit | 28.38 | 44.22 | 16 | 56% |

| | | | | |
|---|---|---|---|---|
| Cost to public payer | 1190 | 1123 | -67 | -6% |
| Volume (patients served) | 1343 | 1407 | 64 | 5% |
| Cost of additional patients | 0 | 44 | 44 | |
| Cost of baseline volume | 1190 | 1079 | -111 | -9% |

Using the above model for the product lifetime, we can make the following observations at product level:

- Originator companies' pre-expiry sales loss of -199 (normalised units) over two years is partially compensated by the post-expiry gain of +84 (calculated at the equilibrium level) over two years, giving a net loss of -115 (normalised units) over the lifetime. In other words, originators lose 28 % of their protected sales when the RP period is changed from 8+2 to 6+2 years. This translates to a decrease in originator's gross profit of -117 (normalised units), which is a 15% loss over the product lifetime, approximated as a 16-year period.

  We know that pharmaceutical industry is one of the most R&D intensive sector and they reinvest a large share of their revenue into innovation for new products and technologies. This share is 20% on average globally[13] and we can assume that the revenue loss will translate to a loss of innovation budget and thus a loss of development of new innovative products and/or incremental (i.e. cheaper) product innovation (e.g. for combination products or new formulations).

- Generic companies' start to benefit from sales two years earlier compared to baseline, and thus reach equilibrium level two years earlier. These two extra years of equilibrium generic sales of +48 (normalised units) are equal to +16 (normalised units) gross profit gains.
- Healthcare payers pay less overall due to a decrease in the average price they need to pay for a standard unit of the product. If we look at the annualised average price healthcare payers pay (calculated by dividing total sales and total volume in each year of the final 8 years of the product lifetime) in the different RP regimes, we note that, as expected, the average price drops faster to the equilibrium value in the case of the new standard RP regime (see Figure 5 below). If we consider the 'peak' volume sold of the originator product pre-expiry under the baseline situation and use the average price in each year under the different RP regimes to calculate post-expiry adjusted sales, we can assess the total savings healthcare payers would make in the RP 6+2 regime given equal volumes purchased. In the baseline RP 8+2 regime, the total lifetime sales is 1190 (normalised units) and in the new RP 6+2 regime the same volume at the new prices would be 1079 (normalised units). Thus in the RP 6+2 regime healthcare payers would pay -111 (normalised units) less, which is -9% less when considering the lifetime sales of the product.

[13] See https://www.drugdiscoverytrends.com/pharmas-top-20-rd-spenders-in-2021/

In the real situation, however, healthcare payers may not realise this nominal saving but choose to purchase more units of the medicine at a lower price for the healthcare system and expand coverage of patients. This can be considered that payers 'reinvest' part of the savings in the same market and increase purchase of generic products at higher volumes for the benefit of the patient. We can thus calculate the total real sales of originator plus generics product volumes, which can be used to monetise patient benefit. Under the baseline situation, total sales value over the product lifetime is 1190 (normalised units), while under the RP 6+2 regime it is 1123 (normalised units), equating to -67 (normalised units) or -6% saving to healthcare payers, on the products that are RP protected. Note, however, when considering the RP protected medicines represent some 20-23% of the pharmaceutical expenditure, and that from the total healthcare systems spending in the EU, the pharmaceutical expenditure represents less than 20% (see Analytical report Figure AFF-3, OECD Health Statistics), the savings at the healthcare system level is marginal.

- Patients benefit due to the increased volume of the medicine sold after RP expiry (2 years earlier) which then reach more patients creating higher level of health benefits. In the model, the total volume increases as soon as generic products enter the market and volume of generic products surpasses that of the originator product by year 4 after generic entry. In the new standard RP 6+2 regime the total volume sold increases by +64 (normalised units) or 5% over the product lifetime above the baseline of 1343 (normalised units) under the RP 8+2 regime. However, the extra volume of products available to patients manifest itself in the transition period between expiry and reaching the equilibrium value.

**Figure 5 Normalised price of medicines over the final 8 years of the product lifetime**


Monetising the systemic effects: Using the model in this study where only static effects are considered, we saw the normalised consequences for various stakeholders originating from a typical product where the last measure of protection to expire is RP. We can convert the normalised units to monetary value by equating the peak sales of 100 (normalised units) to the average peak sales calculated for the basket of RP products of approximately €160m per year. Note that per product level change should be considered as nominal since the actual individual product sales have a wide range around this average. At a systemic level, for a basket of products over years, however, the calculated values are expected to have predictive power.

Therefore, we need to assume the number of products per year to be affected by this policy measure. In the coming 15 years, we estimate that on average 40-50 new active substances will be authorised by EMA in each year (see Figure RI-9.1 and pipeline data in Analytical report and recent report[14]). From the current level of 30-40, we expect the baseline to evolve to 50-60 by the end of the period. As discussed, 30% of new authorised products are expected to be affected, however, products that address UMN or medicines with no return on investment (Option B) will not have reduced RP period. Overall, we estimate 20-25% of new medicines or 9-12 products will be affected annually by the measure.

[14] Global Trends in R&D, IQVIA Institute for Human Data Science, 2022. Available at: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-trends-in-r-and-d-2022/iqvia-institute-global-trends-in-randd-to-2021.pdf

In the following we summarise the economic value calculated for each stakeholder group.

**Table 1 Changes calculated between baseline and RP 6+2 per stakeholder group**

| Stakeholders | Product level change | % change | Annual systemic change (9-12 medicines) |
|---|---|---|---|
| Originator non-contested sales | **-€318m** | **-28%** | -€3,343m |
| Originator contested sales | **+€134m** | **21%** | +€1,411m |
| **Originator gross profit** | **-€188m** | **-15%** | -€1,969m |
| Generic sales | **+€77m** | **56%** | +€806m |
| **Generic gross profit** | **+€25m** | **56%** | +€266m |
| **Cost to public payer** | **-€107m** | **-6%** | -€1,126m |
| **Patients treated** | **+102** | **5%** | 1,075 |
| **Δ of Patients treated** (monetised) | **+€70m** | n/a | +€739 |
| **Patients + payer monetised gain/loss** | **+€178m** | **+9%** | +€1,865 |

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

Caveats to the model used:

Data: IQVIA MIDAS data includes sales revenue data corresponding to list or ex-manufacturer price without accounting for rebates or discounts (especially in hospital sector) on the one hand and costs including wholesale, distribution, value-added tax and social security expenses on the other to healthcare payers.

Opportunity cost: We present data at current euro level without inflation or cost of capital / commercial risk accounted for. This latter is a factor for commercial actors where monetary gains and losses are normally discounted in business calculations and may change decisions related to product developments accordingly. In contrast, healthcare payers pay on an ongoing basis.

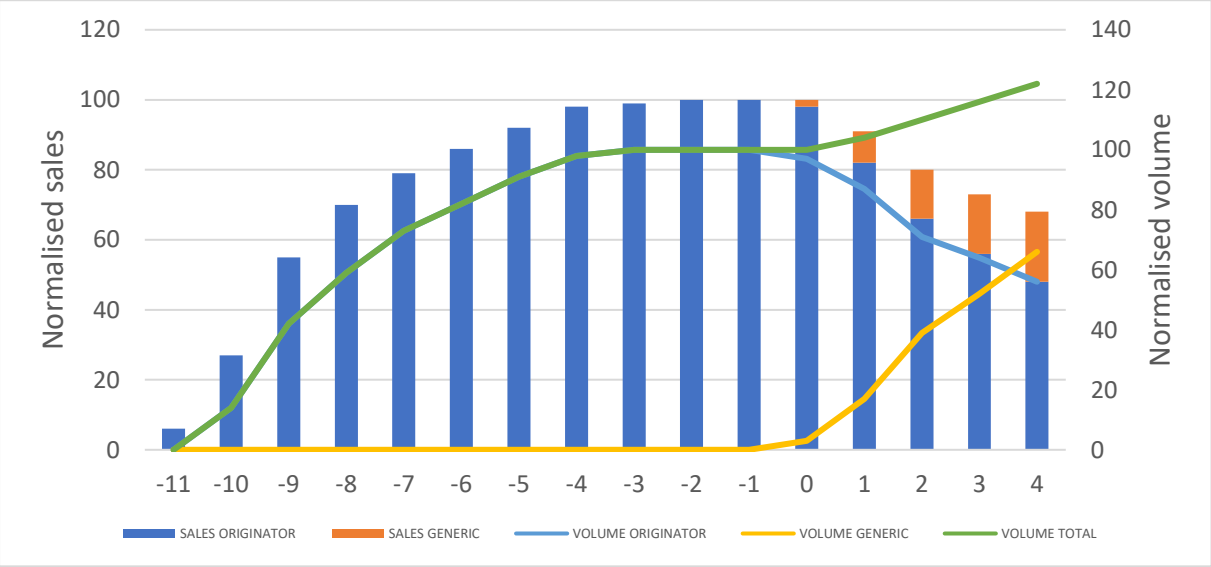
Business behaviour: There may be changes in the trajectory pre- or post-expiry compared to the current RP 8+2 regime, because companies change behaviour and aim to earn similar level of total pre-expiry monopoly rent during the reduced RP period. This may be achieved by

entering more markets earlier leading to the same pre-expiry overall sales and volumes of product sold. There is however the risk that the shorter RP period will lead to higher negotiated prices and relatively lower volumes of product sold in the pre-expiry period, or even a reduction in the number of products that enter EU markets.

*d. Modelling the economic impact of special incentives through increasing regulatory protection*

We use the same data as presented above and assume that after the Y-1 there will be an additional year of peak sales protected by a 1-year RP period. We will use the result of this model to estimate the proportionate effect of incentives for 6 months (comparative trials, access incentive in option A) to 1 year (UMN incentive). Again, we assume that pre-expiry sales trajectory is unchanged, the market dynamics of generic competition post expiry is unchanged. In the figure below thus data associated with a new Y-1 is added and the baseline Y5 is removed to maintain the overall product lifetime of 16 years.

**Figure 6 Normalised volume and sales data for products with 8+2+1 years of RP period**




| | Baseline | RDP 8+2 +1 | change | change % |
|---|---|---|---|---|
| Originator non-contested sales | 712 | 812 | **100** | 14.0% |
| Originator contested sales | 392 | 350 | **-42** | -10.7% |
| **Originator gross profit** | 765.6 | 824.6 | **59** | 7.7% |

| | | | | |
|---|---|---|---|---|
| Generic sales | 86 | 62 | **-24** | -28% |
| **Generic gross profit** | 28.38 | 20.46 | **-7.9** | -28% |
| **Cost to public payer** | 1190 | 1224 | **34** | 2.9% |
| **Volume (treated patients)** | 1343 | 1311 | **-32** | -2.4% |
| **Patients + payer monetised gain/loss** | 1190 | 1241 | **51** | 4.3% |

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

Using the above model for the product lifetime, we can make the following observations at product level:

- Originator companies increase pre-expiry sales due to additional year of monopoly sales by 100 (normalised units) or 14% of lifetime protected sales. In terms of gross profit, this is 47 more monetised unit, or 7.7% increase.
- Generic companies' start to benefit from sales one year later, and thus generic sales are reduced by 24 (normalised units), and gross profit is reduced by 8 (normalised unit) which is equal to a reduction of 28% sales, compared to baseline.
- Healthcare payers pay more overall due to an increase in the average price they need to pay for a standard unit of the product. We consider again the 'peak' volume sold of the originator product pre-expiry in baseline and use the average price in each year under the different RP regimes to calculate sales. The total cost for healthcare payers is thus -51 (normalised units) over the product lifetime compared to baseline
- Patients lose -32 (normalised units) in decreased volumes of the medicine over the lifetime of the product compared to baseline

### Monetising the systemic effects for 1-year extension of RP for medicines addressing UMN (Option A and C)

This measure affects RP protected medicines as last protection, altogether 35% of all new medicines. Of these we expect 15-20% to address UMN. Applying these rates on the 40-50 annual new authorised medicines as per our dynamic baseline, 3 special UMN incentives per year is expected on average. It should be noted however that annual peak sales can deviate from the average value used in the model and for products with substantially larger expected annual revenue, the incentive may well worth the increased commercial cost/risk that is expected to be associated with developing a product that meet (at the early phases of development and up until authorisation) the UMN criteria.

**Table 2 Changes calculated for 1-year extension of RP protection per stakeholder group**

| 1 year increase in RP | Product level change | Systemic change (3 medicines) |
|---|---|---|
| **Originator gross profit** | **+€94m** | **+€282m** |
| Generic gross profit | -€13m | -€39m |
| Cost to public payer | +€54m | +€162m |
| **Δ of patients treated** (monetised) | -€28m | -€84m |
| **Patients + payer monetised gain/loss** | **-€82m** | **-€246m** |

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

### Monetising the systemic effects for 6-month extension of RP for comparative clinical trials (Option A and C)

Similar to the previous incentive, this measure could benefit RP-protected products, around 35% of all new medicines would be eligible. Conducting comparative trials should be feasible for many medicines, but not for all· Also, if the cost of the comparative trial is too high as opposed to the reward, companies will decide to decline the incentive. We expect that half of the RP products could benefit from it, or 8 medicines annually. Of course, higher sales medicines would have a higher compensation, regardless the cost of the trial.

It should be noted that this data is expected to generate new knowledge for better decision making at an earlier time point and thus represent additional fixed cost compared to baseline. We assume the additional costs of conducting comparative trial with standard of care amount to €20-50 m (the model uses the middle value of the range), referring to the paediatric trials as a benchmark[15]. Therefore the incentive could attract developers to factor in comparative trial design in their clinical study programme. There is no information on how stakeholders (including developers and regulators) would respond to statistically insignificant or negative outcome emerging from the comparative effectiveness arm of the study.

**Table 3 Changes calculated for 6-month extension of RP protection per stakeholder group**

| 6-month increase in RP | Product level change | Systemic change (8 medicines) |
|---|---|---|
| **Originator gross profit** | **+€47m** | **+€378m** |
| **Cost of comparative trial for originator** | **+€35m** | **+€280m** |
| Generic gross profit | -€6.5m | -€52m |
| Cost to public payer | +€27m | +€218m |
| **Δ of patients treated** (monetised) | -€14m | -€112m |
| **Patients + payer monetised gain/loss** | **-€41m** | **-€328m** |

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

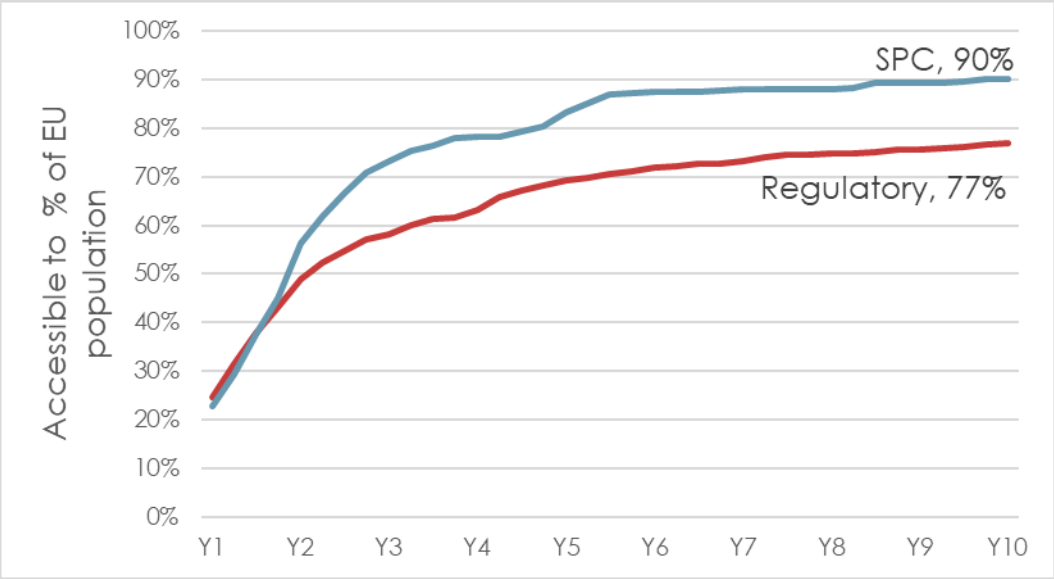
5. *Monetising the systemic effects of measures to improve market access*

The baseline is that there is no obligation or incentive to launch a product in a particular member state. Indeed, products authorised only reach up to 15 Member States (MS) out of the maximum possible 27 (Kyle, 2019) and on average 49% EMA-approved medicines are reimbursed in an EU country (Access case study; IQVIA, W.A.I.T. report 2021). Market launch incentives will not be a corrective measure for per capita utilisation rate of medicinal products but to increase the coverage across member states (breadth) and provide in some cases alternative medicinal products to existing therapies (depth) thereby creating positive spillover effects to better shortage management. Note that we had no access to IQVIA MIDAS sales data in three countries (Cyprus, Denmark and Malta) to ascertain market launch there.

[15] The joint evaluation of the orphan and paediatric regulation estimates the cost of paediatric studies at €22m.

We analysed products with protection expiry between 2016-2024 and recorded positive sales of originator products. For each molecule and each Member State, the first quarter in which meaningful non-zero sales occurred for at least two quarters. This is to eliminate cases where there may be one quarter of sales and then the product is not sold again in that Member State for several years. To follow the evolution of market access over 10 years, the sample was restricted to only those products that are authorised between Q1 2010 and Q4 2011. We have also created a larger sample of products between Q1 2010 and Q4 2014. The patterns for the first seven years in the two samples were very similar. We analysed access as a function of the number of Member States in which each product was available and the corresponding percentage of the EU population that was covered for each product. Taking a simple average across all products gives a representative time series for all RP products and a separate representative time series for all patent/SPC products. This analysis shows that those products that are SPC-protected are accessible to a higher share of the EU population that those that are RP-protected.

**Figure 3 Product accessible to EU population over time per protection type**



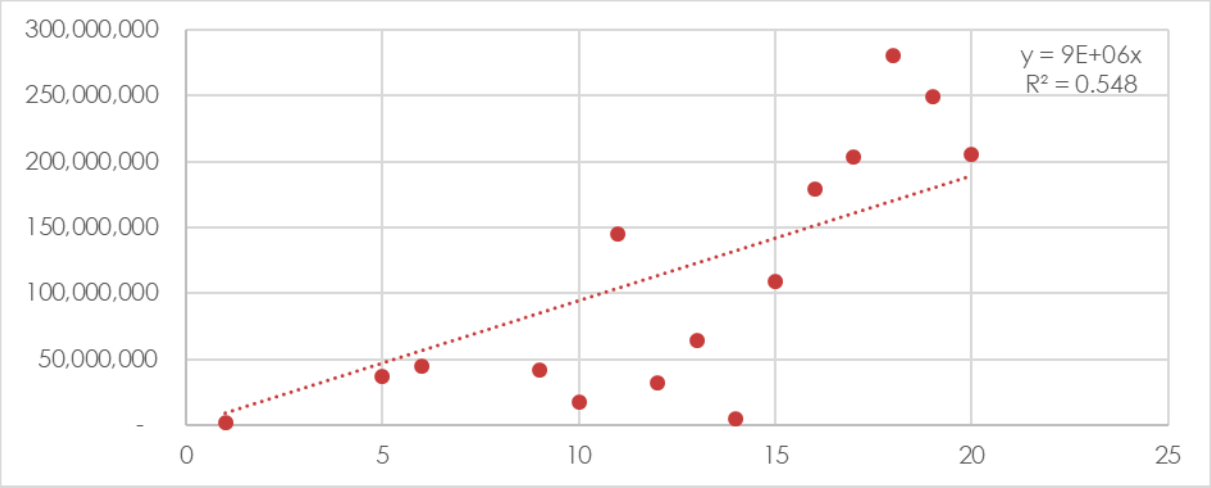

Deeper analysis point to higher coverage of products with higher sales and that larger member states with higher GDP tend to have a higher share of the products on their market. For example, there are 69 and 68 of the 78 products launched in Germany and Italy/Spain.

**Table 4 Distribution of 78 products with RP expiry 2016-2024 launched in member states**

| Number of countries | Number of molecules | Percent | Cumulative % |
|---|---|---|---|

| where product was launched | launched | | |
|---|---|---|---|
| 1 | 3 | 3.9 | 3.9 |
| 2 | 1 | 1.3 | 5.1 |
| 3 | 2 | 2.6 | 7.7 |
| 4 | 2 | 2.6 | 10.3 |
| 5 | 2 | 2.6 | 12.8 |
| 6 | 3 | 3.9 | 16.7 |
| 7 | 1 | 1.3 | 18.0 |
| 9 | 2 | 2.6 | 20.5 |
| 10 | 2 | 2.6 | 23.1 |
| 11 | 5 | 6.4 | 29.5 |
| 12 | 3 | 3.9 | 33.3 |
| 13 | 6 | 7.7 | 41.0 |
| 14 | 2 | 2.6 | 43.6 |
| 15 | 5 | 6.4 | 50.0 |
| 16 | 5 | 6.4 | 56.4 |
| 17 | 5 | 6.4 | 62.8 |
| 18 | 7 | 9.0 | 71.8 |
| 19 | 12 | 15.4 | 87.2 |
| 20 | 10 | 12.8 | 100.0 |

**Figure 4 Average annual peak sales of products with RP expiry 2016-2024 per country launch**




The different options use different policy measures to enhance access to patients. Option A provides an additional RP period of +6 months in case centrally authorised product is placed on all EU market within 5 years of MA. Option B involves obligation to place a centrally authorised medicine on the market in the majority of MS. Finally, option C provides a milestone incentive of +2 year of RP period if a medicinal product is supplied in all MS within a period of 2 years from MA.

Based on the size of the incentives/losses we estimated the compliance as percentage of medicines. From this, we could calculate the costs or savings to the public (Table 5). For option A, we used the same model as for the special incentive for comparative trials, but expecting that only the higher sales medicines would comply, we used a higher average peak sales in the model, €255m, the average of the higher-selling half in our basket of RP protected products. For option B and C, the model of the reduced regulatory protection was used (from option B), to calculate public savings stemming from non-complying medicines. Again, we adjusted the average peak-sales value (to €80m), assuming that the low-sales medicines will be the ones not complying.

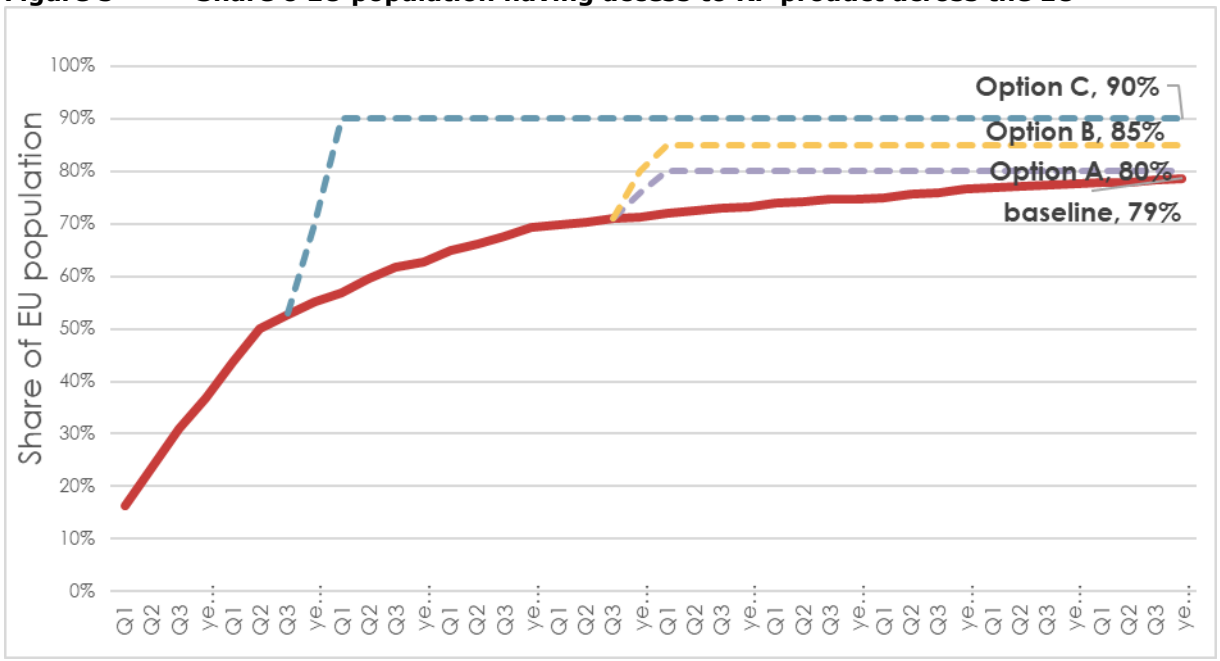
**Table 5 Compliance estimate for each option, commercial value and cost/benefit for public**

| Option | Expected compliance | Originator's reward/loss | Cost/benefit for public |
|---|---|---|---|
| **Option A** +6 months, if in all EU | 50% (6-8 medicines) | +€527 m gross profit +7.5% gross profit for 7 complying medicines | +€455 m public cost |
| **Option B** -5 years, if not in majority of MS | 75% (11-13 medicines) Majority of markets | -€842 m gross profit -34% gross profit for 4 non-complying medicines | €681 m gain from non-complying medicines |
| **Option C** | 66% (10-12 medicines) | -€469 m gross profit | €444 m gain from non- |

| | | | |
|---|---|---|---|
| -2 years, if not in all EU | | -15% gross profit for 5 non-complying medicines | complying medicines |

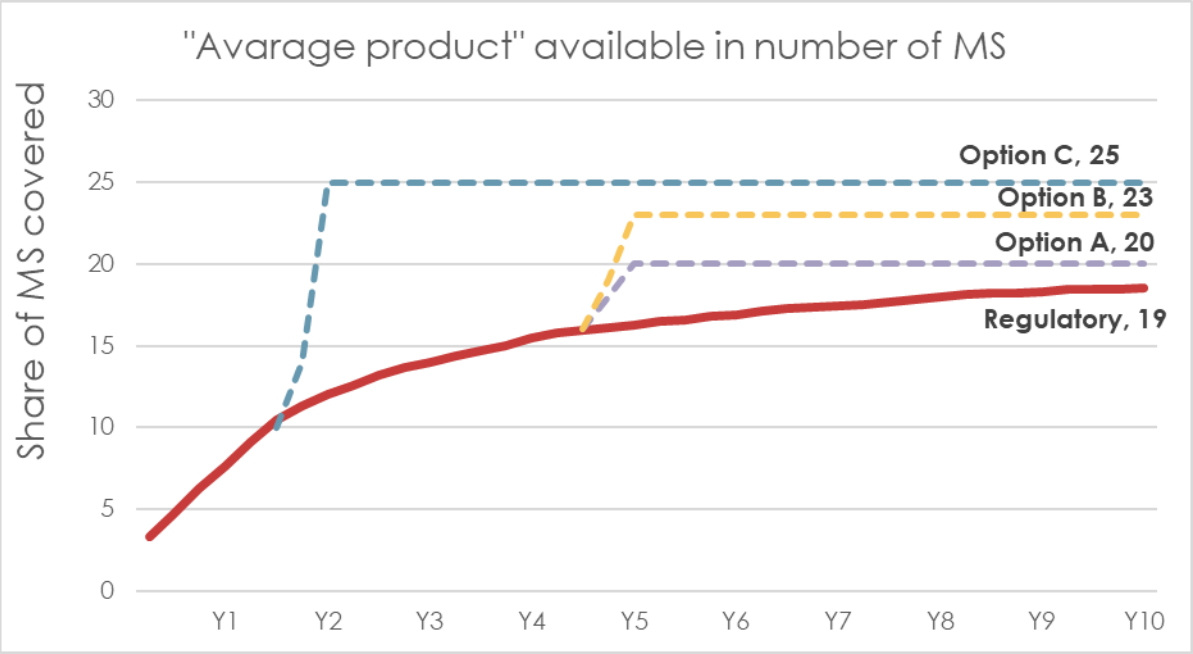
Again, launching products in all EU member states requires additional investments by companies compared to baseline, which will reduce the net gain experienced by companies.

**Figure 5 Share o EU population having access to RP product across the EU**




| Option | Average coverage over 10 years<br>% population | Average coverage over 10 years<br>Number of member states |
|---|---|---|
| Baseline | 65.3% | 15 |
| Option A | 67.6% | 16 |
| Option B | 70.2% | 18 |
| Option C | 80.1% | 23 |

**Figure 6 Social impact of enhanced access to RP product across the EU**




*6. AMR transferable voucher*

Antimicrobial resistance is a global challenge and the cost of inaction is very high when compared to expected societal benefits and cost savings in the mid/long term[16]. Antimicrobial products are not expected to be sold in large volumes on the market or generate large revenue stream and therefore the commercial incentive through the RP system will have limited value. Developers of antimicrobials are often innovative SMEs without significant resources to take these products through the regulatory approval pathway and require alternative instruments for ensuring sustainable R&D of antimicrobials. A transferable regulatory protection voucher (or transferable exclusivity voucher) allows the developer of an antimicrobial product to benefit from an additional year of data exclusivity period on another product in their portfolio or sell the voucher to another company that would use the voucher for their own benefit. This mechanism could provide the developer a reward (or an incentive) for

[16] https://www.oecd.org/health/health-systems/Averting-the-AMR-crisis-Policy-Brief-32-March-2019.PDF

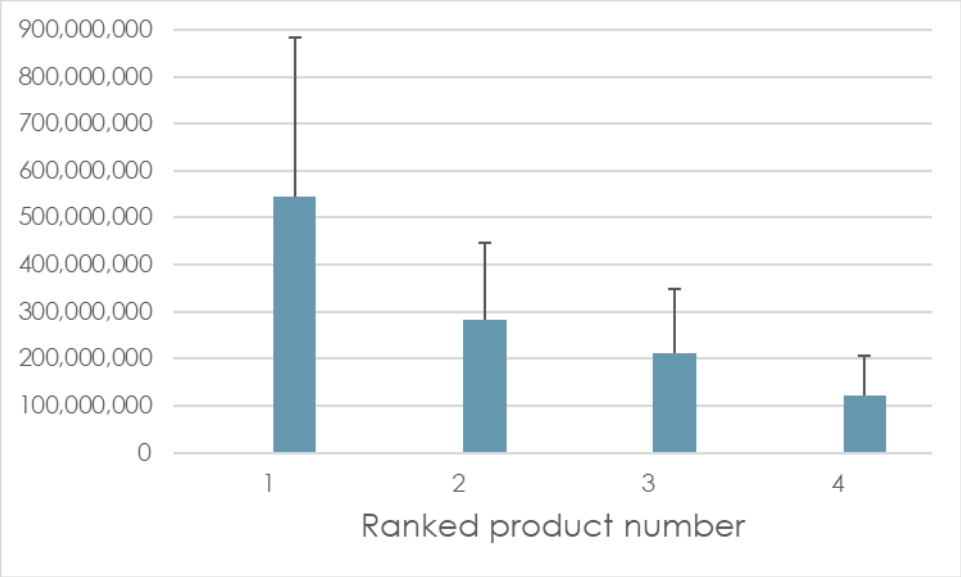
developing an antimicrobial product and meet (partially) the related investment needs of an estimated €1bn per product. [17] While the reward will directly be paid to developer by the buyer of the voucher, the cost of the voucher would eventually be met by healthcare payers of the product developed for other diseases (potentially also benefitting from lower level of AMR).

The transferable voucher is therefore only applicable to a subset of products where RP is the last measure of protection rather than those with patent/SPC. As we noted above, products with high peak sales tend to have SPC as LOP, and thus on average, the cohort of products with RP as LOP will have lower peak sales.

It should however be pointed out that when the voucher is sold on, only part of the value will be captured by the developer of the antimicrobial product (the seller) and the other part will go to the buyer of the voucher. The larger the share that goes to the seller, the more efficient the voucher is as an incentive or reward to develop antimicrobial products.

It has been observed, in the case of the priority review voucher introduced in the USA, that the more vouchers are available for the buyer, the lower price the buyer needs to pay and hence a larger share of the value is retained by the buyer.

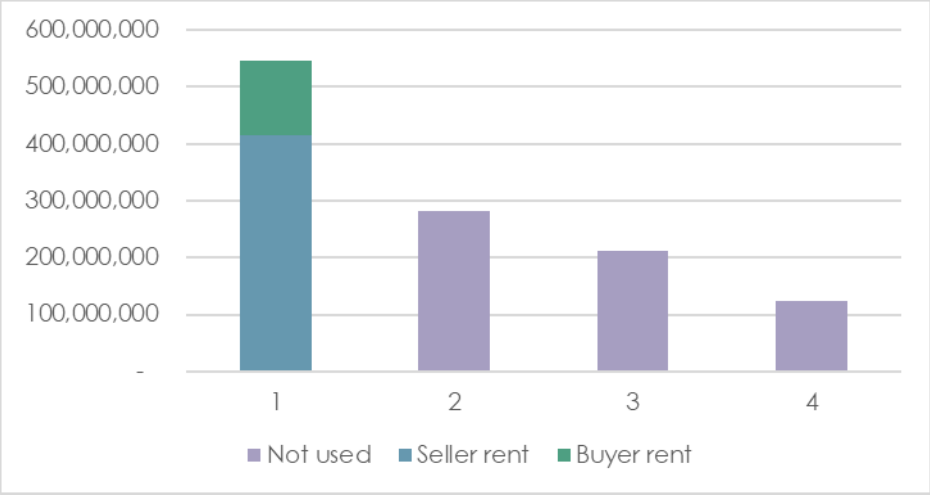
**Figure 7 Average peak annual sales of products with RP expiry 2014-2024**




[17] New drugs to tackle antimicrobial resistance (2011) The Office of Health Economics

The ‘erosion’ of the value of the voucher will increase with increasingly more vouchers concurrently available on the market. Similarly, the seller’s share is changing dependent on the number of vouchers simultaneously competing for products to transfer the voucher to. In the figures below, we see that share that goes to the seller of the voucher (i.e. developer) will decrease and the total incentive in the system reach a plateau. Thus the system designed to support the developer becomes less efficient. Note that the total incentive plateau is at about €500m that is half of the expected development cost of an antimicrobial product. It is therefore clear that the transferable voucher in this model will not cover the total development cost of the developer.

**Figure 8 Share of the seller and buyer in the value of the voucher for (top) n=1 voucher per year and (bottom) n=3 vouchers per year**



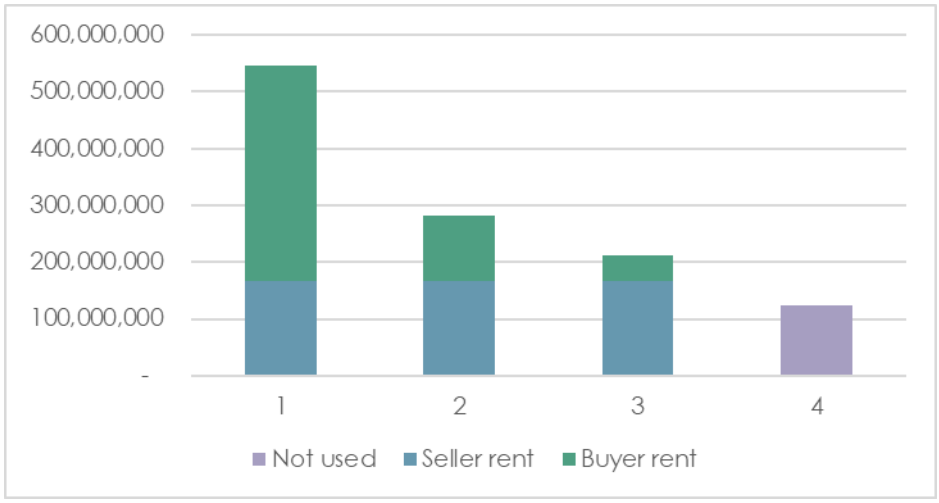
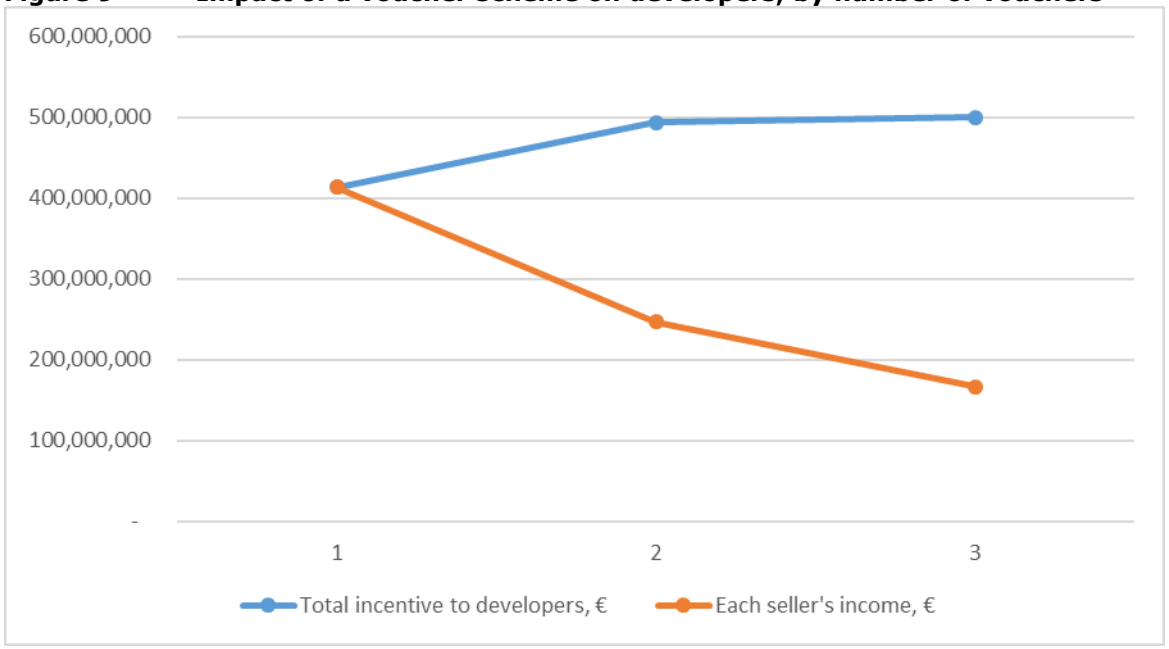
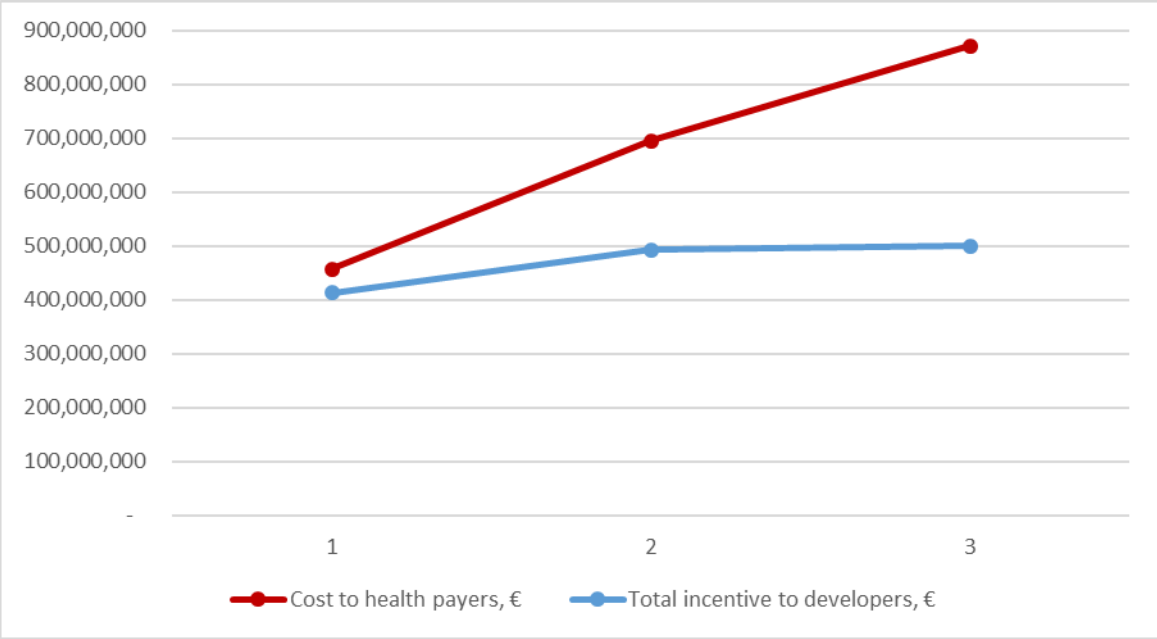



**Figure 9 Impact of a voucher scheme on developers, by number of vouchers**



The cost to healthcare payers (i.e. difference of peak sales and equilibrium sales for a given product) will also increase from a value initially close to the value of the voucher (1.1 times the total incentive) to a higher multiple of 1.75. Note however this analysis compares only the cost rather than the benefit of developing antimicrobials. OECD estimates that AMR already costs about €1.1bn every year to the EU Member States healthcare systems.

**Figure 10 Comparison of total incentive to developers and total cost to health payers, by number of vouchers**




The distribution of the average peak sales of products that have RP expiry as LOP and the number of vouchers will therefore determine the cost and benefit to the various stakeholders. In our cohort we focussed on high-revenue products and therefore we used a normalised product sales and volumes curve that is expected to represent this cohort of products more closely (i.e. higher rate of generic entry and originator price erosion, see Figure 2). We use the model introduced earlier and apply to the three scenarios that link to the number of simultaneous vouchers in issue. The corresponding costs and benefits are detailed below:

**1. Three transferable vouchers are granted per year**

**For originators:** The top three products in each year will benefit from an extra year of RP extension; using the average values for these (€545m, €283m, and €211m) we obtain €872m per year net gain in revenue compared to baseline, which accumulates to €13.1bn over 15 years for

originators at current euro values. The corresponding share of innovation budget generated for industry (20%) is €174m annually or €2.6bn over the 15 years.

**For developers:** The figures earned by originators may be compared to the amount they had paid as buyers of the transferable vouchers to antimicrobial developers as sellers of the vouchers. Developers obtain €500m for their three vouchers annually or €7.5bn over the 15 years. While no discount is considered for cost of goods and cost of capital for originators, these companies can afford the cost of the voucher as the annual net gain from the extended RP is greater than the annual cost of the vouchers. Nevertheless, it is worth noting that the annual €174m innovation budget generated through the RP extension does not cover the cost of buying the transferable vouchers from sellers. Finally, the total AMR development incentive of €500m shared across three developers provides a fraction of the development cost of three antimicrobial products (about 17%) they had invested in.

**For generic companies**: The cost of delayed market entry for generics of the three products per year was calculated as €322m or €4.8bn over 15 years.

**For healthcare payers:** The nominal cost calculated at constant peak volume of the originator product sold, national healthcare systems pay an additional €561m compared to baseline per year or €8.4bn over 15 years.

**For patients:** Patients have costs and benefits associated with the voucher: Developing antimicrobials has a significant patient benefit that is hard to monetise but as pointed out before, any reduction of the current high cost of AMR (€1.1bn per year) in the national healthcare systems is the ultimate aim of the voucher system. As before, we may attribute the share of the revenue for innovation (€174m per year, or €2.6bn over 15 years) or better the amount originators pay developers for the vouchers (€500m per year that is €7.5bn over 15 years) as patient benefit.

However, patient will not be served from lower coverage of the other products that are protected by an extended RP period compared to baseline, with reduced volume distributed to patients -55 (normalised units) or a reduction of -4%.

**2. One transferable voucher is granted per year**

**For originators:** Only the top selling product in each year will benefit from an extra year of RP extension; using the average value for this (€545m) we obtain €458m per year net gain in revenue compared to baseline, which accumulates to €6.9bn over 15 years for originators at current euro values. The corresponding share of innovation budget generated for industry (20%) is €92m annually or €1.4bn over the 15 years.

**For developers:** The developer that obtained the voucher will obtain €413m (as the average price of the top and top+1 product) in each year or €6.2bn over the 15 years. It appears that the annual net gain from the extended RP companies earn is sufficient to pay the price of the voucher. The AMR development incentive of €413m for one developer in each year provides a larger fraction of the development cost of an antimicrobial product than the previous scenario where three developers shared the total incentive.

**For generic companies**: The cost of delayed market entry for generics of the product with extended protection was calculated as €169m per year or €2.5bn over 15 years.

**For healthcare payers:** The nominal cost calculated at constant peak volume of the originator product sold, national healthcare systems pay an additional €294m compared to baseline per year or €4.4bn over 15 years.

**For patients:** Again, we can attribute the share of the revenue for innovation (€92m per year; €1.4bn over 15 years) or better the amount originators pay developers for the vouchers (€413m per year; €6.2bn over 15 years) as patient benefit.

However, patient will lose coverage of the product that is protected by an extended RP period compared to baseline, which through a reduced volume distributed to patients can be equated to €305m per year or €4.6bn over 15 years.

### 3. Transferable voucher is granted every two years

Here we assume that only the top selling product will benefit from an extra year of RP extension every other year. There is however the potential for higher selling products on the market. The Table below It does not appear to provide any further efficiency gain in the system compared to the previous scenario and selecting this makes no policy sense as a large share of the originator's gain will already have been paid to developers, long before originators can reap the benefits of their investment. Of course, if there is no qualifying antimicrobial for a transferable voucher each year (which may well be the case if no sufficient incentive/profit margin exist in the system) pipelines will dry up, and the system will have reduced direct costs and benefits for all stakeholders. Nevertheless, there remains a distinct risk that a resulting lack of preparedness for a future pandemic of antimicrobial resistance will be counted in trillions of euros lost globally.

**Table 6 Average peak annual sales of top products with RP expiry 2014-2024 segmented bi-annually**

| Year (RP expiry) | Top 1 (sales, €) | Top 2 (sales, €) |
|---|---|---|
| 2014-2015 | 978,000,000 | 493,000,000 |
| 2016-2017 | 473,000,000 | 120,000,000 |
| 2018-2019 | 469,000,000 | 386,000,000 |
| 2020-2021 | 703,000,000 | 408,000,000 |
| 2022-2023 | 1,270,000,000 | 174,000,000 |
| **AVERAGE** | **778,600,000** | **316,200,000** |

| | | |
|---|---|---|
| STD | 345,033,766 | 160,680,428 |

*7. Costs and benefits of Option C (preferred option)*

Table 7 summarises the benefits and costs for the preferred option by adding up the different elements from the previous sections.

**Table 7**: costs and benefits of pivotal measures in the preferred option

| Option C | Cost/benefit for public payer and patients | Cost/benefit for originators | Cost/benefit for generic industry |
|---|---|---|---|
| 2 year conditional protection for **all EU launch in 2 years** | €444 m gain<br>+15% access | -€469m gross profit<br>(5 non-complying MP) | +€63m gross profit |
| +1 year extension of RP for medicines addressing **UMN** | + €246m cost<br>+ 1-2 new UMN addressing medicines | + €282m gross profit<br>(3 incentives) | - €39m gross profit |
| +6 months extension of RP for conducting **comparative clinical trials** | + €328m cost<br>+ faster access and cost saving thanks to improved reimbursement decisions | + €378m gross profit<br>+€280m cost<br>(8 medicines) | - €52m gross profit |
| **Transferable exclusivity voucher** | +€441m cost<br>+ 1 new antibiotic | +€387m gross profit<br>(1 voucher) | - €54m gross profit |
| **Total balance** | **+ €571m cost**<br>+ 1-2 new UMN medicines<br>+comparative clinical data<br>+15% access<br>+1 new antibiotic | **+€298m gross profit** | **- €82m gross profit** |

Table 8 summarises costs and benefits of the horizontal measures.

**Table** 8.: costs and benefits of horizontal measures in the preferred option

| | | **1 year average** | **15 years average** | | | **1 year average** | **15 years average** |
|---|---|---|---|---|---|---|---|
| **Benefits (horizontal measures)** | | | | **Costs (horizontal measures)** | | | |
| Streamlining savings for businesses | € millions | 22 | 337 | Streamlining costs for regulators | one-off | 25.2 | 25.2 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Streamlining savings for regulators | € millions | 50 | 754 | Streamlining costs for regulators | recurrent | 50.5 | 757.5 |
| Streamlining income for generics | € millions | 82 | 1,237 | **Sum of costs (streamlining)** | **€ millions** | **75.7** | **782.7** |
| **Sum of benefits (streamlining)** | **€ millions** | **155** | **2,329** | Digitalisation costs for regulators | one-off | 235 | 235 |
| Digitalisation savings for businesses | € millions | 11 | 169 | Digitalisation costs for regulators | recurrent | 47 | 705 |
| Digitalisation savings for regulators | € millions | 100 | 1,507 | **Sum of costs (digitalisation)** | **€ millions** | **282** | **940** |
| **Sum of benefits (digitalisation)** | **€ millions** | **112** | **1,676** | Enhanced support for SMEs and non-commercials | cost for industry (recurrent) | 2 | 30 |
| Enhanced support for SMEs and non-commercials | € millions | 11 | 169 | Enhanced support for SMEs and non-commercials | cost for regulators (recurrent) | 6 | 90 |
| | | 7 | 112 | **Sum of costs (SME support)** | **€ millions** | 8 | 120 |
| | | 3 | 39 | **TOTAL costs** | **€ millions** | **2,169** | **28,891** |
| **Sum of benefits (SME support)** | | **21** | **321** | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **TOTAL benefits** | **2,273** | **34,101** | | | | | |

The preferred option has a variant too, in which the RP is 6+2, but by launching in all Member States the incentive is only 1 year additional protection. Table 9 summarises the costs and benefits in that case:

**Table 9.** Cost-benefit table of incentives in Option C Variation (6+2+1) compared to baseline (8+2)

| Variation to Option C | Cost/benefit for public payer and patients | Cost/benefit for originators | Cost/benefit for generic industry |
|---|---|---|---|
| 1 year general reduction of the RP | +€1,008m | -€991m gross profit | +€133m gross profit |
| 1 year conditional protection for **all EU launch in 2 years** | +€384 m gain<br>+8% access | -€378m gross profit<br>(8 non-complying MP) | +€51m gross profit |
| +1 year extension of RP for medicines addressing **UMN** | + €246m cost<br>+ 1-2 new UMN addressing medicines | + €282m gross profit<br>(3 incentives) | - €39m gross profit |
| +6 months extension of RP for conducting **comparative clinical trials** | + €328m cost<br>+ faster access and cost saving thanks to improved reimbursement decisions | + €378m gross profit<br>+€280m cost<br>(8 medicines) | - €52m gross profit |
| **Transferable exclusivity voucher** | +€441m cost<br>+ 1 new antibiotic | +€387m gross profit<br>(1 voucher) | - €54m gross profit |
| **Total balance** | **+ €377m gain**<br>+ 1-2 new UMN medicines<br>+comparative clinical data<br>+8% access<br>+1 new antibiotic | **-€602m gross profit** | **+€39m gross profit** |

## Methodology and analytical models used for the evaluation

This section summarises the methods used for task 2 (data identification, collection and analysis) and task 3 (stakeholder consultations). The tables below outline the specific work packages and the related outcomes of how the findings were used and/or reported.

**Table 10.** Task 2: Data identification, collection and analysis.

| Work package | Outcomes and reports |
|---|---|
| 2.1 Literature Review | Integrated throughout analytical report, case studies, |

| | |
|---|---|
| | evaluation report and impact assessment. |
| 2.2 Comparative Legal Analysis | 7 Country reports |
| 2.3 Secondary Data Analysis | Analytical Report |
| 2.4 Case Studies | Case Study Report and Case Studies |

**Table** 11**.** Task 3: Stakeholder consultations.

| Work package | Outcomes and reports |
|---|---|
| 2.1 Literature Review | Integrated throughout analytical report, case studies, evaluation report and impact assessment. |
| 2.2 Comparative Legal Analysis | 7 Country reports |
| 2.3 Secondary Data Analysis | Analytical Report |
| 2.4 Case Studies | Case Study Report and Case Studies |
| 3.2 Feedback Analysis | 5-page report annexed to the inception report |
| 3.3 Public Consultation | Integrated throughout analytical report, case studies, evaluation report and impact assessment. |
| 3.4 Targeted Survey | Annex to the evaluation report |
| 3.5 Interviews | Individual interview summary notes and integrated throughout analytical report, case studies, evaluation report and impact assessment. |
| 3.6 Workshops | Workshop summary notes (2) |

1. *Data Identification, collection and analysis*

***Literature Review***

Peer-reviewed literature and policy document review was conducted to gather existing knowledge-base and served as a source of facts and figures. We conducted a comprehensive literature review by first defining relevant search terms (Keywords in English, Dutch, German, French and Spanish 2). Abstracts were screened for relevance and for those relevant full text was obtained. For scientific literature (Peer reviewed papers) online databases PubMed and Scopus were utilised. Grey literature (such as government or business reports, policy documents, theses or conference presentations) were identified from the following sources:

- Key EU institutions and agencies such as the European Parliament, the Council, DG SANTE, DG RTD, HaDEA, ECDC and EMA;
- Websites and online repositories of relevant public competent authorities (European and Member State regulators, pricing & reimbursement bodies) and health technology assessment institutions within the scope of this review;
- Google Scholar;

- Wider information sources including industry organisations (e.g. EFPIA, EuropaBio, Medicines for Europe) and patient associations and civil society organisations at EU and Member State level usually as submissions as part of the stakeholder consultation activities.

All full text documents (>550) were catalogued with their meta data (title, year, authors, item type, ISBN, ISSN etc), read and categorised for relevance and then managed using Mendeley where they could be easily identified, accessed and referenced during the writing of subsequent analytical and evaluation reports.

***Comparative Legal Analysis***

Comparative legal analysis aimed to provide information around whether proposed EU policy options for the revision of the general pharmaceutical legislation have been implemented or are currently being considered for implementation in other jurisdictions. The analysis presented the elements that had been implemented (if any) and the assessment or evaluation data that was available.

Five countries (Japan, Canada, South Korea, Australia, USA) were selected based on the secondary data analysis (Task 2.3) which identified them as relevant markets with developed economies. Two additional countries were included after discussion with the EC; 1) China as the largest market in Asia and a major generic medicine producer and sophisticated regulatory system for the same, 2) Israel where innovative legislative solutions were expected.

Information was collected via a standardised country reporting template and accompanying guidance document that clearly laid out the scope of the review and was approved by the EC prior to commencement of data collection. The template contained the following sections:

- Context and background to the legal framework on human medicinal products in [X]
- Overview and mapping of the institutional set-up in [X]
- Authorisation procedure

- Incentives and obligations to address antimicrobial resistance
- Future proofing: Adapted, agile and predictable regulatory framework for novel products
- Rewards and obligations related to improved access to medicines
- Facilitate generic and biosimilar entry to ensure affordable established therapies
- Notification and monitoring to ensure security of supply / availability measures
- Quality and environmental sustainability
- Resolving competing aims and interests within the legislation
- Bibliography

The template was completed based on substantive in country legal research and a literature review in both English and national languages. They were completed by national legal experts who had a good understanding of the context and legal systems. National experts were briefed on the project, the methodologies and the templates, and afforded the opportunity to ask questions via a group webinar to ensure methodological consistency across all countries.

The templates were supplemented by targeted interviews (Table 12) with key stakeholders (competent authorities, pharmaceutical industry association, patient association, payers) which were also conducted by the national experts. Potential interviewees were identified, contacted and followed up at least once in order to get an interview (Table 13). In some cases, interviewee's opted to provide written feedback which was accepted and annexed to the report.

**Table** 12**.** Interview Schedule.

| Country | Contacted and followed up | Interviewed | Written responses |
|---|---|---|---|
| Australia | 7 | 0 | 1 |
| Canada | 17 | 2 | 0 |
| China | 6 | 6 | 0 |

| | | | |
|---|---|---|---|
| Israel | 4 | 0 | 0 |
| Japan | 5 | 5 | 0 |
| South Korea | 4 | 0 | 0 |
| USA | 13 | 0 | 0 |

**Table** 13**.** Indicative Questions for interviewees

- Compared with foreign regulatory frameworks, which features of your country's regulation of pharmaceuticals do you consider distinctive/unorthodox (if any)? When were they introduced? Do you consider these to be advantageous? why?

- How does your country evidence the performance of your pharmaceutical regulatory framework? What are the reported indicators (if any)? How do you demonstrate an acceptable trade-off between speed of regulatory approval and clinical performance evaluation?

- Which foreign regulatory frameworks have the greatest influence on your country's regulation of pharmaceuticals?

- What good practices exist in [X] to:
    - Support innovation and address unmet medical needs?
    - Ensure the prevention of antimicrobial resistance while promoting the development of new products?
    - Regulate new products, new technologies in medicinal products as well as new manufacturing processes?
    - Promote wide market coverage by marketing authorisation holders and access to medicines for patients?
    - Facilitate the entry onto the market of generics and biosimilar medicinal products?
    - Ensure the security of the supply and secure the availability for patients?
    - Ensure a high level of quality throughout the supply chain in various production settings, and mitigate the environmental impact of the production of medicinal products?

- What formal *international* regulatory collaborations do you have in place?

    - Is there work on-going regarding regulatory agility?
    - What are the challenges that remain to be addressed by the legal framework of your country? Have some legislative or policy attempts at addressing these issues remained unsuccessful?

- What legislative or policy priority changes were required during the COVID-19 pandemic. What were the related lessons learnt? Are these changes going to be sustained in your country?

- What is X's vision, strategy or roadmap for pharmaceutical regulatory framework? What are the related timelines?

+ Country-specific questions to explore the innovative legal options in the country identified via desk research and literature review.

Following completion each country report went through several rounds of review and clarification to increase consistency, address gaps and maximise comparability.

***Secondary Data Analysis***

Secondary data analysis comprised compiling over 50 macro indicators relevant to several policy areas and conducting statistical, econometric and trend analysis within the EU and compared to data from other jurisdictions.

In the first instance indicators were defined. SMART[18] indicators were proposed based on the objectives of the original legislation and the 2020 pharmaceutical strategy. These were verified and matched against data sources during a series of online working sessions and final selection made based on availability of data. There was prioritisation of time series data reaching back to pre 2005 as well as availability across the markets of EU, Switzerland, USA, Canada, Australia, Japan, and Korea.

In total we identified 55 indicators (Table 14 by policy area). The indicators were grouped in seven policy areas to address the policy elements in scope for the study with specific indicators selected to inform the main evaluation criteria of effectiveness, efficiency, coherence, relevance and EU added value of the legislation.

**Table** 14**.** Total number of indicators selected by policy area.

| Policy Area | Number of Indicators |
|---|---|
| Industrial and Economic Competitiveness | 13 (IEC 1-13)<br>International (1,2,3,4,5,6,) Internal (7,8,9,10) Sector Profitability (11) Other |

[18] Specific Measurable Achievable Relevant Timebound

| | |
|---|---|
| | (12,13) |
| Research and Innovation | 9 (RI 1-9)<br>Conversion rates (1,2,3,4,5,6) Public Research Funding (7) Private Investment (8) Innovative Products (9) |
| Single Market | 6 (SM1-6)<br>Shortage (1,2,3,4) Therapeutic Area Competition (5,6) |
| Accessibility | 10 (ACC1-10)<br>Access to approved medicines (1,2,3) Time to coverage (4,5,6,7,8,9,10) |
| Affordability | 6 (AFF 1-6) |
| Efficiency | 3 (EFF 1-3) |
| Manufacturing | 3 (M1-3) |
| AMR | 3 (AMR1-3) |
| Environmental | 2 (E1-2)<br>Residues (1) Manufacturing Emissions (2) |

The indicators were populated using 24 existing proprietary or public databases or sources as listed in Table 15. While each specific indicator must be treated individually depending on completion, coverage, data type and presence of time series element, analysis was conducted to the following plan wherever data allowed and as appropriate. Statistical tests were not applied where the relevant observations were less than 30.

- Presentation of longitudinal data covering the period 2000-2020 with stratification where appropriate (e.g. along therapeutic area, indication, product type, company size, legal basis of applications, approval pathway etc).
- Comparison of pre and post legislation periods using parametric (Welch's t-test) or non-parametric (Mann Whitney U test) tests for significance between the pre and post periods.
- Difference-in-differences estimation by comparing the evolution of the EU 'treated' countries relative to other similar but 'untreated' countries, before and after the 2004 revision of the general pharmaceutical legislation.
- Presentation and descriptive analysis of reference groups in other jurisdictions (Japan, US, Switzerland) with statistical comparison wherever possible.

**Table 15.** List of secondary data sources.

| # | Data Source |
|---|---|
| 1 | Belkhir et al. Carbon footprint of the global pharmaceutical industry and relative impact of its major players. Journal of Cleaner Production (2019) |
| 2 | Drugs@FDA |
| 3 | EFPIA |
| 4 | EFPIA Report on Key Trade Data Points on the EU27 Pharmaceutical Supply Chain based on Eurostat |
| 5 | EU Industrial R&D Investment Scoreboard |
| 6 | EU Shortages Database |
| 7 | EudraGMDP/GMP/Sites |
| 8 | Eurostat /Eurostat Healthcare expenditure statistics |
| 9 | IFPMA |
| 10 | Informa Biomedtracker |
| 11 | Informa Datamonitor Healthcare |
| 12 | Informa in-house dataset collected from 20 major funding bodies including Horizon 2020 |
| 13 | Informa Outlook 2019 |
| 14 | Informa Pharmaprojects |
| 15 | Informa Sitetrove |
| 16 | Informa Trialtrove, |
| 17 | IQVIA MIDAS sales/sales volume data |
| 18 | OECD Health statistics/STAN Database |
| 19 | Publicly available trade/economics ministry data |
| 20 | Statista |
| 21 | Umwelt Bundesamt Database "Pharmaceuticals in the environment", including substances on the European Watch List. |
| 22 | US Bureau of Labour Statistics |
| 23 | Utrecht University MAA database |
| 24 | WHO Health Expenditure |

Detailed methodology per indicator along with results of the analysis can be found in the Analytical Report.

***Case Studies***

Case studies were developed focused on specific issues to illustrate linkages and mechanisms behind trends observed in the data.

Alongside ongoing data identification, collection and analysis the 'focus areas' of each case study were agreed iteratively with the EC. The final selection and structure were based upon feasibility criteria (potential to showcase legislative contribution, researchable) and linkage to objectives of policy revisions and intervention logic. Seven case study topics were agreed: 1. Antimicrobial resistance (AMR), 2. Agile/adaptive regulatory systems, 3. SMEs/Regulatory support, 4. Improved access, 5. Affordable generics, 6. Emerging manufacturing and 7. Unmet Medical Need.

Within the scope of and specific to each case study, we next conducted a search of the literature. 1) defining relevant search terms, 2) defining relevant data sources, 3) defining relevant time period, 4) screening and selection of relevant papers, 5) snowballing. For scientific literature online databases PubMed and Scopus were utilised, while for grey literature online search engines (e.g. Google) and databases (e.g. Google Scholar, Policy Commons, Overton) were used along with websites of relevant international organisations (e.g. EMA, EFPIA, International society of pharmaceutical engineering, European Association of Hospital Pharmacists, etc) being screened. Additional sources identified on selected and screened sources were also included where relevant. The documents were analysed and information was put under topic headers to structure the data (different for each case study).

Where relevant and applicable, quantitative analysis of secondary data was undertaken specific to the case study to which it applied. Where this has occurred, methods are provided in detail in the individual case studies.

An overall case study format was proposed based around key research questions and sub questions and is presented below.

- Summary (0.5 pages)
- Retrospective view
    - 1: Nature and extent of the problem (1 page)
    - 2: Objectives of the 2004 regulation (0.5 page)
    - 3: Evaluation of the achievements of the regulation (2 pages)
- Forward looking view
    - 1: Evolution of the problem and residual challenges (1 page)
    - 2: Enhanced policy options (2 pages)
    - 3: Potential impacts of the revisions (2 pages)
    - 4: Synergies and interplay (1 page)

- Key conclusions
- Case study references and data sources

In the case of case study 3. SMEs/Regulatory Support there were substantial knowledge gaps and key information interviews were used to address these. We used semi- structured interviews (Table 16) with representatives of 5 leading industry associations to address knowledge gaps that are not covered by the higher levels of evidence. Interviews were performed with relevant stakeholders. Notes were taken and sent back to the interview respondents for validation. The interview notes were analysed and collated in the same way as the documents and referenced in the case study.

**Table 16.** Interview Protocol for SMEs.

| Specific for SMEs… | What goes well at the moment? | What can/ should be improved? | Suggestions for improvement? |
|---|---|---|---|
| Innovation ecosystem (drug discovery and development):<br>1 resources (capital, human, etc.)<br>2 risks<br>3 collaborations (relationship w/large companies, knowledge institutes)<br>4 IPR | | | |
| Pre-marketing phase:<br>• Regulatory advice, dialogue and training (early-stage SME/ITF Brief Meetings on marketing authorization filing, strategies, orphan drug designation applications, PIPs, scientific advice, etc.)<br>• Scientific advice and protocol assistance (vs. other sources of information; satisfaction; and reasons for asking for advice)<br>• Financial support (financial incentives (fee reductions) in regulatory process; other incentives for SME innovation)<br>• General on: European versus National (CP/MRP/DCP); GMP/GLP; Clinical Trial Directive | | | |
| Regulatory approval and requirements:<br>• clinical<br>• non-clinical<br>• manufacturing | | | |
| Post-approval management (e.g. fee incentives, advice):<br>• label<br>• pharmacovigilance<br>• HTA | | | |

Further information including search terms and inclusion and exclusion criteria for each case study specifically plus the seven case studies can be found in the Case Study Report.

2. *Stakeholder Consultation: Primary Data Collection*

***Feedback for the consultation on the Roadmap/Inception Impact Assessment***

The Roadmap /Inception Impact Assessment was developed by the EC to inform stakeholders and gather feedback on the possible actions at EU level. The study team received an excel file containing 173 answers (feedbacks) to the published Roadmap/Inception impact assessment along with the 86 attachments in PDF format. The answers were translated from other languages to English, the data was checked for duplicates and campaigns were identified using both Excel and manual checking. When respondents did not use open text answers, the attached PDF documents were consulted in detail. The analysis of the answers was based on a set of topics developed after an initial assessment of all submissions. Using Excel and Word, manual cross-checks of all answers were completed, recording topics and sub-topics as well as the number of times they were mentioned.

A factual summary report in English was produced. This comprises a succinct 5-page report, profiling the participants, highlights of the main topics raised overall and by stakeholder groups, following the elements as set out in the technical specifications.

***Open Public Consultation***

A survey questionnaire developed in English and agreed with the EC was conducted electronically and it was published on the Commission's 'Have your say' web portal in all European languages for 12 weeks, from 28 September to 21 December 2021 – along with information materials.

The survey had two main topics and several sub-topics (bulleted in Table 17) and served to determine the balance of opinion (overall, and by stakeholder group) on the relative importance of a given issue. The OPC was a mixture of open and closed questions and utilised skip codes to guide participants through the relevant questions depending on their self-categorisation into stakeholder group. There were no character limits imposed on open answers.

**Table 17.** OPC survey structure.

| |
|---|
| **1)** Backward-looking questions<br>• Other issues to be addressed in this revision<br>• Positive and unintended effects of the legislation<br><br>**2)** Forward-looking questions |

- Unmet medical needs
- Incentives for innovation
- Antimicrobial resistance
- Future proofing: adapted, agile and predictable regulatory framework for novel products
- Rewards and obligation related to improved access to medicines
- Enhance the competitive functioning of the market to ensure affordable medicines
- Repurposing of medicines
- Security and supply of medicines
- Quality and manufacturing
- Environmental challenges

It was anticipated that 500 responses would be received and in total 478 responses were received – shown below -by stakeholder group.

**Table 18.** Number of OPC Responses by stakeholder group**.**

| Stakeholder | Responses Received |
|---|---|
| Industry | 179 |
| Public Authorities | 37 |
| Health Service Providers | 85 |
| Academic | 39 |
| Civil Society Organisations and Citizens | 106 |
| Other | 32 |
| Total | 478 |

All 478 responses were downloaded from the EU Survey portal, translated into English, checked for duplicates and campaigns were identified, using a combination of Excel, statistical software STATA and manual checking. The study team conducted quantitative statistical analysis of closed answers and qualitative analysis of the answers provided in text form. All answers provided in text form (over 4,000 entries across 14 questions) were manually checked and emerging themes for each question were reported in a descriptive narrative for each stakeholder group.

A factual summary report in English, comprising of a succinct 8-page report, was produced. An in-depth analysis report was also produced with more profiling of participants, campaign identification and detailed analysis of stakeholder views on the two main topics of the OPC as well as summary of the position papers submitted in PDF format.

***Targeted Survey (Survey Report)***

Targeted surveys with key stakeholder groups through an online questionnaire were designed to obtain facts and figures – as well as opinions – on the relevance, efficiency, costs and benefits of the current legislation and the scale of anticipated positive or negative impacts of potential new policy elements.

A survey tool was developed and signed off by the EC. The survey had several modules (bulleted in Table 19 below) and incorporated skip codes such that different stakeholder groups were automatically navigated through the questions appropriate for them. All questions were optional and could be skipped or answered with don't know.

**Table 19.** Targeted Survey Structure.

- Survey explanation (purpose, privacy, scope, time, instructions)
- About you/your organisation (Organisation name, type, participant name)
- Functioning of the legislation since 2005 (effectiveness, relevance, coherence, value add)
    - To what extent has the legislation been effective/relevant/coherent/added value with respect to objectives
    - Where has the legislation been most/least effective/relevant/coherent/added value
    - Provision of supporting evidence or data
    - Efficiency (costs and benefits and explanations of answers)
- Elements of future policy options (incentives UMN, AMR, Futureproofing, Access, Competitive Market Functioning, Manufacturing Quality and Environment, Security of Supply, Streamlining)
    - Please rate the impact of the following measures on UMN/AMR/Futureproofing/Access/Competitive Market Functioning/Manufacturing Quality and Environment/ Security of Supply/ Streamlining
    - Further comments on your answers above
- Conclusion (the greatest impacts with supporting data)
- Close (invitation to be contacted with follow up questions)

The questionnaire was delivered electronically using the tool 'Survey Monkey' and 220 participants were directly invited. Invites were sent as individual links were possible to enable tracking of participation and were supported by a letter from the EC endorsing the survey. The EC also

shared the survey link within relevant networks of public authorities. Of the total number of invitations, over 90 invitations were send to 'intermediary' organisations who were asked to disseminate the survey link through their networks (e.g civil society or association members) in order to snowball the sample further. The survey targeted five main stakeholder groups (industry, public authorities, health service providers, academic and civil society) and had agreed participant targets that were considered suitably representative. The survey remained open for just under 15 weeks between the dates 16th November 2021 and 14th January 2022, and invited participants were followed up multiple times in this period to try and boost participation. The number of individuals and intermediaries invited is shown in Table 20.

**Table 20.** Targets and invited participants per stakeholder group.

| Stakeholder | Targeted | Invited (intermediary) |
|---|---|---|
| Industry | 65 | 63 (38) |
| Public Authorities | 50 | 15 (6) |
| Health Service Providers | 20 | 40 (33) |
| Academic | 20 | 63 (7) |
| Civil Society Organisations | 45 | 39 (11) |
| Total | 200 | 220 (95) |

Upon closing the survey, data was downloaded to an excel spreadsheet and imported to STATA. Data was cleaned extensively in STATA with suspected duplicate, test, empty and "nonsense" entries exported in full to excel. Within excel the responses were manually reviewed and decisions taken and recorded on their inclusion. In one case two entries from a single person were combined, where the survey had been completed in two separate and distinct parts. One person submitted an amendment to their responses by email which was enacted into the data set. Two people's data sent by email were manually entered into the data collection tool by the evaluation team and then downloaded with the rest of the data. Having received and downloaded 440 entries to the survey, 209 responses remained for analysis after data cleaning.

The process of identification of campaigns was conducted using a combination of statistical software and manual checking in excel according to the following process:

- Identifying responses that matched on all of the 46 closed questions
- Identifying responses that matched identically on any one of the open questions

- Identifying responses that matched to a score of 94% of characters on any one of the open questions using the function 'matchit' in STATA using the "bigram" option for fuzzy logic.

- Exporting all potential campaign respondents to excel where they were manually grouped

- Any that could not be assigned to a campaign were decategorized and considered independent entries.

Campaigns of ten or more responses matched by any of the three methodologies were considered for further analysis and separate presentation of the key points from open questions. In accordance with the guidance received on the use of data for campaigns one copy of the campaign response was selected per stakeholder group from blocks of matching closed question answers while others were disregarded from any quantitative presentation.

Quantitative analysis focussed on the tabulation and description of the closed questions where in each case the questions were asked with a 5-point scaled response. There was always a 'don't know' option and respondents also had the option to skip any question. The responses were divided into 5 different stakeholder group to which they had self-categorised: i) Industry ii) Civil Society iii) Public Authorities iv) Academic v) Health Services.

Answers were first tabulated as frequencies of each response per question and stakeholder and then individually attributed a score (1 -5) and these scores were tabulated along with the 'don't know' and 'skipped' options. Following this for each question an average score was calculated per stakeholder. These were then normalised into an "all stakeholder score" which weighted each stakeholder group's score equally and accounted for the different participation rates. Within each subcategory the different aspects were ranked to identify overall which were considered the most/least effective, relevant etc. The average scores were mapped back to the original categories through assignment to five evenly sized groups with 3 at the centre so <1.8 was very small/not at all, 1.8-2.59 was small/slightly, 2.6-3.39 was moderate/moderately, 3.4-4.19 was large/largely >=4.2=very large/extremely.

Agreement between stakeholders was assessed using ANOVA. Agreement between stakeholders was classified as high, medium, and low where $p<0.05$ combined with an F score greater than 4 was considered low agreement with strong evidence that stakeholders did not have consensus between them – inter-stakeholder consensus. Medium agreement was assumed where the P value was <0.06 and the F score was above 3. Those with medium and low inter-stakeholder consensus were further explored using Tukey's test for multiple comparisons to identify the divergent stakeholders.

Finally, the standard deviation was calculated per question and per stakeholder and utilised as an indicator of within (intra) stakeholder consensus. A higher standard deviation signalled less intra-stakeholder agreement with those above 1.1 being classified as low agreement and below 0.7 high agreement. Where intra-stakeholder consensus was low and sample size permitted these differences were explored related to

geographical area of respondent (public health authorities) and subcategory of the stakeholder group (Industry, public health authority, academic).

Open questions were analysed qualitatively. Data was outputted to Excel where questions were allocated to Effectiveness, Relevance, Coherence, Efficiency (retrospective) or to policy blocks (anticipated impacts) and then coded into deductive themes. This data was analysed and summarised integrated with interview and open public consultation data.

***Interviews***

Semi-structured interviews supported our qualitative and in-depth explorations of the functioning of the current legislation. They also gathered feedback and input on the initial policy elements described in the Inception Impact Assessment, as seen from the perspective of the key stakeholder groups, across the EU member states.

Candidate interviewees were identified by a range of methods (drawing on the study team's knowledge of the sector and preliminary desk research, expression of interest via the targeted survey, Pharmaceutical Committee workshops, recommendation by other interviewees) and the list was verified and inputted to by the EC. Participants met simple selection criteria: senior figures with good knowledge of the legislation either as individual experts or as senior representatives of organisations with a mandate that encompasses the legislation. Interviews targeted participants across all the identified stakeholder group.

Interviews were conducted according to a topic guide enabling them to be loosely structured. Individual questions were tailored to each interviewee. The topic guide was designed in two parts with the first covering the evaluation criteria while the second part of the discussed the problem analysis, policy options and comparison of the policy options.

Interviews were conducted remotely via Zoom or Teams by a team of ten consultants over the period 7th December 2021 and 26th January 2022. A shortened version of the topic guide was shared ahead of the interview. Interviews were an hour and half long and were recorded (with permission) and an auto-transcription created and stored. On some occasions interviews were conducted in groups with multiple participants and organisations in attendance (Table 21 shows interviews as groups and individuals). Following completion of the interviews, summary notes were written up and key meta data (participant(s), organisation, stakeholder group) were transcribed onto them.

**Table 21.** Interviews targeted and conducted by stakeholder group.

| Stakeholder | Targeted | Conducted | Individuals |
|---|---|---|---|
| Industry | 40 | 29 | 57 |
| Public Authorities | 35 | 9 | 10 |
| Health Service Providers | 15 | 26 | 45 |

| | | | |
|---|---|---|---|
| Academic | 15 | 4 | 6 |
| Civil Society Organisations | 25 | 16 | 20 |
| Total | 130 | 84 | 138 |

Summary notes were imported into Nvivo, coded thematically according to the 2020 objectives of the revisions and abstracts were exported for synthesis into the reports.

***Workshops***

Two remote stakeholder workshops with participants from across the stakeholder groups provided opportunity for the community to deliberate on progress and conclusions to date and supplement previous data collection.

Each half day workshop was hosted via zoom and followed the structure of:

- Introduction from the EC
- Plenary presentation including opening slido (interactive poll) from Technopolis Project Lead
- Breakout groups: Brief presentation followed by participatory discussion.
- Plenary presentation from each breakout group
- Closing presentation on next steps and closing slido from Technopolis Project Lead

In both cases a ‘save the date’ was followed by an invite and a discussion paper on the workshop topics 2 weeks prior to the event. Breakout group topics were provided in advance after agreement with the EC. Participants were able to state a first and second preference for their breakout groups and first choices were facilitated the vast majority of the time. Each breakout group had a facilitator and a presenter (from either Technopolis or a project partner) and a technical support from Technopolis Group. Breakout groups were large and to facilitate participation muting and unmuting of mics was strictly led by the facilitator while participants were also free to use the chatbox continuously and this was tracked and responded to. Observers from the EC were in attendance in all breakout groups. Key details about the workshops are shown in Table 22.

**Table 22.** Details of the workshops.

| | Workshop 1: Evaluation | Workshop 2: Impact Assessment |
|---|---|---|
| Date | 19th January 2022 | 25th April 2022 |
| Invited | 246 | 339 |
| Attended | 208 | 199 |
| Retention at final plenary | 80% | 90% |
| Breakout Groups | 1. Safeguarding Public Health<br>2. Europe's regulatory Attractiveness<br>3. Accommodating advances in science and technology<br>4. Ensuring access to medicines<br>5. Functioning of the EU market for medicines | 1. Enabling innovation including for UMN<br>2. Ensuring Access to Affordable Medicines for Patients<br>3. Enhancing the security of supply of medicines and addressing shortages<br>4. Reducing the regulatory burden and providing a flexible regulatory framework |

## ANNEX 5: EVALUATION

The Evaluation is provided in a separate document, in attachment.

## ANNEX 6: COHERENCE WITH THE REVISION OF THE ORPHAN AND PAEDIATRIC REGULATION

The general EU pharmaceutical legislation regulates the way medicines (including medicines for rare diseases and children) are *authorised* across the EU and sets the framework in which they are marketed.

The Regulation on medicines for rare diseases is an 'add-on' to the general pharmaceutical legislation setting specific measures needed to address the market failure for medicines for rare diseases due to their small populations and potentially limited return on investment. The drivers for unmet medical need in the area of rare diseases remain relevant and therefore requires measures complementary to those provided by in the general pharmaceutical legislation.

Specialised legislation for rare diseases and children, entered into force in 2000 and 2007 respectively and currently being revised, complements the general EU pharmaceutical legislation to specifically support the development in these previously neglected areas, mainly through additional incentives and obligations.

The revision of the general pharmaceutical legislation and of the Regulations on medicines for rare diseases and for children are part of the same intervention aiming at achieving the same objectives set by the Pharmaceutical Strategy, including addressing unmet medical need of patients and access to medicines.

Unmet medical need / *high* unmet medical need

Both revisions will include a criteria-based definition on unmet medical need. The general pharmaceutical legislation will contain a definition for 'unmet medical needs' (UMN). The legislation on rare diseases will contain a definition of '*high* unmet medical needs' (HUMN), as in principle all orphan medicines will automatically satisfy the definition of UMN under the general rules; only a small subgroup of orphan medicines will qualify as 'HUMN'. The Commission has worked with Member States and the EMA and received input from stakeholders via consultations to develop criteria that can be introduced in the legislation. These criteria relate to disease level (whether the disease is life-threatening and/or seriously debilitating) and they relate to product level (whether there is another medicine or therapy already authorised and, if so, whether the treatment under development can satisfactorily cure the disease).

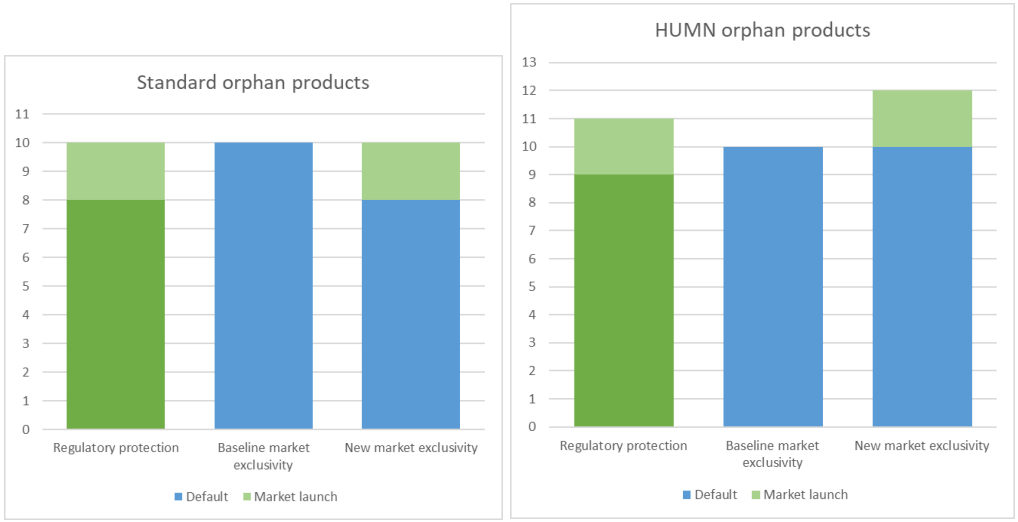
In principle, medicines that satisfy the definition of UMN or HUMN will receive (a) access to early scientific advice and regulatory facilities and (b) access to longer regulatory protection periods (market exclusivity for medicines for rare diseases and data protection for other medicines).

Both the revision of the general pharmaceutical legislation and the revision of the legislation for medicines for rare diseases and children adjust the system of incentives and depart from the 'one size fits all' approach to a 'modulated' one. Therefore, regulatory data protection for medicines

and market exclusivity (in the case of orphan medicines) are modulated to reward companies developing medicines that deliver on needs of patients. Such needs are primarily reflected in the concepts of 'unmet medical need'.

The interplay between the regulatory protection and the orphan market exclusivity (special protection for medicines for rare diseases) will be explained in detail in the revised impact assessment for the Regulations on medicines for rare diseases and for children. Essentially, the market exclusivity will be modulated in the same way as the regulatory protection, 2 or 1 years of the protection will be conditional to all EU market launch (depending which variation of the regulatory protection will be chosen by the legislator). For standard orphan medicines the market exclusivity will be equal to the regulatory protection (as today) and for medicines addressing high unmet medical needs, the market exclusivity will be one year more than the regulatory protection (these medicines will already enjoy a 1-year longer regulatory protection). Please note that the market exclusivity does not only protect from generic competition, but from similar products too (although this latter protection was rarely applied in the past).

The below graph demonstrates the interplay among the two protections for orphan medicines, with the 2-year market launch conditionality:




**Other points of coherence** between the general and orphan medicines legislation are listed below. Together they create an integral system through:

- The revision of procedures for accelerated development and assessment of medicines for major public health needs taking into account novel technologies, in particular, the implementation of the PRIME scheme.

- Upstream cooperation among actors of the pharmaceutical lifecycle which foresees the reinforcement of mechanisms for cooperation and coordination between the regulatory authorities, Health Technology Assessment (HTA) authorities and payers building on the possibilities of the new HTA rules.

- Simplification of procedures and reduction of burden for generic/biosimilars. For example, currently it is not possible to apply for a marketing authorisation for a generic/biosimilar before the orphan market exclusivity period is over (i.e. 10 years after obtaining the marketing authorisation) whereas for other medicines this is possible when the data protection expires and before expiry of market protection. In the new system, application for marketing authorisation for generic or biosimilar medicines will become possible *before* the expiry of market exclusivity.

- Future-proofing of the legislation, meaning its adaptation to rapid technological changes, including personalised medicine, will benefit patients as described in section 8. This will allow the full use of opportunities brought by gene therapies and personalised medicine which in many cases may concern medicines for rare diseases.

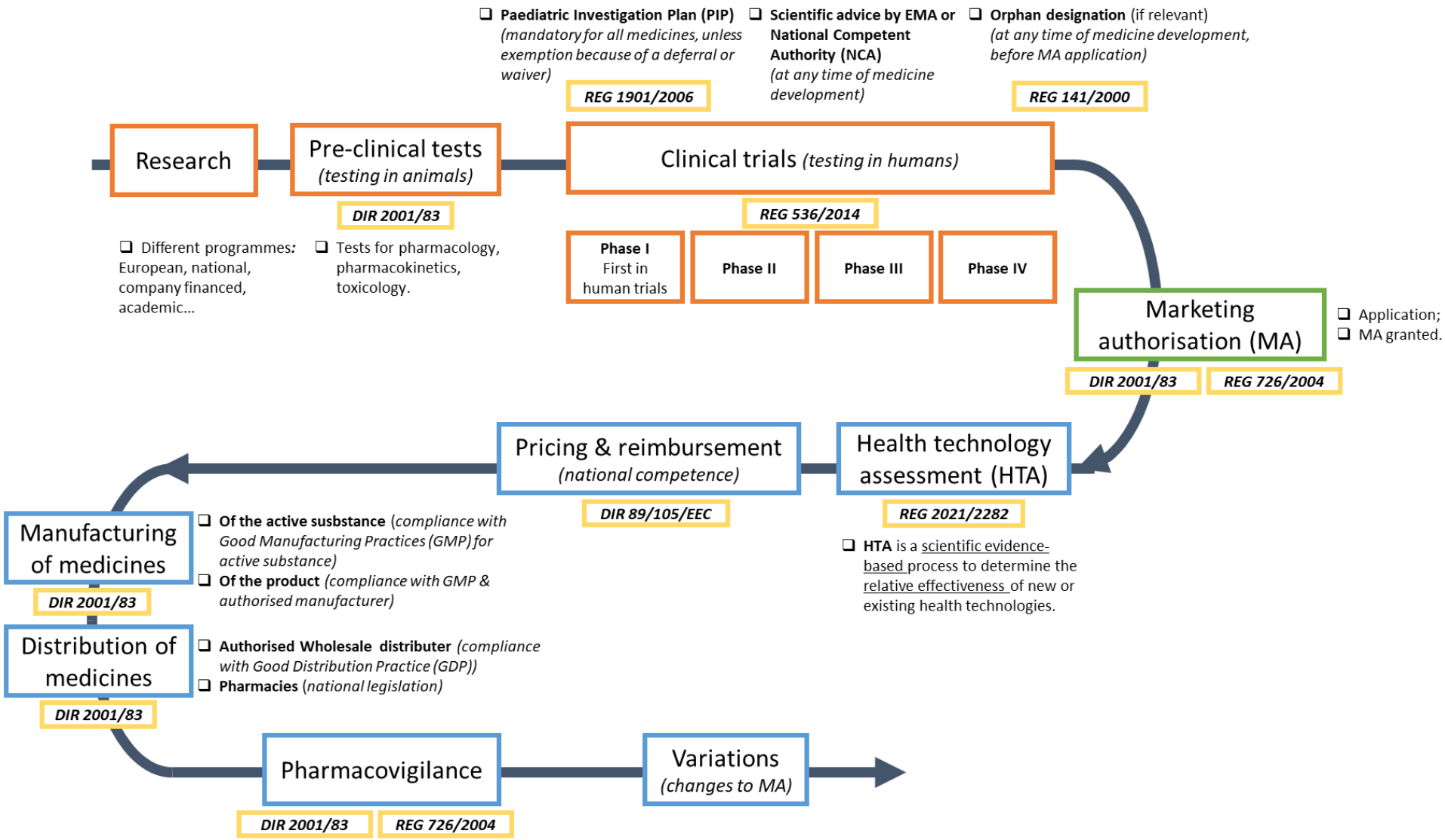
In the case of transferable exclusivity vouchers (TEVs), at first glance, there may seem to be incoherence between the two regimes. The conclusion in the Impact Assessment for the revision of the legislation on medicines for rare diseases is that TEVs can be considered as an ineffective incentive to generate innovation, whereas in the case of antimicrobials they may be a more plausible incentive if applied strictly.

In fact, this different conclusion stems from the 'special' character of the antimicrobial sector and the particularity of the market failure in this case. Both cases relate to incentivising products for a limited number of patients (rarity of the disease in the first and desire to use the new antimicrobial as little as possible in the second). However, contrary to rare diseases, the societal risk of AMR (which potentially concerns the whole population and not just a few patients) and its actual and potential economic consequences combined with the very limited pipeline of antimicrobials with a new mechanism of action suggests that the advantage of having TEVs specifically for novel antimicrobials as an 'insurance policy' against resistant antimicrobials may surpass the disadvantages of the high costs for the very limited number of TEVs that are likely to enter the market.

## ANNEX 7: OVERVIEW OF MARKETING AUTHORISATION PROCEDURES

ANNEX 8: VISUAL OVERVIEW OF THE LEGAL FRAMEWORK

| National procedure | Mutual recognition procedure (MRP) | Decentralised procedure (DCP)* | Centralised Procedure (CP) |
|---|---|---|---|
| **… where one MS authorise medicines for its own territory.** | **…where additional MSs recognise the national MA of another MS and authorise the medicine for their own territory.** | **…where several MSs authorise a medicine for their own territory.** | **…where a MA is valid in all MSs.**<br><br>**This procedure is <u>mandatory</u> for some products.** |
| **Market access** | | | |
| **National territory.** | **National territory of all MSs involved.** | | **EU internal market.** |
| **Procedure overview** | | | |
| **Procedures and assessment time depend on national legislation.** | **Based on MA already granted by one MS;**<br><br>**Recognition of that MA by other MSs.** | **Scientific assessment by one MS;**<br><br>**Consultation of MSs involved.** | **Scientific assessment by EMA;**<br><br>**Consultation of the MSs;**<br><br>**Authorisation granted by COM.** |
| | **Total time if agreement among MSs**<br>***→ 210 days*** | ***→ 240 days*** | **Total time if positive opinion by EMA**<br><br>***→ 277 days*** |
| | ***If disagreement among MSs → referral procedure to CMD(h)/ CHMP*** | | |


❑ Paediatric Investigation Plan (PIP) (mandatory for all medicines, unless exemption because of a deferral or waiver)
REG 1901/2006
❑ Scientific advice by EMA or National Competent Authority (NCA) (at any time of medicine development)
❑ Orphan designation (if relevant) (at any time of medicine development, before MA application)
REG 141/2000
Research
Pre-clinical tests (testing in animals)
DIR 2001/83
Clinical trials (testing in humans)
REG 536/2014
❑ Different programmes: European, national, company financed, academic…
❑ Tests for pharmacology, pharmacokinetics, toxicology.
Phase I First in human trials
Phase II
Phase III
Phase IV
Marketing authorisation (MA)
DIR 2001/83
REG 726/2004
❑ Application;
❑ MA granted.
Health technology assessment (HTA)
REG 2021/2282
❑ HTA is a scientific evidence-based process to determine the relative effectiveness of new or existing health technologies.
Pricing & reimbursement (national competence)
DIR 89/105/EEC
Manufacturing of medicines
DIR 2001/83
❑ Of the active susbstance (compliance with Good Manufacturing Practices (GMP) for active substance)
❑ Of the product (compliance with GMP & authorised manufacturer)
Distribution of medicines
DIR 2001/83
❑ Authorised Wholesale distributer (compliance with Good Distribution Practice (GDP))
❑ Pharmacies (national legislation)
Pharmacovigilance
DIR 2001/83
REG 726/2004
Variations (changes to MA)

## ANNEX 9: OVERVIEW OF ECOSYSTEM AND THE LEGAL FRAMEWORK

### 1. The pharmaceutical ecosystem

The Pharmaceutical Strategy for Europe[19] describes the pharmaceutical ecosystem and changes in the landscape that transform industry and medicines development from the old model of chemical blockbuster medicines to biological medicines, advanced therapy medicines, combined medicines with software and personalised medicines. Health data is key to fully exploiting the huge potential of new technologies and digitisation. This vision is echoed in the health ecosystem of the updated European industrial strategy[20].

The EU pharmaceutical ecosystem covers activities from pre-clinical research to manufacturing and includes actors ranging from manufacturers (including medical devices and equipment and personal protective equipment), healthcare services; health tech and related services[21]. Overall, it covers **24.8 million direct jobs**, **493 000 firms** (including 99.7% SMEs) and contributes to **9.5% of EU value added**[22]. The EU provides an attractive market for the pharmaceutical industry, especially with regards to the activities and support provided by the European Medicines Agency and the EU-wide marketing authorisation. These elements are key in attracting R&D to the EU and are regulated by the general pharmaceutical legislation. At global level, the EU health industries are also key players in competition with North America and Asia. As an example, in 2018, North America accounted for 48.9% of global sales of medicines compared to Europe (incl. Switzerland) accounting for 23.2%[23]. The EU also accounts for 24% of the world's API production compared to 65.5% being produced in Asia Pacific. The EU pioneered in sophisticated biologic innovative medicines (and biosimilar medicines), however, Asia and the US are rapidly catching up[24].

In the ecosystem, 'big pharma'[25] are increasingly outsourcing functions, including clinical trials and manufacturing, and are focusing investment on a limited number of therapeutic areas while disinvesting from others[26]. Emerging biopharma companies – often SMEs – are driving a large portion of innovation and development. According to a recent report from IQVIA[27], emerging biopharma companies were responsible for a record 65% of the molecules in the R&D pipeline in 2021, up from less than 50% in 2016 and 33% in 2001. Top pharmaceutical companies' share of the total R&D pipeline has been shrinking over the last decade.[28]

Big pharma is increasingly disinvesting from risker upstream research and instead access products that are already in later clinical trials stages through acquisitions of small biotech companies or start-ups with promising portfolios of patents[29]. Once the molecule reaches a certain maturity (e.g. completing phase II clinical trials) and still looks commercially promising, big pharma companies come in, they partner, buy the molecule or buy the company at the stage of the expensive late-stage clinical trials, marketing authorisation and market launch. Licensing is also used extensively in the

[19] COM(2020) 761 final.
[20] COM(2021) 350 final European industrial strategy | European Commission (europa.eu).
[21] SWD(2021)351 final – page 138.
[22] SWD(2021)351 final – page 137.
[23] Would the last pharmaceutical investor in Europe please turn the lights out (efpia.eu).
[24] SWD(2021)351 final – page 139.
[25] Understood as multinational companies dominating the industry sales and traditionally responsible for all aspects of the medicines discovery pipeline.
[26] European pharmaceutical research and development. STUDY Panel for the Future of Science and Technology. European Parliament Research Service, p. 10.
[27] Global Trends in R&D: Overview through 2021, IQVIA, February 2022.
[28] Ibid, footnote 27.
[29] Ibid, footnote 27.

pharmaceutical sector, though small firms and start-ups also rely on venture capital to finance their R&D.[30]

## 2. The legal framework

### a. Basic legislative acts

The **general EU pharmaceutical legislation** consists of Directive 2001/83/EC and Regulation (EU) No 726/2004 forming one policy intervention. Directive 2001/83/EC provides the framework for authorisation and monitoring of medicines post-authorisation (pharmacovigilance) for nationally authorised medicines, manufacturing and wholesale distribution and authorisation of actors in the supply chain, advertising and falsified medicines. The Regulation establishes the European Medicines Agency and its governance and provides also the framework for authorisation of medicines through a centralised procedure and for pharmacovigilance of these medicines. When it comes to technical requirements for the authorisation application and the lifecycle management of medicines, the Regulation refers regularly to the common requirements in Directive 2001/83/EC. harmonises the way medicines are authorised across the EU. This legislation is grounded on the fundamental principle that a medicine for human use may only be placed on the market once authorised based on a positive benefit-risk of its quality, safety and efficacy, and that applies regardless of the authorisation procedure.

Medicines may either be authorised centrally by the Commission based on a positive scientific assessment by the European Medicines Agency (EMA), the centralised procedure (CP), or nationally by an individual or a group of Member States. A medicinal product authorised via the CP is not necessarily accessible in all Member States, as its actual placing on the market may depend on the launch strategy of companies and national pricing and reimbursement decisions.

The general pharmaceutical legislation also regulates the post-authorisation monitoring of the medicine (pharmacovigilance), as well as manufacturing, distribution and advertising.

The **specialised legislations for rare diseases and children**[31] ("The Orphan and Paediatric Regulations") complements the general EU pharmaceutical legislation (that also apply to medicines for rare diseases and children) to specifically support the development in these previously neglected areas, mainly through specific, additional incentives and obligations. Both the Orphan and Paediatric Regulations are designed to address specific unmet medical needs of small populations: (i) the Orphan Regulation aims at enabling research, development and authorisation of new medicines for rare diseases through specific incentives and (ii) the Paediatric Regulation works mainly with obligations. It compels companies already developing products for adults to screen them for possible use in children. It provides rewards once this obligation has been fulfilled, to compensate for the additional costs.

The revision of these specialised legislations, also ongoing, follows coherent objectives with the revision of the general pharmaceutical legislation: promoting innovation to better address unmet medical needs, ensuring access of patients to innovative medicines and reducing regulatory burden[32]. Taken together, they aim to ensure the right balance between giving incentives for innovation to

[30] Kyle M., 'The Alignment of Innovation Policy and Social Welfare Evidence from Pharmaceuticals', Innovation Policy and Economy 20, 2020.

[31] Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products, OJ L 18, 22.1.2000, p. 1, EUR-Lex - 32000R0141 - EN - EUR-Lex (europa.eu) and Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use, *OJ L 378*, 27.12.2006, p. 1, EUR-Lex - 32006R1901 - EN - EUR-Lex (europa.eu).

[32] However, the revision of the general pharmaceutical legislation has also other aims (such as ensuring that medicines are affordable, reducing environmental impact), not covered by the revision of the specialised legislations.

strengthen the research base of the EU pharmaceutical industry and the need for patients to have access to affordable medicines.

Advanced therapy medicines[33] are also regulated under specialised legislation. This legislation is also an 'add-on' the general pharmaceutical legislation for this specific product category and concerns in particular technical requirements adapted to the particular characteristics of these products, special incentives for SMEs and their assessment. The legislation on advanced therapy medicines is not subject to revision and as such not in the scope of this impact assessment.

These legislations are complemented by more specific ones, applicable at different stages of the lifecycle of medicines.

### b. Other legislative acts and policies applicable to medicinal products

#### i. At the research and development stage

The **Regulation on clinical trials**[34] harmonises the processes for the assessment and supervision of clinical trials throughout the EU. The evaluation, authorisation and supervision of clinical trials are the responsibilities of Member States and the Regulation ensures harmonisation. The regulation also allows as of 2022 a more efficient process for the approval of multinational trials. Having a single application and a single package will streamline the registration, assessment and supervision processes for EU clinical trials. This will also facilitate the conduct of trials in small populations scattered in several countries.

The **proposed Regulation on the European Health Data Space** (EHDS)[35] will provide a common framework across EU Member States for access to quality health data for use in research and development of new treatments.

The **European innovation Council** (EIC)[36] established under the Horizon 2020 programme aims at identifying and supporting breakthrough technologies and game changing innovations with the potential to scale up internationally and become market leaders. It supports all stages of innovation from R&D on the scientific underpinnings of breakthrough technologies, to validation and demonstration of breakthrough technologies and innovations to meet real world needs, to the development and scaling up of start-ups and small and medium-sized enterprises (SMEs).

The **Innovative Health Initiative Joint Undertaking**[37] (IHI JU) is a public-private partnership between the European Union, represented by the European Commission, and several health industries from the biopharmaceutical, biotechnology and medical technology sectors. IHI brings together diverse stakeholders (universities, companies large and small, and other health stakeholders) in collaborative projects that address disease areas where there is a high burden on patients and/or society. The initiative focuses on cross-sectoral projects supporting the development

[33] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 321, 10.12.2007, p. 121.

[34] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0536&qid=1653648430017.

[35] Proposal for a Regulation of the European Parliament and of the Council on the European Health Data Space, COM(2022) 197 final, Proposal for a regulation - The European Health Data Space (europa.eu).

[36] For more details, see https://eic.ec.europa.eu.

[37] Council Regulation (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe and repealing Regulations (EC) No 219/2007, (EU) No 557/2014, (EU) No 558/2014, (EU) No 559/2014, (EU) No 560/2014, (EU) No 561/2014 and (EU) No 642/2014, OJ L 427, 30.11.2021, p. 17, EUR-Lex - 32021R2085 - EN - EUR-Lex (europa.eu)

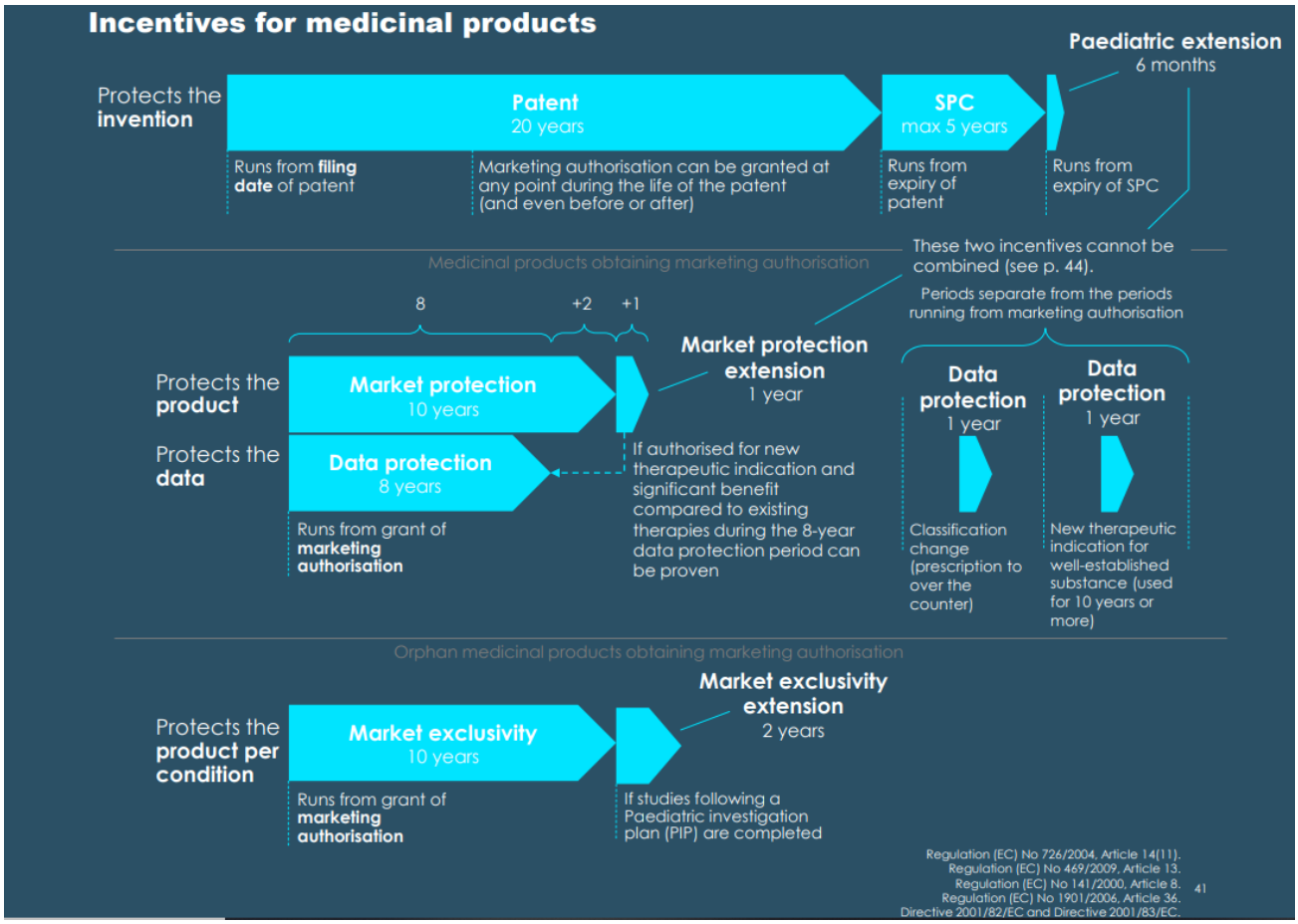
of safe, effective, people-centred and cost-effective products and services that target key unmet public health needs.

### ii. At the authorisation stage

The authorisation procedures are laid down in the general pharmaceutical legislation but aspects linked to authorisation are completed by other regulations.

Beyond the **general patent rules** applicable to medicines, the **Regulations on supplementary protection certificates (SPCs)**[38] provide for supplementary intellectual property rights extending patent protection for specific medicines. SPCs aim to offset the loss of patent protection for medicines that occurs due to the compulsory lengthy testing and clinical trials these products require prior to obtaining marketing authorisation.

The diagram below provides an overview of the current IP and regulatory protection rules for medicines in the EU.




*Source: Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe - Copenhagen Economics/European Commission.

[38] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products, OJ L 152, 16.6.2009, p. 1, EUR-Lex - 32009R0469 - EN - EUR-Lex (europa.eu) and Regulation (EU) 2019/933 of the European Parliament and of the Council of 20 May 2019 amending Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products, OJ L 153, 11.6.2019, p. 1, EUR-Lex - 32019R0933 - EN - EUR-Lex (europa.eu).

The ongoing review of the SPC regulation[39] will put in place a unitary SPC and/or a single ('unified') procedure for granting national SPCs. This will make SPCs more accessible and efficient, and will impact the health sector.

### iii. At the market launch stage

Following marketing authorisation companies take decisions on the market launch in Member States based on commercial considerations[40]. These decisions are influenced by the national decisions on pricing and reimbursement of the medicines concerned, since pricing and reimbursement is the competence of Members States[41].

The **Directive on transparency of measures regulating the prices of medicines** and their inclusion in the scope of national health insurance systems[42] aims at obtaining an overall view of national pricing arrangements, and providing public access to them for all those involved. This Directive regulates the procedural aspects of the Member States' decisions on pricing and reimbursement, e.g. timelines for decisions on pricing and reimbursement, publication of criteria for reimbursement and negative reimbursement decisions have to be justified. It does not impact on the level of price.

To help national authorities in their reimbursement decisions national Health Technology Assessment (HTA) bodies may assess the medicines. The HTA is a scientific evidence-based process to determine the relative effectiveness of new or existing health technologies.

The **Regulation on HTA**[43] establishes a Coordination Group of HTA national or regional authorities, a stakeholder network and lays down rules on the involvement in joint clinical assessments and joint scientific consultations of patients, clinical experts and other relevant experts. The regulation also reduces duplication of efforts for national HTA bodies and industry, facilitates business predictability and ensures the long-term sustainability of EU HTA cooperation. The new rules will come in to force in 2025 and should complement the efforts of the EU general pharmaceutical legislation to incentivise innovation with a strengthened and expanded HTA capacity.

### iv. After the market launch stage

Once a medicine is authorised and placed on the market, it is subject to pharmacovigilance. Pharmacovigilance relates to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The general EU pharmaceutical legislation details the pharmacovigilance obligations.

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[39] Medicinal & plant protection products – single procedure for the granting of SPCs (europa.eu).

[40] The authorisation of a medicinal product does not mean that it will be immediately accessible to all European patients. Factors such as the size of the population or the organisation of health systems and national procedures influence these decisions. Companies tend to begin negotiations with the Member States that may grant a higher price, often the countries with the highest GDP per capita. The willingness to pay a high(er) price in a Member State with a high GDP may limit the ability of a smaller Member State to negotiate a price in line with its GDP; hence, differences in the accessibility and affordability across the EU.

[41] The decision for pricing and reimbursement is based on national policies, which pertain to Member States and thus are outside the remit of the EU legislation and of this revision.

[42] Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems, OJ L 40, 11.2.1989, p. 8, EUR-Lex - 31989L0105 - EN - EUR-Lex (europa.eu).

[43] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU, OJ L 458, 22.12.2021, p. 1, EUR-Lex - 32021R2282 - EN - EUR-Lex (europa.eu).

In addition, the **Regulation on the performance of pharmacovigilance activities**[44] outlines the practical details to be respected by marketing authorisation holders, national competent authorities and the EMA and the **Regulation on post-authorisation efficacy studies**[45] specifies the situations in which such studies may be required.

After an initial authorisation has been granted, market authorisation holders can also develop changes to the medicines. The **Regulation on variations**[46] sets the procedures for post-authorisation changes to a marketing authorisation for medicines. These changes can e.g. be changes in address of the company, active substance, strength, pharmaceutical form or route of administration. The Commission also intends to review this regulation so as simplify the system and reduce administrative burden for medicine authorities and companies.

### c. Legislation in adjacent areas

The **legal framework for blood, tissues and cells**[47] (BTC) is used for medical treatments and therapies, including innovative therapies. The ongoing review will promote the safety of patients and donors, facilitate innovation and contribute to adequate supply of the relevant therapies. Blood, tissues and cells may be starting materials for medicines. Particularly important for the pharmaceutical sector is the strengthening the safety and quality requirements of BTC to align with the standards of the pharmaceutical framework for the highest risk preparations. It will also address the (re)emergence of communicable diseases, including lessons learnt from the COVID-19 pandemic, and is thus contributing to the European Health Union.

The **regulation on medical devices**[48] and **the regulation on in vitro diagnostic medical devices**[49] deal with medical devices, which are products or equipment intended for a medical purpose. In the EU, they must undergo a conformity assessment to demonstrate they meet legal requirements to ensure they are safe and perform as intended. They are assessed at Member State level, but EMA is involved in the assessment sometimes. In some cases, the bodies responsible for the conformity assessment must seek a scientific opinion from EMA before issuing a CE certificate. This is the case essentially when medicines are concerned (e.g. medical devices with an ancillary medicinal substance, companion diagnostics). In some other cases (when the device in ancillary to the medicines), the combined product requires a marketing authorisation.

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[44] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council, OJ L 159, 20.6.2012, p. 5, EUR-Lex - 32012R0520 - EN - EUR-Lex (europa.eu).

[45] Commission Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required, OJ L 107, 10.4.2014, p. 1–4, EUR-Lex - 32012R0520 - EN - EUR-Lex (europa.eu).

[46] Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, OJ L 334, 12.12.2008, p. 7, EUR-Lex - 32008R1234 - EN - EUR-Lex (europa.eu).

[47] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC, OJ L 33, 8.2.2003, p. 30, EUR-Lex - 32002L0098 - EN - EUR-Lex (europa.eu) and Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 7.4.2004, p. 48, EUR-Lex - 32004L0023 - EN - EUR-Lex (europa.eu).

[48] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, OJ L 117, 5.5.2017, p. 1, EUR-Lex - 02017R0745-20200424 - EN - EUR-Lex (europa.eu).

[49] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU, OJ L 117, 5.5.2017, p. 176, EUR-Lex - 02017R0746-20170505 - EN - EUR-Lex (europa.eu).

## ANNEX 10: ANALYTICAL REPORT

The Analytical report is provided in a separate document, in attachment.

## ANNEX 11: IMPACT ANALYSIS OF ALL MEASURES

The Impact analysis of all measures is provided in a separate document, in attachment.

## ANNEX 12: STUDY REPORT ON IMPACT ASSESSMENT

The Study report on impact assessment is provided in a separate document, in attachment.

## ANNEX 13: STUDY REPORT ON EVALUATION

The Study report on evaluation is provided in a separate document, in attachment.

## ANNEX 14: FACTORS INFLUENCING ACCESS TO AFFORDABLE MEDICINES

This annex sets out the different regulatory steps and related decision making processes that have an impact on access and affordability of medicines ("access chain"). Section 1 describes the different steps in the "access chain" from authorisation of medicines to patient access. Section 2 provides further details on pricing and reimbursement policies across the EU and how they can influence access to affordable medicines.

### 1. The access chain: from market authorisation of medicines to patient access

Marketing authorisation is but the first of a number of steps for patients to have access to a medicine. Patient access also requires, following relevant applications by companies, positive HTA assessments and positive pricing and reimbursement decisions by Member States. In addition to those steps, for patients to have access *across the entire EU*, companies have to launch the respective medicine in each Member State. Finally, for a patient to have actual access to a medicinal product, a prescriber has to decide that a medicine is the right treatment choice and prescribe it. The steps from marketing authorisation to patient access can be described along an access chain, which is summarised in the table below. Further details on each step are provided in the following subsections of this section.

***Table 1. Overview of the access chain: marketing authorisation to patient access***

| **STEPS** | **Scope** | **Legal framework** |
|---|---|---|
| 1. Marketing authorisation | Quality, safety, efficacy;<br><br>Positive benefit-risk balance | General pharma framework |
| 2. EU-level Health Technology Assessment (clinical HTA aspects) | Relative clinical effectiveness and relative safety, in comparison to comparator treatment(s) reflecting the standard of care;<br><br>Supports conclusions on added therapeutic (clinical) value | Regulation (EU) 2021/2282 |
| 3. Company decision to launch the medicine in a Member State | Submission of application by the company to national HTA, pricing and reimbursement bodies | |
| 4. National Health Technology Assessment | Takes into account the EU-level assessment of clinical HTA aspects;<br><br>Focuses on context-specific, non-clinical HTA aspects (e.g. economic, organisational);<br><br>Supports conclusions on cost-effectiveness, budget impact, value for money | National/regional legislation |

| | | |
|---|---|---|
| 5. National pricing and reimbursement | Decisions on reimbursement and pricing;<br><br>Takes into account added therapeutic (clinical) value, economic considerations (cost-effectiveness, budget impact, affordability), healthcare system and societal context | National/regional legislation<br><br>Directive 89/105/EEC (covering only timeline, process) |
| 6. Prescription | Evidence-based medicine, taking into account clinical guidelines and medical protocols and the individual patient situation | |

### *1.1 Marketing authorisation*

For the marketing authorisation of a medicine, the regulator will consider the quality, safety and efficacy of the medicine and authorise it if the medicine has a positive benefit-risk balance for the patient. Accordingly, data requirements for marketing authorisation reflect the need to show quality, safety and efficacy of a particular medicine. "Downstream" steps in the access chain (health technology assessment, pricing and reimbursement) often require additional data to show an added value of a newly authorised medicine compared to already existing medicines/treatments (see sections 1.2, 1.4 and 1.5).

It should however be noted that even medicines which appear similar at the time of launch may over time prove to have different efficacy or safety profiles in particular subgroups of patients. Furthermore, the effect of treatment in individual patients may differ from the population-level effects seen in clinical trials. With greater choice, patients will have a better chance of finding a treatment most appropriate to their needs. For these reasons, EU regulations on marketing authorisation do not require that new medicines be superior to medicines already on the market.

### *1.2 EU-level Health Technology Assessment (clinical HTA aspects)*

Health technology assessment (HTA) evaluates the added value of a new medicine in comparison to existing medicines (or other treatments) that reflect the current standard of care. HTA is an evidence-based approach that helps Member States to provide the optimal health care outcome for patients with limited budgets. Accordingly, HTA is used by Member States across the EU in particular for innovative and costly medicines, as a tool to support pricing and reimbursement decisions. However, there is considerable diversity across Member State HTA systems in terms of procedural frameworks, methodological approaches, and available resources and expertise.

In 2022, Regulation (EU) 2021/2282 on health technology assessment entered into force. It provides a legal framework for strengthened EU cooperation on HTA, focusing on clinical aspects of HTA (including the development of common methodologies). From 2025 onwards, Member State HTA bodies will jointly assess *clinical* HTA aspects (comparative clinical effectiveness and safety) of centrally authorised innovative medicines (Joint Clinical Assessment).[50] Such Joint Clinical

[50] Step-wise implementation of the product scope: oncology and advanced therapy medicines from 2025, orphan medicines from 2028, all centrally authorised innovative medicines (new active substances) from 2030.

Assessments will have to be taken into account by Member States in their national HTA processes. Joint Clinical Assessments will be high quality, timely scientific reports (available within 30 days from marketing authorisation). They will enable Member States to focus their limited national HTA resources on assessing more context-specific, non-clinical aspects of HTA (see section 1.4).

Clinical data generated for marketing authorisation purposes (to demonstrate safety and efficacy of the individual product) are not always considered sufficient for HTA and down-stream pricing and reimbursement purposes, which rely on demonstration of comparative effectiveness and safety (i.e. added therapeutic value over existing medicines/treatments).[51,52,53] HTA bodies generally require clinical trials that include an active comparator arm (rather than a placebo-controlled trial or a single-arm trial). HTA bodies also often see challenges with clinical trial data that are less mature and come with higher uncertainties, e.g. in the context of conditional marketing authorisations.[54] When HTA bodies consider the available clinical data inappropriate or insufficient for demonstrating an added therapeutic value, this can lead to delays and negative results in the downstream decision-making process on pricing and reimbursement.[55, 56, 57]

From a company perspective, the conduct of clinical trials that generate the comparative evidence required for HTA purposes can be more risky, more costly or take longer. Companies have also faced challenges related to lack of clarity on data needs for HTA, given the diversity of HTA systems and methodological frameworks across Member States. Companies have therefore traditionally (first) focused on the data needs for marketing authorisation when designing their clinical trials. This is however changing and there have been increasing calls by pharmaceutical companies and other stakeholders for more early dialogues on evidence needs along the lifecycle of products and for scientific advice on evidence generation.[58, 59]

For this reason, the new HTA Regulation (Regulation (EU) 2021/2282) provides also a legal framework for scientific advice by HTA bodies to companies on clinical trial design (common HTA advice, agreed at the level of the Member State Coordination Group on HTA), in parallel with scientific advice by the European Medicines Agency provided for marketing authorisation purposes. While respecting the different remits of marketing authorisation and HTA, this parallel scientific advice aims to ensure the generation of evidence that meets the requirements of both frameworks. Parallel scientific advice has already been successfully piloted in the context of EU-funded projects (in particular the Joint Actions EUnetHTA in cooperation with EMA).[60]

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[51] Evidence gaps for drugs and medical devices at market entry in Europe and potential solutions - KCE (fgov.be).

[52] Bloem LT, Mantel-Teeuwisse AK, Leufkens HGM, De Bruin ML, Klungel OH, Hoekman J. Postauthorization Changes to Specific Obligations of Conditionally Authorized Medicines in the European Union: A Retrospective Cohort Study. Clin Pharmacol Ther. 2019;105(2):426-35.

[53] Banzi R, Gerardi C, Bertele V, Garattini S. Conditional approval of medicines by the EMA. BMJ. 2017;357:j2062.

[54] In the interest of public health, a conditional marketing authorisation may be granted for such medicines on less comprehensive clinical data than normally required subject to legally binding obligations for the marketing authorisation holder to generate the comprehensive data after the authorisation.

[55] Vreman RA, Bouvy JC, Bloem LT, Hövels AM, Mantel-Teeuwisse AK, Leufkens HGM, Goettsch WG. Weighing of Evidence by Health Technology Assessment Bodies: Retrospective Study of Reimbursement Recommendations for Conditionally Approved Drugs. Clin Pharmacol Ther. 2019 Mar;105(3):684-691. doi: 10.1002/cpt.1251. Epub 2018 Nov 8. PMID: 30300938; PMCID: PMC6587700.

[56] Ibid, footnote 53. Banzi

[57] Ibid, footnote 54. In the interest of public health

[58] Ibid, footnote 53. Banzi

[59] Ibid, footnote 54. In the interest of public health

[60] Parallel joint scientific consultation with regulators and health technology assessment bodies | European Medicines Agency (europa.eu)

### *1.3 Company decision to launch the medicine in a Member State*

It should be noted that while a marketing authorisation at EU level allows for a medicine to be placed on the market in all Member States, the actual market launch in a given Member State is exclusively the decision of the marketing authorisation holder. Company decisions are commercial decisions that take into account whether there is a 'market' for the medicine in a given Member State from a business point of view, considering factors such as market size, price levels, promotion and distribution networks, regulatory requirements, current or future patient population, medical protocols and national pricing and reimbursement policies such as external reference pricing (see Section 2 on pricing and reimbursement policies for further details). Factors related to the healthcare system can also influence the decision, e.g. the availability of specialised equipment or infrastructure to deliver the medicine (in particular in the case of advanced therapy medicines), or national treatment preferences. If the conditions for a positive business case are met, the company will initiate the procedures required for market launch in that Member State (by submitting applications for HTA, pricing and reimbursement, in accordance with national legal/procedural frameworks).

Smaller and less wealthy countries will often see fewer product entries (due to smaller market potentials). For these countries, the time to availability is also significantly longer. The average time to market from marketing authorisation in Europe differs greatly: for example, for cancer drugs, in the period 2011-2018, it ranged from 17 to 1.187 days, with the shortest delays in Germany, the UK and Austria (less than 31 days) and the longest delays in Greece and Estonia (more than 950 days).[61] In other cases, medicines became available in Central and Eastern Europe only several years after marketing authorisation[62], with market launch delayed up to three years on average in Central-Eastern Europe.[63] It should however be noted that a lack of access to a specific medicine does not necessarily imply lack of access to effective treatment, if appropriate therapeutic alternatives are accessible.[64]

### *1.4 National Health Technology Assessment*

For medicines for which HTA is conducted to support pricing and reimbursement decisions (usually for innovative, costly medicines), the national HTA procedure is usually triggered by marketing authorisation holders launching a pricing and reimbursement application in the Member State concerned.

Currently, HTA bodies assess both clinical aspects (comparative effectiveness and safety) and non-clinical aspects (e.g. economic, organisational, social, ethical) at national level. From 2025 onwards, assessments of clinical HTA aspects will be conducted jointly at EU level (Regulation (EU) 2021/2282), and HTA work at national level is expected to focus on non-clinical HTA aspects (see section 1.2). Clinical HTA analyses support pricing and reimbursement authorities in drawing conclusions on added therapeutic value, while economic HTA analyses support them in concluding on cost-effectiveness, value for money and budget impact.

[61] Uyl-de Groot, C., Heine, R., Krol, M., and Verweij, J. 'Unequal Access to Newly Registered Cancer Drugs Leads to Potential Loss of Life-Years in Europe, Cancers, 2020.
[62] Vogler, S., Schneider, P., and Zimmermann, N., 'Evolution of Average European Medicine Prices: Implications for the Methodology of External Price Referencing', PharmacoEconomics, 303-309, 2019.
[63] Maini, L., & Pammolli, F., Reference Pricing as a Deterrent to Entry: Evidence from the European Pharmaceutical Market, 2017.
[64] OECD (2018), Pharmaceutical Innovation and Access to Medicines, OECD Health Policy Studies, OECD Publishing, Paris, https://doi.org/10.1787/9789264307391-en.

### *1.5 National pricing and reimbursement decision*

Pricing and reimbursement rules and policies are an exclusive competence of Member States (Article 168 TFEU). Due to historical, political, legal and economic developments, a large variety in pricing and reimbursement regulations have developed across Member States. Moreover, the overall organisation and funding of national healthcare systems differ significantly.[65]

National and/or regional pricing and reimbursement policies assess the size of the patient population and budget impacts, and negotiate the price. Often, late market entries in some Member States are driven by a combination of business decisions and national pricing/reimbursement policies, such as external reference pricing, leading marketing authorisation holders to market their medicines first in Member States where a high price can be obtained (see section 2 on pricing and reimbursement policies across the EU for further details). Some Member States, e.g. Greece, require proof of a positive reimbursement decision in comparable countries before an HTA assessment can be initiated.[66]

Pharmaceutical expenditure is largely subsidised by national health systems in order to ensure the adequate provision of medicines to all citizens. In this context, Member States adopt measures to regulate the prices of medicines and the conditions of their public funding. Such measures influence the prescription and utilisation of medicines in each Member State and also affect the decisions of and possibilities for pharmaceutical companies to sell their products in national markets. Industry stakeholders claim delays in national pricing and reimbursement decisions that would contribute to postponing the market entry of medicines after the granting of a (central) marketing authorisation. However, a factor that can contribute to delays in national pricing and reimbursement decisions is a lack of appropriate evidence on the added therapeutic value of the product, or evidence that suggests only a minor added therapeutic value (see sections 1.2, 1.4 and 2.2).

**Directive 89/105/EEC ('Transparency Directive')** is the only EU legal instrument in relation to the applicable national rules on pricing and reimbursement of medicines. The Directive is built on the principle of minimum interference in the organisation of national social security systems. It lays down a series of procedural requirements to ensure the transparency of national decisions on pricing and reimbursement, such as a timeline of 180 days (with the possibility of extension or suspension of the timelines), and procedures such as requirements for publishing the outcomes of national decisions. In light of the Treaty rules on free movement of goods (Article 34 TFEU), the Directive has the objective to avoid barriers to trade created by national measures.[67]

It should be noted that the Transparency Directive refers to the transparency of the pricing and reimbursement process, but not the transparency of prices. In general, prices are publicly available only in form of 'list prices'. These list prices are increasingly disconnected from the actual prices paid. Typically and in particular for products with high price and high uncertainty, confidential price discounts[68] or managed entry agreements are in place (see section 2 on pricing and reimbursement

[65] Health System in Transition Reviews (HiT) (who.int)

[66] Kourlaba, Georgia & Beletsi, Alexandra. (2021). Time to Patients' Access to New Medicines in Greece: Evaluation of Health Technology Assessment (HTA) Process from July 2018 until January 2021.

[67] An update of the Directive had been proposed by the European Commission in 2012, however it was officially withdrawn in 2015. A dedicated study will be launched in 2023 to take stock of the implementation challenges and to explore how Directive 89/105/EEC could further contribute to the affordability objectives of the Pharmaceutical Strategy.

[68] There is little public data on confidential prices; however there are indications that it may be broadly on average around 20% of the pharmaceutical budget, with high variation across products and countries. Steven G. Morgan, Sabine Vogler, Anita K. Wagner, Payers' experiences with confidential pharmaceutical price discounts: A survey of public and

policies). In a 2022 working paper, the OECD summarised the complex impacts of the **lack of price transparency**: "*It can be argued that confidentiality assists payers in achieving more favourable net prices, and companies in price discriminating between countries, which promotes equitable access [...]. At the same time, however, confidentiality is undermining the confidence of both payers and patients about the industry, and further challenging policy makers in attempting to find a balance between rewarding innovation, delivering affordable access, and maintaining the sustainability of health systems.*"[69]

### *1.6 Prescription and use*

For a patient to have access to prescription medicines, a prescriber will first have to consider whether this medicine is the appropriate choice for the patient. Then, the patient will need to accept and adhere to the proposed treatment. Prescribers make an informed choice based on clinical guidelines or treatment protocols that provide information on the added clinical benefit of the available treatment options and support the identification of a first line choice. Clinical guidelines sometimes take into consideration the affordability to health systems and patients. Inclusion of a medicine in clinical guidelines and treatment protocols is an important factor influencing a company's decision to launch a medicine in a given market. The prescription of medicines can also be influenced by industry promotion and detailing. A company will seek to gain prescriptions by actively differentiating its product from alternative treatments, through promotion activities vis-à-vis doctors, training of nurses, patient support programmes, etc.

### **1.7** ***Alternative access chains***

The health impact of late market entries is mitigated by the fact that innovative therapies are often accessible for patients through exceptions, such as compassionate use/named patient use schemes. Some countries have established "(innovation) funds" for defined medicines which are expensive but still considered important for patients, so they are financed out of funds that bypass the "standard" reimbursement processes. Furthermore, a medicine may be brought to a national market outside the national reimbursement scheme and will need to be paid for by private insurance or out-of-pocket payments. Depending on the national health systems, medicines may enter the market without national pricing or reimbursement decisions. This would be the case for many non-prescription medicines. However, in the absence of a reimbursement decision, the patient has to pay out-of-pocket.

## 2. Pricing and reimbursement policies across the EU

Member States have developed a large variety of pricing and reimbursement institutional frameworks and policies, some of which are explained in further detail below.[70] While there are overviews and comparisons of the different systems, the impact of the different organisational systems on access and affordability is complex and has not yet been modelled in a comprehensive way.

Regarding the institutional framework, a wide variety of different organisations and structures have been set up in the various EU Member States. The organisations responsible for marketing authorisation, health technology assessment and pricing and reimbursement may be part of the same organisation (e.g. Portugal, Cyprus, Czechia), organised decentrally (e.g. Denmark, Spain, Italy),

statutory health systems in North America, Europe, and Australasia, Health Policy, Volume 121, Issue 4, 2017, Pages 354-362, ISSN 0168-8510.

[69] OECD Health Working paper 146. Exploring the consequences of greater price transparency on the dynamics of pharmaceutical markets. 2022. c9250e17-en.pdf (oecd-ilibrary.org)

[70] Medicines Reimbursement Policies In Europe. WHO Europe. 2018

combining regulatory and HTA functions (Finland, Hungary) or combining pricing and/or reimbursement and HTA functions (Latvia, Luxembourg, Malta, Netherlands).[71]

### *2.1 External reference pricing*

The large majority of Member States apply, amongst others, external reference pricing (ERP), which considers a basket of prices of the same medicine in other countries (e.g., the average, or the average of a certain number of the lowest prices, or the lowest price) as a basis for pricing – and sometimes also reimbursement – decisions.[72] Considering that ERP strongly influences national prices, it has a direct impact on any companies' business case for launching medicines in different national markets. Accordingly, ERP influences also the path of launch of medicines across Europe.

**Sequencing of market entry in the EU – typical patterns of pharmaceutical companies**

Marketing authorisation holders choose the sequence of market entry to maximise their gains and limit the spill-over of lower prices in a given Member State on another Member State. There are fixed costs associated with entering a national market (e.g., procedural, or related to the packaging). Pharmaceutical companies primarily focus on Member States with significant market potential, taking into account the population size and the public pharmaceutical budget per capita. Companies set their prices based on the market conditions in Member States with greater market potential and purchasing power, not necessarily considering the affordability for lower income countries.[73] Overall, pharmaceutical companies tend to launch their medicines (first) in northern and western Member States with high purchasing power. The sequence of launch typically starts in Germany, where there is free pricing in the first year[74], followed by other large markets with high purchasing power, such as Italy, France, Spain, or smaller markets with high price levels, such as Denmark, Sweden or Luxemburg. To limit the spill-over effects resulting from the ERP system, the marketing authorisation holders and public authorities have to agree on confidential prices, while maintaining higher list prices. ERP applies to list prices, and is detrimental to transparency of prices. While ERP may improve affordability, it can have an impact on accessibility. For instance, the Slovak Ministry of Health allowed for a 10% higher launch price than reference pricing countries so that pharmaceutical companies would not delay launching. Evidence shows that manufacturers often delay market access to Belgium to avoid creating a Belgian reference price – as it is typically not among the highest in the EU.[75]

### *2.2 Value based pricing*

Another common method is the value based pricing, which implies that prices are formed by reference to a medicine's value (value for money). Value is most often measured by cost per QALY (quality adjusted life years). Some medicines may have a low cost per QALY and would be

[71] Mapping of HTA national organisations, programmes and processes in EU and Norway (Study by European Commission)

[72] Euripid Guidance Document on External Reference Pricing (ERP)

[73] Access to high-priced medicines in lower-income countries in the WHO European Region

[74] Once a medicine receives marketing authorisation, it can be launched on the German market at a price determined by the pharmaceutical company. An HTA is conducted during the first year as a basis for negotiations on the price that will be reimbursed from the thirteenth month. If the negotiated reimbursement price is below the price charged during the first year, no payback is required from the company. Payer Policies To Support Innovation and Access To Medicines in the Who European Region – WHO OMI technical report - https://www.who.int/europe/publications/i/item/9789289058247

[75] Fontrier, AM., Gill, J. & Kanavos, P. International impact of external reference pricing: should national policy-makers care?. Eur J Health Econ 20, 1147–1164 (2019).

considered good value for money. Medicines with a high cost per QALY would not be considered good value for money. To give an idea of the range of values, prevention and vaccination have typically a low cost per QALY (from 500-5000 EUR e.g. HPV vaccination, maternal vaccination for pertussis), whereas certain interventions have systematically higher QALYs (e.g. end-of life oncology treatments, rare diseases can be over 100 000 EUR/QALY).[76, 77] In these cases, there is a political and ethical choice to be made (whether a QALY is a QALY, no matter to whom it accrues). However, QALYs are easier to interpret when comparing interventions to the same person – to prioritise treatments that bring more benefits (at a lower cost/QALY) to the same patient. Explicit thresholds are in place in e.g. Poland, Hungary, Slovakia and Ireland[78] – around the range of 30 000 - 50 000 EUR/QALY. A debate about pros and cons is recurrent[79] – a major downside is that regardless of the R&D and production costs, the value-based price would tend to be set at the relevant threshold.[80]

While innovative medicines receive marketing authorisation on the basis of an evaluation of their quality, efficacy and safety and a positive benefit-risk balance, as explained, downstream actors (HTA bodies and pricing and reimbursement authorities) require evidence on therapeutic added value (see section 1 on the access chain). Several studies across multiple indications and countries (e.g. Germany[81], France, or Italy[82]) suggest that a significant percentage of innovative medicines come to the market with insufficient evidence on added therapeutic value or evidence that suggests only a minor added therapeutic value, while industry sets prices for these medicines nevertheless at high level to cover R&D, production and other costs.[83,84] In such situations, it becomes difficult for payers to justify spending large amounts of their budgets on medicines that cannot show proven and significant added therapeutic value.

It should however be noted that for marketing authorisation purposes, a new medicine is and should not be required to be superior to medicines already authorised. This is because the effect of treatment in individual patients may differ and with greater choice of treatment, patients will have a better chance of finding a treatment most appropriate to their needs (see section 1 on the access chain). In other words, even if medicines are not superior to other medicines based on a direct,

[76] Kocot, E., Kotarba, P. & Dubas-Jakóbczyk, K. The application of the QALY measure in the assessment of the effects of health interventions on an older population: a systematic scoping review. *Arch Public Health* 79, 201 (2021). https://doi.org/10.1186/s13690-021-00729-7

[77] Postma, M.J., Noone, D., Rozenbaum, M.H. *et al.* Assessing the value of orphan drugs using conventional cost-effectiveness analysis: Is it fit for purpose?. *Orphanet J Rare Dis* 17, 157 (2022). https://doi.org/10.1186/s13023-022-02283-z

[78] Rogalewicz, Vladimir & Barták, Miroslav. (2017). QALYs and cost-effectiveness thresholds: critical reflections.

[79] Bertram, M. Y., Lauer, J. A., De Joncheere, K., Edejer, T., Hutubessy, R., Kieny, M. P., & Hill, S. R. (2016). Cost-effectiveness thresholds: pros and cons. *Bulletin of the World Health Organization*, *94*(12), 925–930. https://doi.org/10.2471/BLT.15.164418

[80] Such process can be observed in oncology medicines, Howard et al. (2015) document price increases in the anticancer medicines market of about 10% a year in the past 20 years, after controlling for increased benefits (survival). Cost changes are deemed unlikely to be behind the price increases. David H. Howard & Peter B. Bach & Ernst R. Berndt & Rena M. Conti, 2015. "Pricing in the Market for Anticancer Drugs," Journal of Economic Perspectives, vol 29(1), pages 139-162.

[81] Wieseler, B. et al. (2019) New drugs: where did we go wrong and what can we do better? BMJ 2019;366:l4340 doi: 10.1136/bmj.l4340

[82] Analysis on added therapeutic value of innovative pharmaceuticals by national authorities find similar results (cf. HAS statistics in France, or GRADe classification in Italy).

[83] Improving Access To Innovative Medicines Opinion by the Expert Panel on Effective Ways of Investing in Health (EXPH) factsheet_innovative_medicines_en_0.pdf (europa.eu)

[84] Revue Prescrire N° 448, p. 142-143

average comparison, those medicines can still offer important second or third line treatment options for individual patients.

### *2.3 Costplus-pricing*

With costplus-pricing, the price of medicines is set by assessing production costs (incl. R&D costs, manufacturing, regulatory processes and compliance, overheads, operational costs) and adding a profit margin.[85] Although, in theory, this pricing policy is straightforward with clear and justifiable pricing rules that provide a level of certainty for budgetary planning and profits for the suppliers, it is not widely used for setting medicines prices at the ex-manufacturer or ex-wholesaler level. This may be partially due to the fact that it is currently difficult to implement because obtaining reliable cost information from suppliers is difficult.[86] Another, more fundamental reason may be that it is accepted that in a market economy, which is considered a crucial driver for investment and innovation, particularly valuable innovations yield higher returns than less valuable ones, rewarding the risk-taking investor for success in creating value. HTA-based pricing approaches reflect a choice for value-based pricing.

There is a lack of transparency on research and development costs, often triggering criticism by policymakers and stakeholders.[87] The pharmaceutical industry estimates the research and development (R&D) costs for developing a medicine between US$2.2 billion and 2.9 billion. However, this figure is heavily contested by others. Irrespective, industry uses these figures to rationalise and justify the high prices charged for certain medicines.[88] Although companies' annual reports provide certain insights on overall R&D spending, companies do not disclose the relevant R&D costs spent on individual medicines brought onto the market. Either way, the market risks associated with R&D costs need to be put in perspective with the generated revenues.

Another point of concern is that the contribution of public funding to R&D costs is not known, as such contributions reflect risks born by the public as opposed to the investor. By way of example, there is no clarity on the amounts of public funding spent on biomedical R&D in European countries. While the pharmaceutical industry claims that it has been paying for all costly clinical trials, this was contradicted by a study[89] financed by the Dutch government.

### *2.4 Managed entry agreements*

A managed entry agreement (MEA) is a contractual arrangement between a manufacturer and health care payer/provider that enables access to (or reimbursement of) a novel medicinal product, subject to conditions. The objective of a MEA is twofold: to allow access to new high-priced medicines that would otherwise not be affordable, and to manage the uncertainty of limited evidence on clinical outcomes.[90] There are two basic categories of MEAs: finance-based (such as price–volume agreements) or performance-based (based on health outcomes).[91] Confidentiality is a major feature

[85] AIMs-fair-pricing-model-Accompanying-paper-to-the-fair-pricing-calculator_June2021.pdf (aim-mutual.org)
[86] World Health Organization. (2021). Cost-plus pricing for setting the price of pharmaceutical products: WHO guideline on country pharmaceutical pricing policies: a plain language summary. World Health Organization. https://apps.who.int/iris/handle/10665/341902. License: CC BY-NC-SA 3.0 IGO
[87] https://www.who.int/europe/publications/i/item/9789289058193
[88] Schipper, Irene & de Haan, Esther & Cowan, Roberta. (2019). Overpriced Drugs Developed with Dutch Public Funding.
[89] Ibid, footnote 89.
[90] Vogler S (2022): Payer policies to support innovation and access to medicines in the WHO European Region. Copenhagen: World Health Organization, Regional Office for Europe
[91] Medicines Reimbursement Policies in Europe. 2018. https://apps.who.int/iris/bitstream/handle/10665/342220/9789289053365-eng.pdf?sequence=1&isAllowed=y

of all types of MEA. In some Member States, it is not even known which medicines are subject to an MEA, or which types of MEA are in use.[92] Experts agree that MEA are becoming more prevalent and could result in increasingly non-transparent prices "involving a mix of rebates across groups of medicines, discounts by indication, or based on volumes or expenditure caps, all of which mean it is complex to compute the final transaction price of a product."[93]

### *2.5 Policies for generic and biosimilar competition*

Member States have implemented a variety of pricing and reimbursement policy measures for off-patent medicines (including generic and biosimilar medicines) to promote competition, increase spending efficiency and contribute to access to innovation at affordable prices on patent expiry, while freeing up funds for innovative medicines.[94] Those include – but are not limited to – incentives for prescribing biosimilars and policies related to INN prescribing, switching by physicians and substitution by pharmacists. When it comes to biosimilars, acceptance and trust of biosimilar medicines by patients and health professionals is of utmost importance to enhance biosimilar uptake. There have been concerns by health professionals and patients as regards comparability of the biosimilar and originator, even though the available switching data does not indicate that switching from a reference product to a biosimilar is associated with any major efficacy, safety, or immunogenicity issues.[95,96] Recently, EMA and HMA published a joint statement to confirm the interchangeability of biosimilars to address this issue.[97]

**Biosimilar competition**

'Older' products (i.e. with expired protection period) are an important factor of pharmaceutical spending. Competition – generic and biosimilar – improves access and drives down prices. Due to the typically high prices charged for biological medicines, creating competition for their markets through the introduction of biosimilar versions can generate substantial cost savings[98]. In Germany, the waiting time for patients with rheumatoid arthritis to be treated with a biologic has been reduced from 7.4 years to 0.3 years after the introduction of biosimilars.[99] Looking at list price changes in markets with biosimilar competition, by 2020, biosimilars reduced the cost by almost 1/3.[100] One study estimated the impact of biosimilar entry in terms of healthcare systems savings between 2007 and 2020 for eight EU countries

[92] Pauwels K, Huys I, Vogler S, Casteels M, Simoens S. Managed entry agreements for oncology drugs: lessons from the European experience to inform the future. Front Pharmacol. 2017;8:171. doi:10.3389/fphar.2017.00171

[93] OECD Health Working paper 146. Exploring the consequences of greater price transparency on the dynamics of pharmaceutical markets. 2022. c9250e17-en.pdf (oecd-ilibrary.org)

[94] Vogler S (2022): Payer policies to support innovation and access to medicines in the WHO European Region. Copenhagen: World Health Organization, Regional Office for Europe

[95] Mestre-Ferrandiz, J., Towse, A. & Berdud, M. Biosimilars: How Can Payers Get Long-Term Savings?. *PharmacoEconomics* **34,** 609–616 (2016).

[96] Barbier L, Ebbers HC, Declerck P, Simoens S, Vulto AG, Huys I. The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review. Clin Pharmacol Ther. 2020 Oct;108(4):734-755. doi: 10.1002/cpt.1836. Epub 2020 Apr 30. PMID: 32236956; PMCID: PMC7540323.

[97] https://www.ema.europa.eu/en/documents/public-statement/statement-scientific-rationale-supporting-interchangeability-biosimilar-medicines-eu_en.pdf

[98] Farfan-Portet M-I, Gerkens S, Lepage-Nefkens I, Vinck I, Hulstaert F. Are biosimilars the next tool to guarantee cost-containment for pharmaceutical expenditures? The European Journal of Health Economics. 2014;15: 223-8.

[99] https://www.pharmatimes.com/magazine/2021/may_2021/15_years_of_biosimilar_access_in_europe

[100] IQVIA. The Impact of Biosimilar Competition in Europe. 2020. Available from: https://health.ec.europa.eu/system/files/2021-01/biosimilar_competition_en_0.pdf

(France, Germany, Italy, Poland, Romania, Spain, Sweden, and the UK), ranging from €11.8 billion to €33.4 billion.[101]

The importance of biosimilar competition has been growing since the first products entered the market in 2006. In 2020, biosimilar medicines accounted for 9% of the sales value of biological medicines in Europe. Nonetheless, uptake of biosimilars varies greatly across Europe. The share of sales of biosimilar medicines among all pharmaceutical sales in hospitals ranges from less than 2% in Bulgaria to 16.5% in Norway (the latter invested heavily in generating and disseminating evidence about safety of switching patients to biosimilar medicines). This variation may be partly explained by the range of different policies to encourage biosimilar uptake.[102]

### *2.6 Cross-country cooperation activities: regional joint negotiations or joint procurement*

Several national governments have established cross-country collaboration initiatives on pricing, reimbursement and/or procurement to address the challenges with ensuring access to high-priced medicines.[103] The BeNeLuxA Initiative, for instance, has concluded successful joint negotiations and further collaborates on horizon scanning, HTA, price and reimbursement negotiations and information sharing. The Nordic Pharmaceutical Forum and the Baltic Procurement Initiative have successfully concluded several joint tender processes for medicines and vaccines. Joint procurement is seen by some as a promising tool to help make small markets more attractive for suppliers, and therefore contributing to availability of medicines that would otherwise not be supplied.

### *2.7 Related EU cooperation activities*

The decisions on the pricing and reimbursement of medicines are an exclusive competence of Member States (Article 168 TFEU). However, the Pharmaceutical Strategy points out that EU and national rules that do not directly regulate prices or reimbursement levels may also have a bearing on the affordability of medicines. In the implementation of the Strategy, the Commission has relaunched the cooperation between National Competent Authorities for Pricing and Reimbursement and the Healthcare Payers (NCAPR group). Through this group, the Commission supports mutual learning and best-practice exchange, including on pricing, payment and procurement policies. This work is based on voluntary and non-legislative actions.

[101] Haustein R, De Millas C, H er A, et al. Saving money in the European healthcare systems with biosimilars. Gabi Journal. 2012;1(3–4):120–126.

[102] Draft final report on the Study on Best Practices in the Public Procurement of Medicines (2022), not published.

[103] In the Union, there are six such collaborations: the Baltic Procurement Initiative (May 2012, Estonia, Latvia and Lithuania); the BeNeLuxA Initiative (2015, Belgium, the Netherlands, Luxembourg, Austria (since 2016) and Ireland (since 2018)); the Fair and Affordable Pricing (FAAP) (2017, Czechia, Hungary, Poland and Slovakia); the Nordic Pharmaceutical Forum (2015, Denmark, Norway, Sweden and Iceland, Finland); the Valletta Declaration (2017, Greece, Ireland, Italy, Malta, Portugal, Romania, Spain, Cyprus (since 2017), Slovenia and Croatia (since 2018)); for details see the report Cross-country collaborations to improve access to medicines and vaccines in the WHO European Region, World Health Organization 2020.

## ANNEX 15: AMR

1. Market failure hinders the commercial development of new antimicrobials[104]

The commercial success of a medicine has typically been dependent on a combination of its sales (volumes) and price. The antibiotics market suffers from a unique set of problems in these two respects. First, higher sales volumes are more likely to drive the rapid emergence of antimicrobial resistance (AMR) therefore health policies aim at reducing or delaying the use of new antimicrobials. Second, the price of antibiotics is rather low comparing to other therapeutic areas[105]. Consequently, there is lack of breakthrough candidates, new innovative antimicrobials that would slow down antimicrobial resistance (AMR)[106]. According to the World Health Organization (WHO), 11 new antibacterial medicines have been approved (by either the European Commission or Food and Drug Administration or both) since July 2017. With some exceptions, the newly approved antibiotics have limited clinical benefit over existing treatment, as over 80% (9/11) are from existing classes where resistance mechanisms are well established and rapid emergence of resistance is foreseen. The current clinical antibacterial pipeline contains 43 antibiotics and combinations with a new therapeutic entity. Only few of them meet at least one of the WHO innovation criteria (absence of known cross-resistance, new binding site, mode of action and/or class)[107]. Overall, the clinical pipeline and recently approved antibiotics are insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance[108].

2. Push and pull incentives

To tackle this issue, a combination of **push incentives** (i.e. funding for antimicrobial R&D&I, primarily via grants that are not expected to be repaid) and **pull incentives** (i.e. financial reward for successfully developed and approved antimicrobials) is typically referred to. In May 2022, the G7 Health and Finance Ministers acknowledged the need to "address antibiotic market failure" and commit to a "particular emphasis on supporting relevant pull incentives".[109]

A financial reward to successful antimicrobial developers can notably be provided:

- In the form of **purchase of antimicrobials or purchase of a guaranteed access in the form of "reservation contract[110]"** (outcome-based pull incentives). The revenue guarantee provided by reservation of access to antimicrobials can be fully or partially delinked from sales.
- In the form of a **Transferable Exclusivity Voucher** that antimicrobial developers can sell to another marketing authorisation holder (MAH), allowing this other MAH to **extend the data protection period** of its own product. The sales value of the voucher would then provide a return on investment that is not linked with the actual sales of the antimicrobial itself.

[104] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7931625/
[105] To Push or To Pull? In a Post-COVID World, Supporting and Incentivizing Antimicrobial Drug Development Must Become a Governmental Priority (acs.org)
[106] The antibiotic subscription model: fostering innovation or repackaging old drugs? - The Lancet Microbe
[107] 2020 antibacterial agents in clinical and preclinical development: an overview and analysis (who.int)
[108] https://www.who.int/news/item/15-04-2021-global-shortage-of-innovative-antibiotics-fuels-emergence-and-spread-of-drug-resistance
[109] 2022-05-20-g7-health-ministers-communique-data.pdf (g7germany.de)
[110] The public sector and antimicrobial producers sign a service contract, through which the antimicrobial producers receive a remuneration for ensuring the availability and supply of antimicrobials, should the antimicrobials be ordered. The antimicrobials are not purchased.

Considering the high costs of bringing new antimicrobials on the market (the Boston Consulting Group estimated that a global pull incentive requires per first-to-market (in its class) antibiotic of around USD 2.5 billion over ten years), some authors consider that pull incentives should be implemented at global level. According to these authors, G7 countries, the EU, and China are responsible for 80% of global pharmaceutical sales[111], focusing on these markets offers the highest probability of success in implementing a globally aligned, sustainably sized subscription model. Under this approach, the "fair" EU contribution to pull incentive would be expected to be around USD 550 - 680 million per medicine over 10 years (considering that the EU represents around 22-27% of the GDP of the G7, EU and China).

3. Innovative financing solution - national schemes and regulatory incentives that tackle market failures for antimicrobials

In the EU, some Member States introduced national reimbursement interventions and/or other initiatives as policy tools to tackle AMR. The models seek to tie payments to antibiotic developers to the societal value of having that medicine available to the public. In return, the developer will supply the antibiotic at a volume as required. In 2018, Sweden has started a pilot project in order to ensure good availability of certain existing antibiotics via the implementation of a partially delinked guaranteed reimbursement model[112]. The key concept is that Sweden will pay at a national level the difference between actual regional sales and the guaranteed revenue[113]. Five antibiotics were chosen for this pilot. The model ensures access to existing antibacterials that have been authorised at EU/national level that may otherwise not be marketed in Sweden due to small market size. The pilot will be finalised in April 2023.

In Germany, there is an accelerated reimbursement review process and exception of antimicrobials from the internal price reference group. France also allows higher prices for certain antibacterials.

In 2020, the UK has launched a pilot project that aims to procure new, valuable antibacterials on the basis of a multi-year contract, in which the manufacturer has to provide as many doses of the antibacterial as needed in exchange to an annual guaranteed revenue[114]. The annual guaranteed revenue for each of the selected products is fully delinked from the sales and based on the HTA assessment undertaken by the National Institute for Health and Care Excellence (NICE), considering not only the direct health gain to patients treated, but additional elements such as the transmission value (the benefits of avoiding infection spread) or diversity value (the benefits of having multiple antibiotics available). Contracts will generally last for three years but may be extended up to 10 years. Currently, two antibiotics are participating in the trial - cefiderocol (Fetcroja) by Shionogi and Pfizer's ceftazidime with avibactam (Zavicefta). It is noteworthy that both antibiotics are authorised in the EU. Fetcroja[115] that belongs to the cephalosporin class of antibiotics was authorised in April 2020 and is used for complicated urinary tract infections. Zavicefta[116] received the European marketing authorisation in June 2016 and is a combination of two active substances: ceftazidime that

[111] Incentivizing Innovation to Tackle Antimicrobial Resistance | BCG
[112] Sweden to test an access-focused model for new antibiotics: Contracting for Availability • AMR.Solutions
[113] Questions and answers- Agreements signed for a pilot study of a new reimbursement model (folkhalsomyndigheten.se)
[114] https://www.england.nhs.uk/blog/how-the-nhs-model-to-tackle-antimicrobial-resistance-amr-can-set-a-global-standard/
[115] https://ec.europa.eu/health/documents/community-register/html/h1434.htm
[116] https://ec.europa.eu/health/documents/community-register/html/h1109.htm

belongs to the cephalosporin class of antibiotics and avibactam that blocks the action of bacterial enzymes called beta-lactamases.

4. International initiatives

To incentivize the creation of new treatments (antibiotics and antifungals), the US Congress enacted the Generating Antibiotic Incentives Now Act (GAIN Act)[117] of 2012, which provides benefits to manufacturers of Qualified Infectious Disease Products (QIDPs) including 5 years of additional non-patent exclusivity. For QIDP designation, the sponsor is required to demonstrate that the drug is an "antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections"[118]. The results of this program have so far been disappointing, largely because QIDP eligibility criteria were not sufficiently targeted to unmet need[119].

The US does not currently have a subscription model for antibiotics in place. However, the PASTEUR (Pioneering Antimicrobial Subscriptions to End Upsurging Resistance) Act[120] is currently under discussion (timelines not known). It aims to implement a de-linked subscription model to boost novel antimicrobial development, encourage the appropriate use of existing drugs, and safeguard a domestic supply. It would provide the guaranteed payments from the federal government to developers ranging between $750 million to $3 billion for "unlimited access" to an antibiotic, paid out over five to 10 years. The budget of the PASTEUR Act would be $11 billion over 10 years (including $500 million for stewardship programs), with the goal of financing between three and 14 contracts, depending on their value.

On-going financial initiatives

Further to the above-mentioned incentives, several funding initiatives support the antibiotic development via push incentives:

- activities under DG RTD in Europe including the Innovative Medicines Initiatives (IMI)[121] and IMI2[122];
- AMR Action Fund[123] (worldwide collaboration between the pharmaceutical industry, WHO, EIB and Wellcome Trust);
- The Biomedical Advanced Research and Development Authority (BARDA)[124] in the US;
- The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator known as the CARB-X[125] (a global nonprofit public-private partnership).

[117] GENERATING ANTIBIOTIC INCENTIVES NOW (fda.gov)
[118] Qualified Infectious Disease Product Designation Questions and Answers | FDA
[119] https://academic.oup.com/ofid/article/7/1/ofaa001/5716891
[120] H.R.8920 - 116th Congress (2019-2020): The PASTEUR Act | Congress.gov | Library of Congress
[121] https://www.imi.europa.eu/projects-results/project-factsheets/nd4bb
[122] https://www.imi.europa.eu/projects-results/project-factsheets/amr-accelerator
[123] AMR Action Fund Announces First Investments in Adaptive Phage Therapeutics and Venatorx Pharmaceuticals
[124] https://www.phe.gov/about/barda/Pages/AMR.aspx
[125] https://carb-x.org/

5. Future initiatives

The EU co-funded Joint Action on AMR and Health Care Associated Infections (EU JAMRAI) developed **a multi-country pull incentive strategy**[126].

The EU-JAMRAI strategy is based on two key elements: (i) A **guaranteed revenue** paid to antimicrobial producers **for ensuring access** to antimicrobials (i.e. subscription model[127]) **through national contracts;** (ii) A **supranational entity** - **coordinating** the implementation of the subscription models.

A supranational entity launches a joint open tender, which:

- specifies eligible antimicrobial characteristics in coordination with relevant global stakeholders, e.g. EMA, EC bodies, World Health Organization (WHO) and national competent authorities and,
- encompasses a contract template including national access and stewardship requirements as well as a suggested revenue guarantee (which is up to negotiation between national authorities and the pharmaceutical industry). The annual guaranteed revenue can be either partially or fully delinked from the volume-based sales.

Marketing authorisation holders apply for the tender. Once the tender participants are agreed, each country negotiates individually with the marketing authorisation holder and ultimately enters into a contract. National authorities commit to guarantee a certain revenue to the antimicrobial producer(s) in exchange to ensuring sustainable access to antimicrobials.

DG HERA could implement the EU-JAMRAI proposal through the organisation of a joint procurement where Member States would buy a guaranteed access to existing antimicrobials (service contract) for a given volume and period. The joint procurement could target either newly approved antimicrobials, and/or old antimicrobials which are not available in all EU Member States. In both cases, the incentive will provide access, but may not be big enough to incentivise innovation.

6. Prudent use of antimicrobials

Infections caused by antibacterial drug-resistant bacteria are an important public health threat in Europe and worldwide. New treatment alone will not be sufficient to combat the threat of AMR. It is well known that AMR is accelerated by the misuse and overuse of antimicrobials[128]. The prudent use of antimicrobials is a cornerstone in addressing antimicrobial resistance. The revision of the pharmaceutical legislation will not only restrict the use of antimicrobial by introducing the prescription status for all antimicrobials for systemic use, but also to oblige industry to closely follow its products and possible implications on AMR through the AMR lifecycle management plan. The proposed enhanced environmental risk assessment and imposition of relevant risk minimisation measures on the manufacture, use and disposal of antimicrobials will also contribute to reducing AMR though the environment.

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126 https://eu-jamrai.eu/wp-content/uploads/2021/03/EUjamrai_D9.2_Strategy-for-a-multi-country-incentive-in-Europe_INSERM-FHI.pdf

127 Sweden and UK currently implement subscription models as pilot studies for a small selected number of antibiotics. In the Swedish model, the revenue is partially delinked from the sales, while in the UK model, the revenue is fully delinked. Both models ensure access to existing antibacterials that may otherwise not be marketed, but may not be large enough to substantially incentivise antibacterial R&D. The first impact assessments of the Swedish model are expected to be shared in November 2022.

128 Antimicrobial resistance (who.int)

## ANNEX 16: MAPPING MEASURES AGAINST PROBLEM DRIVERS

| Measure | Problem driver/problem |
|---|---|
| Reduce standard regulatory protection period | Expensive innovative medicines |
| Market launch measure | Medicines not launched in the EU<br>Companies do not initiate negotiations for pricing or reimbursement |
| Prolonged regulatory protection for medicines addressing UMN | High commercial risk to develop and introduce new medicines addressing UMN |
| Transparency of public financial support to conduct clinical trials | Expensive innovative medicines |
| Regulatory protection for comparative trials | Evidence for HTA/pricing and reimbursement bodies not generated |
| Changes to scope, definition, classification advice and codification of rolling review and PRIME<br>Sandbox environment | System caters insufficiently for innovation<br>Framework lacks agility |
| Binding system for scientific assessment for repurposed medicines | High commercial risk to develop and introduce new medicines addressing UMN |
| Simplified obligations for non-commercial entities to become MAH | High commercial risk to develop and introduce new medicines addressing UMN |
| Strengthened Bolar provision | Expensive innovative medicines<br>Delayed market entry for generics and biosimilars |
| Transferable exclusivity voucher for novel antimicrobials | Limited income and profit for MAHs of these products |
| Prudent use of antimicrobials | Inappropriate use of these products |
| Measure on shortages and security of the supply chain | Withdrawals of medicines<br>Vulnerability of the supply chain<br>Patients without treatments |
| Strengthened ERA requirements | Insufficient regulation |
| Stronger oversight of manufacturing supply chains | Vulnerability of the supply chain |
| Simplification and streamlining measures | Inefficiencies in the system |
| Measures regarding novel combination products | System caters insufficiently for innovation |
| New concepts, e.g. adaptive clinical trials and use of real world evidence | System caters insufficiently for innovation |
| Electronic product information | Inefficiencies in the system<br>Shortages |
| Adapted working methods of EMA and European Medicines Regulatory Network | Inefficiencies in the system |
| Early dialogue, coordinated scientific advice | Evidence for HTA/pricing and reimbursement bodies not generated<br>System caters insufficiently for innovation |

**Annex 5: Evaluation Staff Working Document**

## Table of Contents

***Glossary***

| *Term or acronym* | *Meaning or definition* |
|---|---|
| Accessibility | A medicine becomes accessible to patients once it has been authorised, is being marketed, and can be reimbursed in a Member State. |
| Affordability | Relates to payments to be made by patients (out of pocket on healthcare or through co-payments) which can be described as affordability at micro level and to the sustainability of public funding of the healthcare sector raised through social security contributions or taxes (affordability at macro level). |
| AMR | Antimicrobial resistance. |
| API | Active Pharmaceutical Ingredient. |
| ATMPs | Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells defined in Artcicle 2 of Regulation (EC) No 1394/2007. |
| Biological medicine | A medicine whose active substance is made by or derived from a living organism. Biological medicines contain active substances from a biological source, such as living cells or organisms (human, animals and microorganisms such as bacteria or yeast). |
| Biosimilar | A biosimilar is a biological medicine that is highly similar to another biological medicine which has already been approved. Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines. |
| BTC | Blood, tissues and cells. |
| CAT | The Committee for Advanced Therapies is the European Medicines Agency's committee responsible for assessing quality, safety and efficacy of advanced therapy medicinal products (ATMPs) and following scientific developments in the field. |
| CBA | Cost-benefit assessment. |
| CHMP | The Committee for Medicinal Products for Human Use is EMA's committee responsible for human medicines. |
| CMA | Conditional marketing authorisation is the approval to market a medicine that addresses patients' unmet medical needs on the basis of data that is less comprehensive than that normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide comprehensive clinical data in the future. |
| CMDh | The Coordination Group for Mutual recognition and Decentralised Procedures – Human is EMA's committee responsible for the examination and coordination of questions relating to the marketing authorisation of human medicines in two or more Member States in accordance with the mutual recognition or decentralised procedure. |
| COM | European Commission. |

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| COMP | The Committee for Orphan Medicinal Products is the Agency's committee responsible for recommending orphan designation of medicines for rare diseases. |
| CP | The centralised authorisation procedure (CP) is the European Union-wide procedure for the authorisation of medicines, where there is a single application, a single evaluation and a single authorisation granted by the European Commission valid throughout the European Union. |
| Data protection | Period of protection during which pre-clinical and clinical data and data from clinical trials handed in to the authorities by one company cannot be referenced by another company in their regulatory filings. |
| DCP | The decentralised procedure (DCP) is the procedure for authorising medicines in more than one European Union Member State in parallel. It can be used for medicines that do not need to be authorised via the centralised procedure and have not already been authorised in any Member State.The DCP was introduced by Directive 2004/27/EC, after the 2004 revision. |
| EEA | The European Economic Area (EEA) include all EU Member States and also Iceland, Liechtenstein and Norway. |
| EFTA | The European Free Trade Association (EFTA) include Iceland, Liechtenstein, Norway and Switzerland. |
| EMA | The European Medicines Agency ('the Agency') is an EU agency founded in 1995 which is responsible for the scientific evaluation, supervision and safety monitoring of medicines, both human and veterinary, across Europe. |
| ERA | Environmental Risk Assessment. |
| ERN | European reference networks (ERNs) are virtual networks involving healthcare providers across Europe. Directive 2011/24/EU on patients' rights in cross-border healthcare together with Delegated Decision 2014/286/EU and Implementing Decision 2014/287/EU provide for the setting up of ERNs, 24 of which were established in 2017. The purpose of these networks is to facilitate discussion of complex or rare diseases and conditions that require highly specialised treatment, and concentrated knowledge and resources. |
| EU | European Union |
| EudraVigilance | A centralised European database of suspected adverse reactions to medicines that are authorised or being studied in clinical trials in the European Economic Area (EEA). |
| FDA | United States Food and Drug Administration. |
| GDP | Good Distribution Practices |
| GDPR | General Data Protection Regulation |
| GMP | Good Manufacturing Practice |
| GMO | Genetically Modified Organism |

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| Generic medicine | A generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s). The generic can only be marketed after expiry of the data and market protection. |
| IA | An impact assessment (IA) identifies and describes the problem to be tackled, establishes objectives, formulates policy options, assesses the impacts of these options and describes how the expected results will be monitored. The Commission's impact assessment system follows an integrated approach that assesses the environmental, social and economic impacts of a range of policy options, thereby ensuring that sustainability is an integral component of Union policymaking. |
| ICER | An incremental cost-effectiveness ratio (ICER) is a summary measure representing the economic value of an intervention, compared with an alternative (the comparator). An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of 'extra cost per extra unit of health effect' for the more expensive therapy versus the alternative. |
| IP | Intellectual property |
| IQVIA | IQVIA is a contract research and analyticalservices organisation that collects data including global pharmaceutical sales data. Such sales databases were used for this evaluation. |
| MA | A marketing authorisation (MA) is the mandatory approval process before a medicine enter the market of one, several or all European Union Member States. |
| MAH | Marketing authorisation holder |
| Marketing authorisation application | An application made to a European regulatory authority for approval to market a medicine within the European Union. |
| Marketing authorisation grant | A decision granting the marketing authorisation issued by the relevant authority. |
| Market exclusivity | The period after the marketing authorisation of a medicine for a rare disease when similar medicines for the same indication cannot be placed on the market. Under the current legislation, the market exclusivity has a duration of 10 years. |
| Market protection | Period of protection during which generics cannot be placed on the market. |
| Medical condition | Any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome). |
| Megatrend | Megatrends are long-term driving forces that are observable now and will most likely have significant influence on the future. Megatrends are closely interlinked between each other and simultaneously affect many different stakeholders. Thus, a systemic and global understanding of the issue under study is |

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| | necessary to fully picture and illustrate the dynamics at stake. See also: https://knowledge4policy.ec.europa.eu/foresight/tool/megatrends-hub_en" \l "explore |
| MRP | The mutual recognition procedure (MRP) is a procedure through which an authorisation of a medicine in one European Union Member State is recognised by another Member State. |
| MS | Member States (MS) are countries member of the EU. |
| National authorisation procedure | The national authorisation procedure is a marketing authorisation procedure where individual Member States authorise medicines for use in their own territory. This procedure depends on national legislation. |
| NAS | New active substances. |
| NCA | National Competent Authority. |
| NCE | New Chemical Entity. |
| "Off-label" use | Use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration. |
| Oncology | A branch of medicine that specialises in the prevention, diagnosis and treatment of cancer. |
| Orphan condition | A medical condition, as defined above, that meets the criteria defined in Article 3 of Regulation (EC) No 141/2000; a life-threatening or chronically debilitating condition affecting no more than five in 10 thousand persons in the EU. |
| Orphan designation | A status assigned to a medicine intended for use against a rare/ orphan condition. The medicine must fulfil certain criteria for designation so that it can benefit from incentives such as market exclusivity. |
| Orphan indication | The proposed therapeutic indication for the purpose of orphan designation. This specifies if the medicinal product subject to the designation application is intended for diagnosis, prevention or treatment of the orphan condition. |
| Payer | An entity responsible for financing or reimbursing healthcare. |
| PDCO | The Paediatric Committee (PDCO) is EMA scientific committee responsible for activities associated with medicines for children. It supports the development of such medicines in the European Union by providing scientific expertise and defining paediatric need. |
| Personalised medicine | A medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy |

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| | for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention. |
| Pharmacovigilance | The monitoring of the safety of an authorised medicine and the detection of any change to its benefit-risk balance. |
| PIP | A paediatric investigation plan is a development plan designed to ensure that the data required to support the authorisation of a paediatric medicine are obtained through studies of its effect on children. |
| PRIME | The priority medicine (PRIME) scheme has been launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need. Through this voluntary schemethe Agency offers early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks, to optimise development plans and enable accelerated assessment of medicines applications. |
| QALYs | Quality-adjusted life years (QALYs) refers to a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to one year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life and freedom from pain and mental disturbance. |
| Rare disease | Diseases with a particularly low prevalence; the European Union considers diseases to be rare when they affect no more than 5 per 10,000 people in the European Union. |
| RUP | Repeat Use Procedure is the use of the Mutual Recognition Procedure (MRP) after the completion of a first MRP or Decentralised Procedure (DCP) for the recognition of a marketing authorisation by other Member States. |
| SA | A scientific advice (SA) is the provision of advice by the Agency on the appropriate tests and studies required in developing a medicine, or on the quality of a medicine. |
| SDGs | The United Nations Sustainable Development Goals (UN SDGs) are 17 goals with 169 targets that all UN Member States have agreed to work towards achieving by the year 2030. They set out a vision for a world free from poverty, hunger and disease. |
| SmPC | A summary of product characteristics (SmPC) describes the properties and the officially approved conditions of use of a medicine. |
| SMEs | Micro, small and medium-sized enterprises. |
| SPC | The supplementary protection certificate (SPC) is an intellectual property right that serves as an extension to a patent right. The |

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| | patent right extension applies to specific pharmaceutical and plant protection products that have been authorised by regulatory authorities. |
| SWD | Staff working documents (SWDs) are required to present the results of all impact assessments and evaluations/fitness checks. |
| Therapeutic indication | The proposed indication for the marketing authorisation. A medical condition that a medicine is used for. This can include the treatment, prevention and diagnosis of a disease. The therapeutic indication granted at the time of marketing authorisation will be the result of the assessment of quality, safety and efficacy data submitted with the marketing application. |
| UMN | Unmet Medical Need. |

Certain footnotes use abbreviated references; full references can be found in the bibliography at the end of this Staff Working Document.

# 1. INTRODUCTION

## 1.1 Purpose and scope of the evaluation

The purpose of this evaluation is to assess how well the EU general pharmaceutical legislation, i.e. Directive 2001/83/EC[1] and Regulation (EC) No 726/2004[2], has performed since the last comprehensive revision in 2004. Its objective is to check whether the legislation is still 'fit for purpose' to protect public health, and to meet the needs of the EU patients in terms of access to innovative medicines, their availability and supply across the EU, as well as in terms of competitiveness of the EU pharmaceutical industry. The evaluation looks into the performance of the legislation during the COVID-19 pandemic and its suitability to achieve the objectives of the Pharmaceutical Strategy for Europe[3].

The Pharmaceutical Strategy for Europe aims at creating a future-proof regulatory framework that supports industry and promotes research in therapies that actually reach patients in order to fulfil their therapeutic needs, while addressing market failures. It provides among its flagships initiatives a revision of the general pharmaceutical legislation to help achieve the following objectives of the strategy, while guaranteeing the authorisation of safe, efficacious, high-quality medicines:

- Ensure greater access and availability of pharmaceuticals to patients;
- Ensure affordability of medicines for patients and health systems financial and fiscal sustainability;
- Enable innovation including for unmet medical needs, in a way that harnesses the benefits of digital and emerging science and technology and reduces the environmental footprint;
- Support EU influence and competitiveness on the global level, reduce direct dependence on manufacturing in non-EU countries, seek a level playing field for EU operators.

Given the political priority and importance of this initiative, this evaluation is part of a 'back-to-back process,' i.e. a single process of evaluation and impact assessment based on the same consultation strategy. The findings of the evaluation informed the impact assessment for the revision of the general pharmaceutical legislation.

The evaluation covers most parts of Directive 2001/83/EC and Regulation (EC) No 726/2004 (further details in Annex 9). Provisions on pharmacovigilance[4] are included as far as they are relevant to the objectives of the evaluation. Out of scope of this evaluation are provisions in Directive 2001/83/EC concerning:

- The registration of homeopathic medicinal products[5];

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[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67.
[2] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.4.2004, p.1.
[3] COM(2020) 761 final, Pharmaceutical Strategy for Europe.
[4] Title IX of Directive 2001/83/EC and Title II, Chapter 3 of Regulation (EC) No 726/2004.
[5] Title III, Chapter 2.

- The registration of traditional herbal medicinal products[6];
- Advertising and information to patients[7];
- Safety features and falsified medicines[8]; and
- Sale at a distance to the public[9].

The evaluation includes aspects of medicines covered by the *specialised* EU legislation i.e. on advanced therapy medicinal products[10], medicine for rare diseases[11] and medicines for children[12], insofar these are under the *general* pharmaceutical legislation (further details in Annex 9). The legislation on medicines for rare diseases and on medicines for children were subject to a separate evaluation[13]. The results of this evaluation have been taken into account.

The evaluation covers all 27 EU Member States, the three EEA-EFTA countries[14] and the United Kingdom; the latter applied the legislation for the entire evaluation period, i.e. 2005-2020.

The legislation is assessed using the evaluation criteria of effectiveness, efficiency, relevance, coherence and EU added value. A mixed quantitative and qualitative **methodology** was used (see Annex 4). It included peer-reviewed literature and policy document review to gather existing knowledge base and as a source of facts and figures; secondary data analysis of over 50 macro indicators relevant to industrial & economic competitiveness, research & innovation, to access, affordability and single market effects, including statistical, econometric and trend analysis in the EU, compared to data from other jurisdictions. In addition, case studies were developed focusing on specific issues[15] and illustrating linkages and mechanisms behind trends observed in the data. Finally, extensive stakeholder consultations were conducted and resulting primary data analysed from the feedback on the Roadmap/Inception Impact Assessment[16] and the public consultation, targeted surveys, interviews and a workshop.

Nonetheless, some **evidence limitations** affect the robustness of findings: (1) Stakeholders were often unable to break down observed effects to drivers of those effects and link those

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[6] Title III, Chapter 2a.
[7] Titles VIII and VIIIa.
[8] The provisions introduced by the Falsified Medicines Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.
[9] Title VIIa.
[10] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 324, 10.12.2007, p.121.
[11] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, OJ L 18, 22.1.2000, p. 1, (Orphan Regulation).
[12] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use, OJ L 378, 27.12,2006, p. 1, (Paediatric Regulation).
[13] SWD(2020) 163 final.
[14] Iceland, Liechtenstein and Norway.
[15] Topics covered: Unmet medical needs; Antimicrobial resistance (AMR); Agile / adaptive regulatory systems; SMEs / Regulatory support; Improved access to medicines; Regulatory barriers for emerging manufacturing technologies; Generic competition of complex medicines: biosimilars and complex non-biological medicines.
[16] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en.

to specific legislative measures in scope. (2) Due to the extended time period of the evaluation, many stakeholders consulted were not able to provide historic perspective on the situation before 2005, or the early years of the implementation of the 2004 revision. (3) Some stakeholder groups (especially civil society and public authorities) found it challenging to mobilise internal resources to provide information, data and evidence across all evaluation dimensions, and provided mainly opinions. As a result, qualitative and quantitative data collected during the evaluation show large variations of quality across stakeholder groups. Much of the quality data collected are linked to more recent years and therefore direct attribution of these effects to the 2004 revision remains limited.

Further, quantitative data definition and data collection approaches changed over time making it challenging to conduct a continuous trend analysis over the 2000-2020 time period. As data collection and indicators are not uniform across all countries, extensive data cleaning and data verification were applied.

## 2 WHAT WAS THE EXPECTED OUTCOME OF THE INTERVENTION?

### 2.1 Description of the intervention and its objectives

Since 1965, the EU pharmaceutical legislation has had the dual objective to safeguard public health and harmonising the internal market for medicines.

It is grounded on the principle that a medicine may only be placed on the market following the granting of a marketing authorisation based on a positive benefit-risk assessment of its quality, safety and efficacy. This requirement safeguards public health.

The general pharmaceutical legislation also regulates the safety monitoring of a medicine (pharmacovigilance), as well as manufacturing, distribution and advertising. The application of the legislation is based on cooperation and division of responsibilities between the EU level and Member States. Medicines may either be authorised centrally by the Commission on the basis of a positive scientific assessment by the European Medicines Agency (EMA), or nationally by an individual or a group of Member States. Moreover, Member States are responsible for the authorisation of manufacturers and wholesale distributors.

The general pharmaceutical legislation is supplemented by *specialised* legislation for medicines for rare diseases, medicines for children, advanced therapy medicines; it applies to these specialised medicines, while the specialised frameworks provide measures to address their specific characteristics. The Orphan Regulation was adopted in 1999 to enable research, development and authorisation of new medicines for rare diseases through specific *incentives*, given the small number of patients affected by rare diseases. The Paediatric Regulation was adopted in 2006 fostering the development and availability of medicines for children, without subjecting children to unnecessary trials or delaying the authorisation of medicines for use in adults. In doing so, the Paediatric Regulation obliges companies already developing medicines for adults to screen them for possible use in children and provides rewards once such obligation – the paediatric investigation plan – has been fulfilled. The Regulation on advanced therapy medicinal products (ATMPs) adapts the technical requirements for the authorisation of medicines that are based on genes, tissues or cells. Specific scientific committees at the EMA have been established to support assessment in all three specialised areas[17]. The Orphan and Paediatric Regulations are currently under revision, following an evaluation published in 2020.

[17] Committee for Orphan Medicinal Products (COMP), Paediatric Committee (PDCO), Committee for Advanced Therapies (CAT).

In addition, the general pharmaceutical legislation is complemented by the clinical trials Regulation[18] which harmonises the processes for assessment and supervision of clinical trials throughout the EU. Clinical trials generate data to substantiate the efficacy and safety of a medicine. Annex 9 provides an overview of the lifecycle of a medicine with the major touchpoints between the general pharmaceutical legislation.

Finally, the general pharmaceutical legislation links to other legal frameworks as medicines may be integrated or used in combination with medical devices[19] or in vitro diagnostics[20]. A medicine may be based on a substance of human origin[21] (e.g. blood, tissues or cells).

Despite the harmonisation provided by the EU pharmaceutical legislation, there is an inherent fragmentation of the EU market for medicines in terms of access, as most medicines go through national pricing and reimbursement processes prior to market launch. Pharmaceutical expenditure is largely subsidised by national health systems in order to ensure the adequate provision of medicines to all citizens. In this context, Member States adopt measures to regulate the prices of medicines and the conditions of their public funding based on their exclusive competence in this field (Article 168 TFEU). Such measures influence the prescription and utilisation of medicines in each country. They also affect the capacity of pharmaceutical companies to sell their products in domestic markets.

Before the 2004 revision, there were three **ways of obtaining a marketing authorisation**[22]:

- Centralised authorisation procedure - the marketing authorisation holder (MAH) can market the medicine and make it available to patients and healthcare professionals throughout the EU on the basis of a single marketing authorisation (MA);

- National authorisation procedure – the MAH can market the medicine and make it available to patients and healthcare professionals in the EU Member State where it was authorised;

- Mutual recognition procedure (MRP) – several Member States recognise the national MA of another MS and authorise the medicine in their own territory;

The 2004 revision added the decentralised procedure (DCP) (several Member States simultaneously authorise a new medicine on their respective territory).

Prior to the 2004 revision, there was an erosion of the EU's position as a leading hub for the pharmaceutical industry and R&D investment[23]. The EU pharmaceutical industry was losing competitiveness and growing less compared to the USA and Japan.

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[18] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1.

[19] Regulation (EU) No 745/2017 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, OJ L 117, 5.5.2017, p. 1.

[20] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU, OJ L 117, 5.5.2017, p. 176.

[21] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 7.4.2004, p. 48 and Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC, OJ L 33, 8.2.2003, p. 30.

[22] The main features are outlined in Annex 7.

In addition, science had progressed steadily and new therapies were on the horizon. There was progress of applied sciences (particularly in biotechnology) and also likely future developments (for example, gene therapy). In parallel, an ever-increasing globalisation in research and development as well as in regulatory practices on scientific and technical criteria for assessment of medicines had taken place. This was not adequately reflected in the EU regulatory framework. This also affected the attractiveness of the EU as a place to research, develop and supply medicines in a timely manner.

The risk of exacerbation of a fragmented EU pharmaceutical regulatory system with further enlargement of the market with new Member States prompted the Commission to devise a number of measures to reverse these trends.

An evaluation study[24] of the marketing authorisation procedures and the regulatory framework showed that the scope of the centralised procedure should be expanded, the EMA's scientific role should be reinforced and more Union coordination was required to resolve disagreements on nationally authorised medicines and to have more efficient market surveillance. There was a need to improve the mutual recognition system, increase harmonisation and facilitate the market entry of generic medicines and biosimilars.

As a consequence, the 2004 revision built on the strengths of the established system with **four main objectives**: i) ensure quality, safety and efficacy of medicines; ii) enable access to medicines; iii) ensure the competitive functioning of the EU internal market; and iv) ensure attractiveness in the global context.

**Specific objectives** aimed to ensure accommodation of innovation; reduction of administrative burden and improvement of adaptability of the regulatory environment; reduction of disparities across Member States and of duplication of effort; and facilitation of free movement of medicines.

To take advantage of the scientific and technological developments and to accommodate **innovation** the intervention changed and expanded EMA's scientific committees to ensure relevant expertise. It mandated EMA to provide scientific advice to marketing authorisation applicants. A new pathway for biosimilar medicines was introduced. It also provided for more effective coordination among Member States' regulatory authorities.

The intervention took measures to **facilitate faster authorisation and access to medicines** for medicines of major interest for public health and therapeutic innovation and for unmet medical needs and through introduction of accelerated assessment of the application for marketing authorisation (reduction from 210 to 150 days) and conditional marketing authorisation[25], which allows earlier authorisation on the basis of less comprehensive clinical data than normally required, where the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required.

Another strand of actions aimed to improve access by making the framework more friendly to generic medicines through the introduction of the decentralised procedure, the optimisation of the mutual recognition procedure and the reduction of the frequency of the renewal of marketing authorisation. The intervention introduced the so-called Bolar provision that allowed companies to start testing generic or biosimilars in advance of patent expiry of the reference medicine. The Bolar provision was expected to speed up market launch of generics as soon as the regulatory or intellectual property (IP) protection lapsed

[23] COM(2003) 383 final and Danzon, 1997.
[24] Study on the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use (January, 2020), available at mphu-map-eyrep_en_0.pdf (europa.eu).
[25] CMA defined in the Glossary.

(Day 1 launch). Other measures aimed to reduce the costs for generic medicines. These measures were expected to reduce market barriers, ensuring the **competitive functioning of the single market**.

Measures to accommodate innovation aimed to ensure **attractiveness of the EU system in the global context** together with measures to reduce disparities across Member States. They included an expansion of the centralised procedure to more innovative medicines and a single application to EMA for an EU wide marketing authorisation by the Commission.

An overview of the relationship between objectives, actions, results and impacts of the intervention is set out in Appendix A. As the impact assessment accompanying the legal proposals of the 2004 revision did not include an intervention logic, this document uses an intervention logic that was created retrospectively for the purposes of this evaluation.

Regarding the broader policy context, the United Nation's Sustainable Development Goals (SDGs)[26] take a holistic approach to achieve better and more sustainable future for all. Although the 2004 revision precedes the SDGs, its objectives are aligned:

- **SDG 3** "*good health and well-being*" and especially **target 3.8**, which aims among others to ensure *"access to safe, effective, quality and affordable essential medicines and vaccines for all";*
- **SDG 9** "*industry innovation and infrastructure*" and especially **targets 9.1** and **9.5,** which focus on the development of "*quality, reliable, sustainable and resilient infrastructure […] to support economic development and human well-being, with a focus on affordable and equitable access for all […]*" and on the need to "*enhance scientific research, upgrade the technological capabilities of industrial sectors in all countries […] to encourage innovation and substantially to increase the number of research and development workers*"

### 2.2 Points of comparison

The main point of comparison is the situation before the 2004 revision. A specific programme to monitor the legislation impacts was not established, though the authorisation procedures were assessed every 10 years[27]. Key performance indicators were not identified, but the revision was expected to provide more authorisations of innovative medicines and faster access to these medicines in the EU, facilitate the market entry of generic medicines and biosimilars as well as strengthen innovation and competition within the pharmaceutical industry to ultimately promote growth and enhance employment opportunities in the sector.

Comparisons are made with third countries in relation to: competitiveness/ attractiveness of EU regulatory system, innovation, access, affordability and antimicrobial resistance both for trends over the evaluation period and for the current situation. The main countries included in this comparison are Japan, Switzerland and US, though certain comparisons also include Australia, Canada, China and Korea.

## 3 HOW HAS THE SITUATION EVOLVED OVER THE EVALUATION PERIOD?

### 3.1 Implementation of the legislation

Even though several Member States were delayed to implement the changes to Directive 2001/83/EC in their national legislation, this had not substantial impact on the actual use of

[26] The 17 Sustainable Development GOALS, United Nations https://sdgs.un.org/goals.
[27] COM(2021) 497 final and Evaluation of the European Medicines Agency – Final report (January 2010).

the new measures. Some differences have been noted though across Member States in the implementation of parts of the legislation. One examlpe is the implementation of the **'Bolar'[28] provision**, a patent derogation to facilitate filing of generic applications. While transposed by all Member States the text adopted in each country allows different interpretations[29]. Implementation ranges from a derogation that is limited to 'experimental' purposes only with no commercialisation activity (like manufacturing) allowed in preparation for market launch (Spain), to the possibility for generic manufacturers to prepare production and regulatory procedures (Netherlands).

Another example is the **Hospital Exemption (HE)** which was introduced by the ATMP regulation and allows for the use of an ATMP without a marketing authorisation, when prepared in a hospital setting on a non-routine basis for an individual patient under the exclusive professional responsibility of a medical practitioner[30]. The HE has been implemented differently across Member States. A recent study covering seven European countries, showed great variations in how quality, safety and efficacy standards are implemented and controlled (i.e. there is substantial variability in the interpretations of HE terminology and the requirements imposed by national competent authorities (NCAs) for its use)[31]. This evidence draws concerns around its potential impact on public health and risks to patient safety.

Furthermore, differences in GMO risk classifications and data requirements (content and format)[32] across the EU. Indeed, assessments of medicines containing or consisting of **genetically-modified organisms (GMOs)** are complex and vary across the Member States (e.g. assessment of their environmental safety). On occasion, it leads to delays in clinical trials and authorisation of GMO-containing medicinal products, making the EU a less attractive region for clinical development and, ultimately, delaying patient access.

In addition, the implementation of provisions related to medicine **shortages**, such as the notification requirements and obligations to ensure appropriate and continued supply, varies significantly across Member States[33]. For instance, whilst some countries require notification of any medicine shortage, regardless of the expected duration, others only require notification if the shortage is expected to last longer than three weeks[34]. As regards obligations on continued suppy, these can vary from stock keeping obligations, to mandatory reporting on stock levels and export restrictions[35].

Within the evaluation period, the **EU Courts** (the Court of Justice and the General Court) provided **guidance on the interpretation** of a number of provisions. This concerns *inter*

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[28] The 'Bolar' provision allows certain experiments to be conducted on a patented pharmaceutical during the lifetime of the patent, to enable generic manufacturers to demonstrate bioequivalence prior to the expiry of a patent.

[29] CMS Cameron McKenna, & Andersen Consulting. (2000). Evaluation of the operation of Community procedures for the authorisation of medicinal products.

[30] Article 28(2) of Regulation (EC) No 1394/2007.

[31] Hills, A., Awigena-Cook, J., Genenz, K., Ostertag, M., Butler, S., Eggimann, A. V., & Hubert, A. (2020). An assessment of the hospital exemption landscape across European Member States: regulatory frameworks, use and impact. Cytotherapy, 22(12), 772-779.e1. https://doi.org/10.1016/j.jcyt.2020.08.011.

[32] Beattie, 2021; Lambot et al., 2021

[33] de Jongh et al., 2021

[34] European Commission, Directorate-General for Health and Food Safety, Jongh, T., Becker, D., Boulestreau, M., et al., Future-proofing pharmaceutical legislation : study on medicine shortages : final report (revised), Publications Office of the European Union, 2021, https://data.europa.eu/doi/10.2875/211485

[35] See Footnote 35

*alia* definitions (e.g. medicinal product by function[36], pharmacological action[37], reference medical product[38]), the scope of the legislation including exceptions (e.g. pharmacy preparations[39], blood products[40] and industrial process[41]), the interaction of off-label use and authorised use[42], the global marketing authorisation concept[43], parallel trade[44], advertising provisions[45], and the marketing authorisation requirements (e.g. on summary on product characteristics[46], burden of proof[47], precautionary principle for the suspension or restriction of the marketing authorisation[48], involvement of experts[49], mutual recognition procedure[50], centralised procedure[51], conditions for taking regulatory actions[52]). While the case law developed provided authoritative interpretation of those provisions of pharmaceutical legislation, it also points to the need for additional clarity, e.g. the provisions on the relation between the scope of Directive 2001/83/EC and the exemptions[53].

### 3.2 A regulatory framework to support innovation and access to medicines

The Commission has worked to balance competition and affordable access to medicines[54] and supported efforts to improve cooperation and coordination between Member States in

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[36] See e.g. judgment of 15 January 2009, *Hecht-Pharma GmbH v Staatliches Gewerbeaufsichtsamt Lüneburg*, C-140/07, EU:C:2009:5, para. 37 and 39.

[37] See e.g. judgment of 6 September 2012, *Chemische Fabrik Kreussler & Co. GmbH v Sunstar Deutschland GmbH*, C-308/11, EU:C:2012:548, para. 29 and 36.

[38] See e.g. judgment of 18 June 2009, *Generics (UK) Ltd, Regina v Licensing Authority (acting via the Medicines and Healthcare products Regulatory Agency*, C-527/07, EU:C:2009:379, para. 24.

[39] See e.g. judgment of 16 July 2015, *Abcur AB v Apoteket Farmaci AB and Apoteket AB.* joined Cases C-544/13 and C-545/13, EU:C:2015:481, para. 60, 61, 64, 67 and 70.

[40] See e.g. judgment of the Court (First Chamber), 13 March 2014, *Octapharma France v Agence nationale de sécurité du médicament et des produits de santé (ANSM), Ministère des affaires sociales et de la santé*, C-512/12, EU:C:2014:149, para. 40.

[41] See e.g. judgment of the Court (First Chamber), 13 March 2014, *Octapharma France v Agence nationale de sécurité du médicament et des produits de santé (ANSM), Ministère des affaires sociales et de la santé*, C-512/12, EU:C:2014:149, para. 46 or judgment of 16 July 2015, *Abcur AB v Apoteket Farmaci AB and Apoteket AB.* joined Cases C-544/13 and C-545/13, EU:C:2015:481, para. 71.

[42] See e.g. judgment of the Court (Grand Chamber) of 23 January 2018, *.F. Hoffmann-La Roche AG, La Roche SpA, Novartis AG and Novartis Farma SpA v Autorità Garante della Concorrenza e del Mercato,* C-179/16, EU:C:2018:25, para. 59.

[43] See e.g. the judgment of 28 June 2017, *Novartis Europharm Ltd v European Commission*, Joined Cases C-629/15 P and C-630/15 P, EU:C:2017:498, para. 65, 69, 71 and 72.

[44] See e.g. the judgment of 6 December 2012, *AstraZeneca AB and AstraZeneca plc v European Commission*, :EU:C:2012:770, para. 130.

[45] See e.g. judgment of 5 May 2011, *Novo Nordisk AS v Ravimiamet*, C-249/09, EU:C:2011:272, para. 51.

[46] See e.g. judgment of 14 February 2019, *Staat der Nederlande v Warner-Lambert Company LLC, C-423/17,* EU:C:2019:125, para. 47.

[47] See e.g. judgment of 3 September 2020, *BASF AS v European Commission* T-472/19, para. 49.

[48] See e.g. judgment of 19 September 2019, *GE Healthcare A/S v European Commission*, T-783/17, EU:T:2019:624, para. 48.

[49] See e.g. judgement of 28 October *2020*, *Pharma Mar, SA v European Commission*, T-594/18, EU:T:2020:512, para. 77 to 85.

[50] See e.g. judgment of 16 October 2008, *Synthon*, C-452/06, EU:C:2008:565, para. 29.

[51] See e.g. judgment of 14 February 2019, *Staat der Nederlanden v Warner-Lambert Company LLC* C-423/17, para. 42.

[52] See e.g. judgement of 14 March 2018, *Proceedings brought by Astellas Pharma GmbH*, C-557/16, EU:C:2018:181, para. 39.

[53] See e.g. judgment of the Court (First Chamber), 13 March 2014, *Octapharma France v Agence nationale de sécurité du médicament et des produits de santé (ANSM), Ministère des affaires sociales et de la santé*, C-512/12, EU:C:2014:149, para. 46 or judgment of 16 July 2015, *Abcur AB v Apoteket Farmaci AB and Apoteket AB.* joined Cases C-544/13 and C-545/13, EU:C:2015:481, para. 71.

[54] Vancell, 2012

areas such as procurement[55]. The HTA regulation contributes to improving the availability for EU patients of innovative health technologies through joint clinical assessments, joint scientific consultations and voluntary cooperation[56].

The 2004 revision was underpinned by measures to facilitate faster authorisation and access to medicines of major public health interest, therapeutic innovation and targeting unmet medical needs, through the introduction of the accelerated assessment procedure and the conditional marketing authorisation procedure (see Section 2.1).The role of the EMA was reinforced, including through its central coordinating role in the European medicines regulatory network and the set up of the SME's office[57]. The office provides advice and assistance to SMEs wishing to bring innovation to the market[58]. Financial incentives (full or partial fee exemptions for pre- and post-authorisation procedures) were also created for SMEs[59].

Furthermore, the mandatory scope of the centralised procedure for authorisation has been gradually extended to new active substances in a number of conditions, including cancer, diabetes, neurodegenerative, viral and autoimmune diseases; medicines derived from biotechnology processes, advanced-therapy medicinal products and orphan medicines. New active substances outside the mandatory scope can use the centralised procedure; as well as those that represent major scientific and technical innovation. As a result, the great majority of new, innovative medicines go through the centralised procedure. Only 3 new active substances were approved via national procedures from 2016 to 2020. Total central EU wide authorisations have more than doubled from a baseline of 30-40 products per year until 2004 to over 80 products by 2020, with new active substances[60] making up about half of all central authorisations[61] (Figure 1).

[55] de Jongh et al., 2021

[56] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU, PE/80/2021/INIT, OJ L 458, 22.12.2021, p. 1.

[57] Set up by Commission Regulation (EC) No 2049/2005 of 15 December 2005 laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises, OJ L 329, 16.12.2005, p. 4, OJ L 321M , 21.11.2006, p. 371.

[58] Support to SMEs increased from 366 requests for scientific advice to the EMA in 2013 to 436 in 2017. In that period, SMEs consistently accounted for around 30% of all requests at EMA level. Source: COM(2021) 497 final – Report from the Commission to the European Parliament and the Council on the experience acquired with the procedures for authorising and supervising medicinal products for human use, in accordance with the requirements set out in the EU legislation on medicinal products for human use.

[59] Financial advantages of SME status https://www.ema.europa.eu/en/human-regulatory/overview/support smes/financial-advantages-sme-status.

[60] New active substances are an indication of genuine innovation, versus authorisation of existing molecules for new indications, or combinations of molecules.

[61] SEC(2006)832 In the first five years of REG (EC) No 141/2000, 22 orphan medicines were authorised for the treatment of 20 different life-threatening or chronically debilitating rare diseases. SWD(2020) 163 final By 2017, 142 unique orphan medicines had received an EU marketing authorisation for 107 orphan indications. In a best case scenario, they were estimated to address the needs of 6.3 million EU patients (out of 35 million people suffering from rare diseases in the EU).

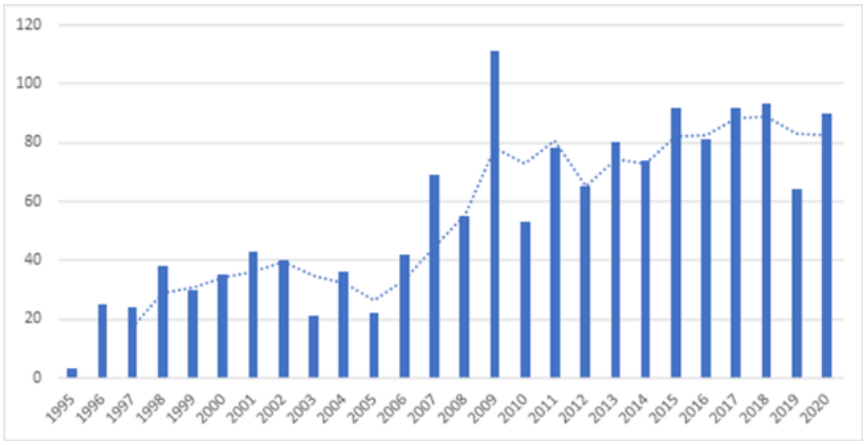


Figure 1: Total number of centrally authorised medicinal products in the EU (yearly, 1995-2020)
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

When comparing central authorisations of new active substances in the EU with equivalent numbers in the US (Figure 2), between 2006-2016 annual authorisations in the two jurisdictions have a smaller gap. However, a new gap opened up in recent years as US FDA authorises more new molecular entities, compared to the EU. Indeed, the majority of new active substances were authorised first by the US FDA over the entire period 2001-2020 (53% to 75%), however 55% of the new active substances were authorised in the EU within 1 year from US FDA approval over 2016-2020.

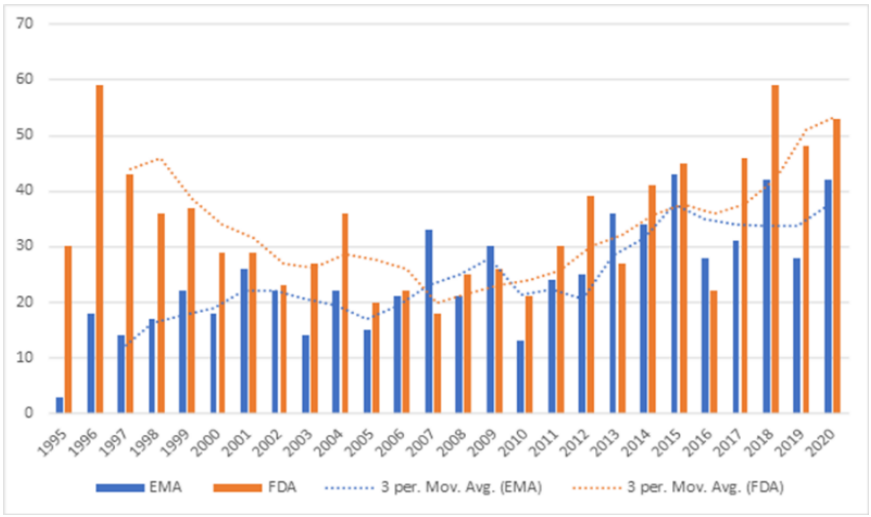


Figure 2: Total number of new active substances/new molecularentities authorised by EMA and FDA
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

By absolute numbers the vast majority of product approvals remains at the national level through MRP/DCP procedures (usually over 1000 products per year). Since the introduction of DCP in 2005, the number of products seeking authorisation through the DCP has shown a marked increase with a parallel reduction in the MRP (Figure 3). The majority of MRP/DCP procedures concern generic medicines: 799 procedures in 2020 related to generics or similar applications.

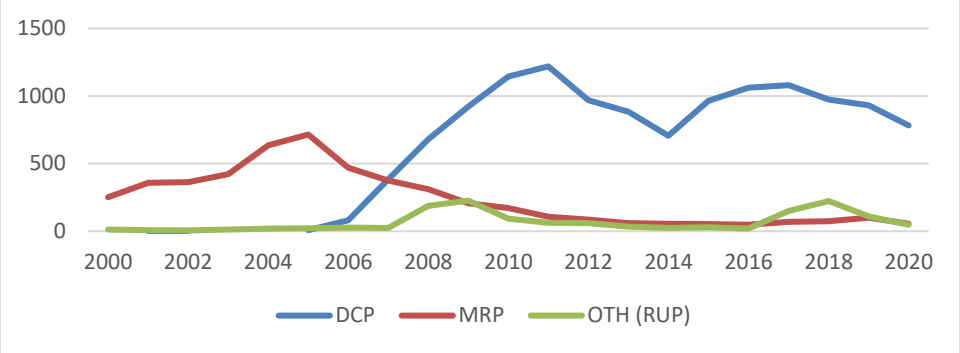


Figure 3: Trend in the number of products seeking authorisation through MRP, DCP and other Repeat Use Procedures (*RUP*) Source: Mutual Recognition Index (MRI) data.

### 3.3 Intellectual property and regulatory protection of pharmaceuticals in the EU

To **incentivise innovation, research and development** of medicines and to allow investment to be recouped, innovative medicines and certain developments such as new indications are protected through *various* forms of intellectual property (IP) rights (patents or supplementary protection certificate) and regulatory protection periods (data protection, market protection as well as market exclusivity for medicines for rare diseases). The same product can benefit from several protection mechanisms in parallel.

Patents give their owner the right to prevent others from making, using or selling the invention without permission. They may be granted for the active substance of a medicine, a production process or use of the medicine. Patent is the basic incentive to pursue activities taking an innovative concept to industrial application by excluding others from exploiting the invention for 20 years from filing date. Secondary patents are usually filed for improved variants of the basic product, new therapeutic indications, or new combinations.

The actual marketing of medicines can often take place late in the patent protection period, due to the lengthy testing and clinical trials these products require prior to authorisation and the duration of authorisation procedure. Therefore, the EU introduced supplementary protection certificates in 1992 to offset part of the loss of patent protection time, by extending the patent expiry by 5 years. The combined IP protection period from marketing authorisation is limited to a maximum of 15 years.

Data and market protection are granted to a specific medicine at the moment of authorisation and protect the medicine against competition from generic or biosimilar medicines. Data and market protection are regulated in the general pharmaceutical legislation, while additional incentives and rewards for orphan and paediatric medicines follow from the specialised legislation.

Regulatory protection periods are linked to the proprietary data on the safety and efficacy of the product generated for the purpose of marketing authorisation. This protection period was standardised at 8 years of data protection, 10 years of market protection and one additional year of market protection for a new indication with significant clinical benefit (8+2+1) in the revised pharmaceutical legislation. Previously there had been variation of the period between Member States. The new system applied from 30 October 2005 onwards. Figure 4 presents a schematic overview of the interplay among patent, SPC and regulatory protection.

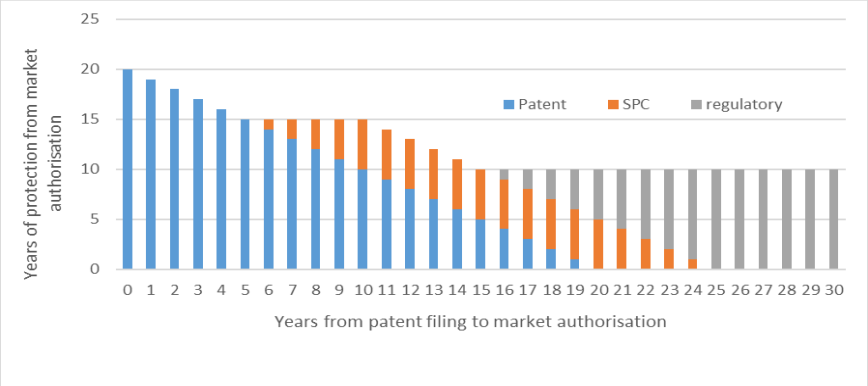


Figure 4: Intellectual property and regulatory protection periods in the EU
Source: DG SANTE, European Commission

Further to the data and market protection periods, an additional year of market protection in case a new therapeutic indication that brings significant clinical benefit; 10-year of market exclusivity for orphan medicinal products, protecting from competition from medicines with the same therapeutic indication; and an extension of 6 months of SPCs to reward paediatric investigations of medicines, and if the investigation concerns an orphan medicine, the orphan market exclusivity may be extended to 12 years.

Due to the multiple possible protections it is useful to focus on the expiry date of the last measure in place that protects the innovator medicine from generic competition. This may be SPC, patent expiry or the regulatory protection expiry, and in some occasions the orphan market exclusivity. A sample of 200 products in France, Germany, Italy and Spain with protection expiry between 2016-2024 shows that IP rights are the last to expire for 60% of the products in the basket, while regulatory protection is the 'last line of defence' for one third of the products (Figure 5). Orphan market exclusivity accounts for 6% of the products. In terms of total sales revenue, SPC protected medicines account for more than 70% of all revenues, this number is 20-23% for those with regulatory protection.

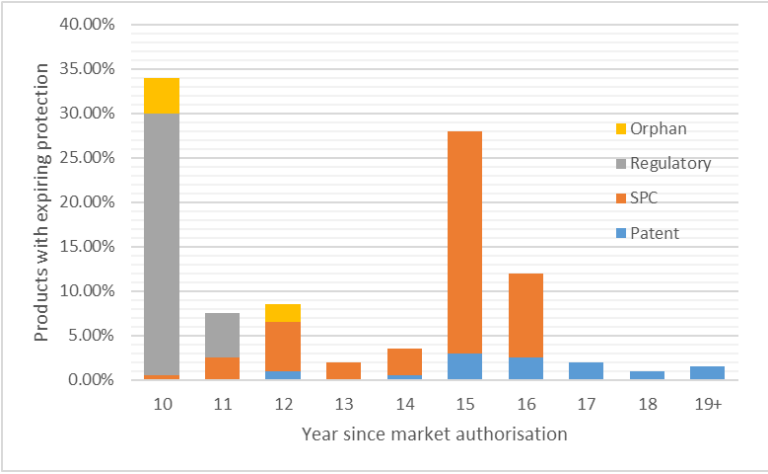


Figure 5: Ratio of medicines by the length of last layer of protection and type of protection
Source: DG SANTE, European Commission, based on IQVIA data

Similar results obtained in a recent study[62] found that 32-40% of products are protected by market protection and showed that pharmaceutical incentives and rewards in the EU are among the most attractive when compared to Canada, China, India, Japan and the United States with regard to the basic regulatory protection periods (Table 1).

[62] Copenhagen Economics, 2018

| Country | Protection | Duration |
|---|---|---|
| Australia | New Chemical Entity + Market Protection | 5 years |
| Canada | New Chemical Entity+ Market Protection | 6+2 years |
| EU | New Chemical Entity+ Market Protection | 8+2+1 years |
| Switzerland | New Chemical Entity | 10 years |
| USA | New Chemical Entity (small molecule) | 5 years |
| USA | Biosimilar Application Approval Exclusivity (biologic) | 4+8 years |
| Israel | Market Protection | 6 or 6.5 years |
| China | New Chemical Entity | 6 years |
| Korea | Post-Marketing Surveillance | Up to 6 years |
| Japan | New Chemical Entity | 8 years |

Table 1: Basic regulatory protection periods for pharmaceuticals globally

## 3.4 Global position of the EU pharmaceutical industry

In the last 20 years, the global market for medicines has rapidly grown. Between 2001 and 2020 global revenues tripled, reaching US$1.27 trillion (€1.2 trillion) in 2020 (Figure 6). The US is the largest market for pharmaceutical products, accounting for about 47% of the global market in 2021, followed by the EU, the second largest market, accounting for 17%. Revenue generated by pharmaceutical companies in the EU has increased over time and was approximately €200 billion in 2020[63].

Increasing revenues and high profitability attract investment into development of medicines. In 2020, the total global spending on pharmaceutical R&D was US$198 billion (€188 billion)[64]. The total number of products in active development globally in 2021 exceeds 6,000, up 68% over the 2016 level[65]. Rich pipelines also translate into more medicine approvals and market launches – 84 new active substances were launched globally in 2021, doubling the number from five years before. 61% of these new launches were first-in-class[66].

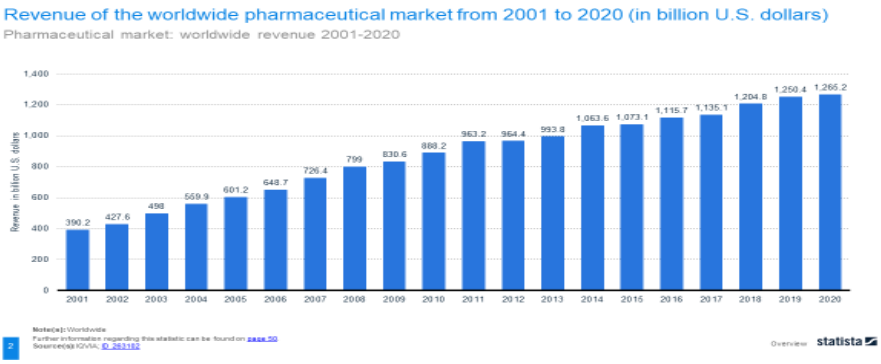


Figure 6 – Revenue of the worldwide pharmaceutical market from 2001 to 2020 (in billion US dollars)
Source: Statistica, 2021

[63] IQVIA data
[64] Statistica, 2021
[65] IQVIA, 2022
[66] Idem. I.e., medicines that use a new and unique mechanism of action for treating a medical condition.

The intensively growing global market has provided the opportunity for the EU's pharmaceutical industry to evolve and capture a significant share of the increase. The EU's total R&D expenditure doubled from around €20bn in 2000 to more than €40bn in 2019[67]. In the US, R&D investment remained almost stationary from 2003 until 2011 (close to €40 billion) and experienced significant growth in the period between 2014 and 2019 (reaching €74 billion). The EU maintained a leading position for new active substances from 1982 to 2003[68], after which time US caught up and is in the lead. Indeed, more recently, 83% of the new medicines approved by the US FDA between 2017 and 2018 originated in the US.

Among other competitors, China is a notable one. R&D investment in the health sector is 23% of the EU's. However, it has been increasing sharply over the last couple of years and is set to level up with the Western peers in the foreseeable future. China's growth in R&D investment is most visible in small biotechs, or emerging biopharma firms[69].

While US firms display an advantage in developing innovative medicines, the EU has become a global champion in manufacturing high-value medicinal products. Looking at the import/export levels and trends of medicines (vaccines, finished products and active pharmaceutical ingredients (APIs)) between 2000-2020, EU exports have multiplied by five and with €215bn worth of exports (Figure 7) Mediciness make up 10% of all exported EU goods in value. Imports have increased too but at a lower rate, resulting in a massive €122bn trade surplus in this product category.

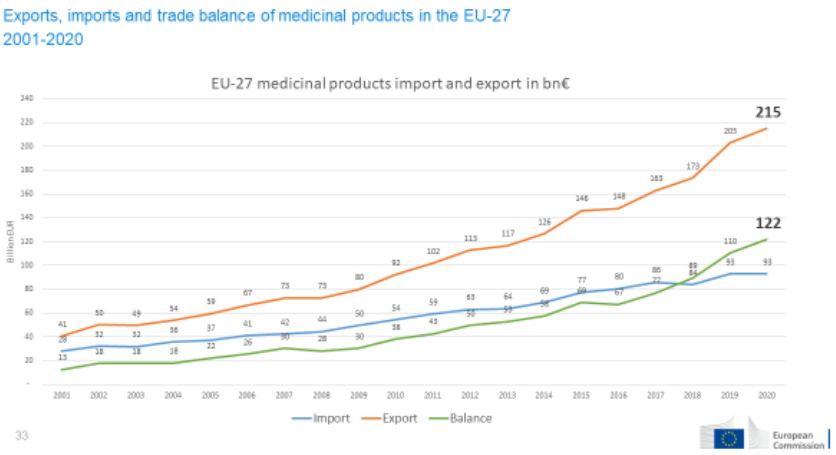


Figure 7: Exports, imports and trade balance of medicinal products n the EU-27. Source: DG SANTE, European Commission, based on Eurostat trade data

Despite the fact that the EU imports large quantities of cheap generic medicines, vaccines and APIs from outside the EU (e.g., from India and China), exports are greater than the imports except for APIs which are almost equal in value[70].

Looking at the profitability of the sector, according to public data, aggregated annual profits of pharmaceutical companies in the USA and Europe grew at annual growth rates of 6.6% and 3.1%, respectively during the 2003-2020 period[71]. Nevertheless, the lower growth rates in Europe are influenced by a marked reduction in profits during 2016-2020. This period of decline in Europe was not observed in Switzerland or Japan, but Canadian companies reported negative profits during the same period.

[67] Analytical report , indicator RI 8, Annex 10
[68] Grabowski and Wang 2006
[69] Ellis, Shannon. "Biotech booms in China." Nature 553.7688 (2018): S19-S19.
[70] Erixon & Guinea, 2020
[71] Analytical report, indicator IEC-11:Profits generated by pharma companies, annex 10.

# 4 EVALUATION FINDINGS

## 4.1 To what extent was the intervention successful and why?

The 2004 revision of the general pharmaceutical framework achieved all four high level objectives to a certain extent. The intervention provided an appropriate regulatory framework for ensuring access to high quality, safe and efficacious medicines to all Member States. It has also enabled competition within the EU internal market and maintained regulatory attractiveness in the global context. Yet, the extent to which each objective was achieved varied, notably ensuring equitable access to medicines for patients in all EU Member States has had the least success. Thus, there are several areas where improvements can be made to build on the achievements of the 2004 revision.

### *4.1.1 Effectiveness and coherence*

This section looks into how effective the general pharmaceutical legislation has been in achieving the main objectives of the 2004 revision, its internal coherence and level of aligment with other legal frameworks.

The evaluation and the feedback of the consultation activities have not revealed specific issues of internal coherence. On the contrary, several (public authorities, industry and healthcare professionals) mentioned explicitly the good internal coherence.

There are also several in-built mechanisms to ensure an adequate coherence between the general pharmaceutical legislation and the specialised pharmaceutical frameworks[72]. While the objectives of the general pharmaceutical legislation are aligned with other specialised pharmaceutical frameworks, there is a varying degree of alignment between the objectives of general pharmaceutical and other EU health and non-health legislation, as well as other EU policies. Indeed, in the past 18 years new challenges have emerged. The Commission President's mission letter[73] to the Commissioner for Health and Food Safety of 2019 spells out supply of medicines, affordability, innovation and a world leading European pharmaceutical industry as key policy objectives. Below, the legislation's performance is measured against these objectives as well.

#### *4.1.1.1 Ensure quality, safety and efficacy of medicinal products*

A recent study assessing the extent to which the current marketing-authorisation system for medicines met its objectives in the period 2010-2017, found that the current system meets the objectives laid down in the legislation. In particular, it gurantees a high level of health protection in the EU. However, rapid scientific developments continue to challenge the system, and the number and complexity of procedures increased substantially[74].

There is consensus across all stakeholders that the **legislation has provided a good framework for safeguarding public health**, and no doubt it has been very successful in addressing this overarching objective. The majority opinion in the targeted survey indicates

[72] (e.g., Article 2, 7, 27, 47 of Regulation (EC) No 1901/2006; Article 10a (1) of Regulation (EC) No 141/2000; Article 8(3) and 3(7) of Directive 2001/83/EC); without prejudice clauses (e.g. Article 2 or Regulation (EC) 1394/2007) and derogations (e.g. Article 9 of Regulation (EC) No 1901/2006; Article 10 to 13 of Regulation (EC) No 1394/2007).

[73] https://ec.europa.eu/commission/commissioners/sites/default/files/commissioner_mission_letters/mission-letter-stella-kyriakides_en.pdf.

[74] COM(2021) 497 final.

that the legislation has been most effective in areas that fall under the objective of ensuring quality, safety and efficacy of medicinal products (see Appendix B[75]).

A few individual academics and NCAs[76] in the public consultation and in interviews highlighted challenges that follow from an early efficacy assessment for other decision-makers (e.g. oncology medicines). A study[77] reported that of the 48 cancer medicines recommended for approval based on a positive benefit/risk assessment by the EMA between 2009 and 2013, 37 out of 68 indications entered the market without evidence of benefit on survival or quality of life. A minimum of 3.3 years after market entry, there was still no conclusive evidence on extended or improved life according to health technology assessment methodologies, and when survival gains were observed over existing treatment options or placebo, they were often marginal. A 2021 study shows that launch prices and post-launch price changes of patented anticancer medicines do not correlate with their clinical benefit[78]. It becomes difficult for payers to justify spending large amounts of their budgets on medicines granted accelerated approval, due to the context of the disease and the unmet need, but which cannot show proven benefit on patient-centred outcomes (e.g. quality of life and survival) in the context of health technology assessment (HTA). There is concern that innovative medicines may not always provide patient benefits commensurate with their costs. It needs to be noted that the EMA's evaluation of medicines is based on their benefits and risks, whilst HTA determines relative effectiveness and the added value of a health technology in comparison with other health technologies, for the purpose of informing national budgetary decisions in health. If the totality of the evidence shows convincingly that a medicine's benefits outweigh its risks, despite possible weaknesses in clinical trials design, medicine regulators can take decisions to bring new medicines to patients in a timely fashion. EMA communicates about its scientific assessment, including any uncertainties identified and the measures taken to minimise any risks in its assessment reports.

**The centralised procedure** (CP) is one of the **major enablers for providing a good framework to safeguard public health** according to interviewees across all stakeholder groups. It has allowed effective and robust authorisation of medicines at EU level. Alongside the CP, the decentralised procedure/mutual recognition procedure (DCP/MRP), the pre-authorisation scientific advice and other services provided by EMA, accelerated assessment and streamlining of processes were acknowledged as key achievements. These procedures have improved quality standards and have ensured safe and efficacious medicines for the EU population.

There has been a clear increase in the use of the centralised procedure over time, with the annual number of authorisations more than doubling on average (Figure 1). However, this may is also be a result of the expansion of the scope of the centralised procedure.

Civil society and health services actors highlighted in interviews that EMA's engagement, involvement and consultation with different stakeholders (including patients) and the scientific advice improved significantly. This has benefited patient safety. Several stakeholders in interviews[79] considered that the 2004 changes led to better quality and safety of product manufacturing. This has been exemplified by the coordinated regulatory action at

[75] Appendix B: Targeted survey overview – areas where the legislation has been effective

[76] Views of two academics (out of forty-two that replied to the open public consultation) and four public authorities (out of forty-eight interviewed).

[77] Davis et al., 2017

[78] Vokinger et al., 2021

[79] All healthcare professionals (total interviewed = 8), 46,6% of industry representatives (total interviewed = 60), 75% of public authorities (total interviewed = 48) and 21% of academics (total interviewed = 13).

EU level to reduce the risk of nitrosamine impurities in medicines, described in the short case study below.

*Regulatory action on nitrosamine impurities*

In 2018, regulators were alerted to high level of nitrosamine impurities, a probable human carcinogen, in blood pressure medicines called 'sartans' produced by one API manufacturer. The EC mandated the EMA to launch a review of all sartans to assess the impact on the impurities on the benefit-risk of these medicines. This was later extended to other categories of medicines. Based on the the review, EMA set a temporary limit for nitrosamine impurities in concerned medicines within a transition period of two years. Medicines that were found to contain unacceptable levels were subsequently suspended (European Medicines Agency, 2019).

In parallel, an EU-wide review in 2019 was launched to understand the presence of nitrosamines in all human medicines and to investigate the risks of presence of nitrosamines through manufacturing. The 2020 review[80] identified several root causes based on which several recommendations were made to reduce the risks of nitrosamine impurities in medicines. The 2021 implementation plan[81] outlined how the EU would work to implement the recommendations for all medicines authorised in the EU. Proposed steps range from providing guidance to reduce nitrosamines impurities to penalties for MAHs and other stakeholders if the quality of medicines is not ensured. However, some API manufacturers encountered challenges in complying with the new requirements, which could lead to medicines shortages. To mitigate the risk of shortages of critical medicines the EMA established a centralised benefit-risk assessment where higher limits might be accepted so that these medicines can continue to be available to patients.

**Medicines quality and consistency** can be indirectly measured by the outcome of inspections on good manufacturing practice (GMP). There has been a strong year-on-year growth in the numbers of GMP inspections in the five years following the implementation of the 2004 revisions (EudraGDMP database)[82]. This reflects the legislative decision to expand and harmonise the oversight of MAHs, manufacturing and supply chains as a means to ensure quality. These activities have been strengthened further over the following 15 years[83]. This extensive programme has resulted in a small number of non-compliance statements (i.e. identified quality problems) of 0.1-1% of inspections (1-24 non-compliance statements each year in the past 10 years)[84]. The number of GMP inspections and certificates issued by EEA authorities was running at around 2 500 a year during the pre-COVID times[85]. Due to the pandemic, the number of inspections – on-site in particular – reduced substantially. To mitigate the impact of disruptions on GMP inspections, the Commission, EMA and the NCAs put forward guidance to MAHs on regulatory expectations and flexibility during the COVID-19 pandemic[86].

The pharmacovigilance revision in 2010 and the creation of the Pharmacovigilance Risk Assessment Committee (PRAC) in 2012 provided the legal basis for improved central **monitoring of suspected side effects of medicinal products**, submitted in the

[80] European Medicines Agency, 2020a
[81] European Medicines Agency, 2020b
[82] The data derive from the EudraGDMP database, however, the EMA Annual Reports include a chapter on inspections and compliance that provides a more accessible analysis of activities over the current and two previous years. As a case in point, see page 59 of the 2007 Annual Report.
[83] European Medicines Agency, 2021b
[84] Data extracted from EudraGDMP database.
[85] See the results of an annual survey of inspections and audits.
[86] EC-HMA-EMA Questions and Answers on regulatory expectations for medicinal products for human use during the covid-19 pandemic (September 2021) https://ec.europa.eu/health/system/files/2021-09/guidance_regulatory_covid19_en_0.pdf.

EudraVigilance database[87] as individual case study reports (ICSR). This reporting allows identifying side effects early on and to act (e.g. by improving product information). The number of ICSRs being submitted and screened annually following the 2004 revision, has shown a growth rate[88]. Around 10% of the individual safety reports had in-depth review by the EMA for a possible adverse drug reaction (ADR), around 20% of these were assessed by PRAC, with half of those resulting in an update of the product information. These potential safety issues can have many causes, therefore the current statistics might not provide sufficient basis for measuring quality improvements directly attributable to the legislation.[89] Still, the above figures provide good indication that the surveillance system was successfully enhanced. Recent studies show the process is identifying more potential risks and enabling quicker and more decisive follow-up action[90].

There was difference of opinion between and within the different stakeholder types as regards pharmacovigilance. Some public authorities, civil society, healthcare professionals and industry were of the view that pharmacovigilance has substantially ensured the safety and quality of medicines; while several healthcare professionals, and industry stakeholders stated that the new pharmacovigilance requirements have considerably increased the resource burden with little added value, albeit without providing examples or data to substantiate their views.

The European medicines agencies regulatory network strategy to 2025[91] confirms there is a need for appropriate **regulatory pathways for alternative preventive and therapeutic approaches** such as bacteriophages and microbiome products which was echoed by interviewed academic stakeholders[92].

Stakeholders' concerns regarding **GMO requirements to medicines** are mirrored in the Commission's study on new genomic technologies[93]. As already mentioned in section 3.1, assessments of medicines containing or consisting of genetically-modified organisms (GMOs) are complex and vary across the EU (e.g. assessment of their environmental safety); this also came out in the public consultation from and in interviews with civil society organisations, industry and public authorities. On occasion, this can lead to delays in clinical trials and authorisation of GMO-containing medicines according to industry stakeholders. Only few industry stakeholders (33 respondents) expressed an opinion on coherence in this area, but more than 20% rated that the frameworks are not at all coherent[94].

During the COVID-19 pandemic, clinical trials with investigational medicines containing or consisting of GMOs intended to treat or prevent COVID-19 received a temporary

[87] EudraVigilance | European Medicines Agency (europa.eu).
[88] European Medicines Agency, 2020c. In 2020, 1.8 million ICSRs related to suspected adverse reactions occurring in the post-authorisation phase were collected and managed in EudraVigilance (1,821,211 – a 9% decrease compared to the previous year). reference: https://www.ema.europa.eu/en/documents/report/2020-annual-report-eudravigilance-european-parliament-council-commission_en.pdf.
[89] Better monitoring may mean revealing pre-existing issues to an extent and there can be many reasons why you have ADR which can include genuine scientific unknowns at the time of the original authorisation or time-limited manufacturing issues and even off-label uses.
[90] Potts et al., 2020.
[91] https://www.ema.europa.eu/en/documents/report/european-union-medicines-agencies-network-strategy-2025-protecting-public-health-time-rapid-change_en.pdf.
[92] Three academics out of the fourteen interviewed.
[93] European Commission, 2021.
[94] Technopolis Study, 2022b.

derogation[95] from EU legislation on GMOs to ensure that the conduct of clinical trials was not delayed due to the complexity of differing national procedures. This derogation is limited to the emergency generated by COVID-19.

As regards protection of public health, stakeholders in the targeted survey were not convinced that this objective was reached as concerns reducing the **environmental footprint of medicines**[96]. Across the different stakeholder consultations, civil society organisations, public authorities and academics in particular highlighted the need for strengthening environmental risk assessment (ERA) requirements and more generally the environmental sustainability aspects in the legislation. Some stakeholders suggested exploring a more explicit role for ERAs in benefit-risk analysis during the assessment process, or even in pharmacovigilance[97].

The ERA was introduced by the 2004 revision for all new marketing authorisation applications[98] and covers environmental risks on the use, storage and disposal of medicines. The largest source of medicines entering the environment is use, however residues of pharmaceutical products may enter the environment during their manufacture or disposal. The ERA has improved transparency around the environmental risks of specific products / APIs, facilitating environmental management. Nonetheless, risks arising from the synthesis, or manufacture of medicines, as well as risks related to antimicrobial resistance fall outside the current scope of the ERA.

Several EU legislative frameworks concern environmental protection and relate to pharmaceuticals in the environment. The evaluation of the **REACH Regulation**[99] showed that regulatory gap exist regarding the risks to the environment and human health (e.g. antimicrobial resistance) related to the manufacturing of active pharmaceutical ingredients (API) and formulation of medicines, due to the fact that medicinal products are exempted from several Titles of REACH and that the pharmaceutical legislation does not cover these risks.

The Water legislative framework, including the **Environmental Quality Standard Directive**[100], the **Groundwater Directive**[101] and the **Waste Water Treatment Directive**[102] aim to ensure the good chemical and ecological status of water bodies and not the

[95] Regulation (EU) 2020/1043 of the European Parliament and of the Council of 15 July 2020 on the conduct of clinical trials with and supply of medicinal products for human use containing or consisting of genetically modified organisms intended to treat or prevent coronavirus disease (COVID-19), OJ L 231, 17.7.2020, p. 12.
[96] See Appendix B: Areas where the current legislation has been effective (survey analysis).
[97] Technopolis, 2022a.
[98] The European Medicines Agency Guidelines on the Environmental Risk Assessment of Medicinal Products for Human Use came into effect in December 2006 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.pdf
[99] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC, OJ L 396, 30.12.2006, p.1.
[100] Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council, OJ L 348, 24.12.2008, p. 84.
[101] Directive 2006/118/EC of the European Parliament and of the Council of 12 December 2006 on the protection of groundwater against pollution and deterioration, OJ L 372, 27.12.2006, p. 19.
[102] Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment, OJ L 135, 30.5.1991, p. 40.

authorisation of chemical substances. Finally, the **Industrial Emission Directive**[103] (IED) does not require a substance specific environmental risk assessment and emissions from the pharmaceutical industry are only generally covered in the CWW (Common Waste Water and Waste Gas Treatment/Management Systems in the Chemical Sector) BAT Conclusions[104] and the WGC (Waste Gas Treatment/Management Systems in the Chemical Sector) BAT Conclusions (under development). Those do not contain emission levels for individual active substances used in medicinal products.

The Commission adopted recently proposals for the revision of the Environmental Quality Standards Directive, the Groundwater Directive[105] and the Urban Waste Water Treatment Directive[106]. These proposals include limits set for some individual pharmaceutical products raising environmental concerns, a limit set for total pharmaceuticals detected and quantified in groundwater and also an additional treatment step for waste water treatment plant that would reduce the release of pharmaceuticals in the treated water. The IED, also under revision, includes the obligation for each installation manufacturing pharmaceuticals in its scope, to implement an Environmental Management System, including a chemical inventory of the hazardous substances present in the installation and an assessment of these substances on human health and the environment. Nevertheless, there is no holistic and systematic approach to address individually the environmental concerns of each pharmaceutical product over its entire life-cycle.

The **European Union Strategic Approach to Pharmaceuticals in the Environment**[107] contains several actions concerning the general pharmaceutical legislation and its actors such as ways to improve the ERA of medicines, completion of assessment by the time of the authorisation with adequate risk management measures, possibility of reducing waste by optimising the package size of pharmaceuticals, and by safely extending expiry dates; facilitate the exchange of best practices among healthcare professionals on the environmentally safe disposal of medicines and clinical waste, and the collection of pharmaceutical residues as appropriate. Several of these aspects are covered in draft guidelines that detail the aspects to be covered by an environmental risk assessment[108] explain how a PBT[109] assessment must be carried out, set a list of precautionary and safety measures in case environmental risks cannot be excluded[110] and a proposed labelling aimed

[103] Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control), OJ L 334, 17.12.2010, p. 17.
[104] Commission Implementing Decision (EU) 2016/902 of 30 May 2016 establishing best available techniques (BAT) conclusions, under Directive 2010/75/EU of the European Parliament and of the Council, for common waste water and waste gas treatment/management systems in the chemical sector, OJ L 152, 9.6.2016, p. 23–42

[105] https://environment.ec.europa.eu/publications/proposal-amending-water-directives_en COM(2022) 540 final
[106] https://environment.ec.europa.eu/publications/proposal-revised-urban-wastewater-treatment-directive_en COM(2022) 541
[107] COM(2019) 128 final.
[108] Determination of physico-chemical properties, fate and ecotoxicity, trigger values for soil, groundwater and secondary poisoning, surface water, sediment, sewage treatment plant, groundwater, soil, secondary poisoning, antibotics, endocrine active substances.
[109] Persistent, bioaccumulative and toxic.
[110] Such as appropriate product storage and disposal, appropriate measure regarding the use of medicinal products, appropriate disposal of unused pharmaceuticals.

at minimising discharge of unused medicine into the environment. Despite these interlinkages the general pharmaceutical legislation is not fully coherent with EU frameworks and policies concerning environmental protection.

**Challenges in definition and classification** can potentially expose patients to unsafe and/or ineffective products. For example, Directive 2001/83/EC covers all 'medicinal products' that are "either prepared industrially or that are manufactured by a method involving an industrial process." This scope does not fully consider changes in the manufacturing of medicines, e.g. low-volume products, bedside-manufactured or single batch personalised medicines, that do not involve an industrial manufacturing process. This situation reduces legal certainty for developers. Concerns were expressed that these medicines may be excluded from the scope of the legislation with less regulatory oversight, thus jeopardising quality and safety of these medicines[111].

The 2019 evaluation[112] and 2022 impact assessment[113] of the EU legislations on **Blood, tissues and cells** (BTC) identified further issues in this respect. Most BTC based substances fall clearly into either the medicinal or BTC legal framework, however, in some cases, it is challenging to decide on classification and determine which legislation applies[114]. While such classification decisions are taken at Member States level, leading to national differences[115], the criteria that define the BTC/medicine borderline are set in Article 2(1) of both Directives (2004/23/EC on the one side and Directive 2001/83/EC on the other side). The BTC framework applies only on the donation, collection and testing of tissues and cells if another legal framework applies on manufactured TC products. Thus, it is important to understand when the EU general pharmaceutical framework applies.

Indeed, there are challenges around the differing interpretation and implementation of the legislation at the Member State level and other relevant legislation (e.g. GMO, ATMP, BTC). Definitions such as 'substantial manipulation', 'use for a different essential function' introduced under Regulation (EC) No 1394/2007, and the use the 'hospital exemption' varies across the Member States in terms of how quality, safety and efficacy standards are controlled. For example, a recent study on how hospital exemption implemented in seven European countries, showed great variations in how quality, safety and efficacy standards are implemented and controlled across the Member States for ATMPs which draws concern around potential impact on public health[116]. This inconsistency across Member States on the implementation of the hospital exemption was also identified in interviews [117]. Another example on the interaction beween specialised pharmaceutical frameworks and implementation at national level concerns **the Paediatric Regulation**. Under this regulation, the differing national rules on the conduct of trials with children may still delay the completion of a paediatric investigation plan (PIP)[118].

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[111] Technopolis, 2022b.
[112] SWD(2019) 375 final - Evaluation of the EU blood and tissues and cells legislation (europa.eu).
[113] SWD(2022) [No number yet] – Impact Assessment of the EU legislation on blood, tissues and cells.
[114] SWD(2019) 375 final.
[115] See annex XVI SWD(2019) 375: Inconsistencies between EU-legal frameworks; a notable exemption to MS driven classification is a classification recommendation provided by EMA's CAT committee for ATMPs.
[116] Hills et al., 2020.
[117] A pathway that empowers EU Member States to permit the provision of an ATMP without a marketing authorisation under certain circumstances. It applies only to custom-made ATMPs used in a hospital setting for an individual patient. Such products may only be produced at the request of a physician and should only be used within the Member State where they are produced.
[118] SWD(2020) 163 final.

Stakeholders have also identified the classification of products as **medical devices and in-vitro diagnostics**[119] as a challenge. For the so-called **combined products**, combining medicines and medical devices, the responsibility of the marketing authorisation holder for respectively the medicine and the medical device part, the responsibility for the overall benefit-risk assessment of a combination product and the procedures involved may not be set out clearly in the frameworks. National competent authorities (NCAs) highlighted in the workshop the need for more clarity on roles and responsibilities and for a more integrated approach in relation to scientific advice on medicines and medical devices[120].

Regarding safety, to note the link of the general pharmaceutical legislation with the **Food Additives Regulation**[121], though only for colours**.** Colours can be used in medicines if they are authorised in the said regulation, subject to the compliance with the purity criteria. Some specific measures have been taken in the field of medicines to allow the necessary time to the pharmaceutical companies to develop alternatives to some food colours also used in medicines, to avoid shortages and ensure safety, quality and efficacy of the alternatives. The recently adopted Regulation (EU) 2022/63 is an example, as it bans the use of titanium dioxide as a food additive, but provisionally allows it in medicinal products (a review clause of three years is forseen for the Commission to re-assess the situation)[122].

#### *4.1.1.2 Ensure access to medicines*

Access to medicines[123] is an area where the legislation is seen to have underperformed the most according to all stakeholder groups, based on the survey responses[124]. Access was examined from three distinct angles: evaluation and marketing authorisation of medicines; approval and reimbursement decisions by HTA bodies and payers; and medicine shortages. Of these aspects, the general pharmaceutical legislation is mainly responsible for the marketing authorisation procedure and, to a lesser extent shortages. Pricing and reimbursement of medicines is completely out of its remit.

Authorisation procedures, especially the centralised procedure, have allowed more new medicines to become available for the EU population (see Figure 1) – this was emphasised by industry and public authorities in interviews. The EU system foresees the possibility for accelerated assessment[125] for medicines of major interest for public health and therapeutic innovation. The number of accelerated assessments in absolute terms and as a proportion of all assessments for new active substances increased in the period 2013-2018, having a decreasing trend after 2016 (Figure 8).

[119] For the evaluation period, the Medical Device Directive has applied, but the incoherences seem to continue under the new MDR and IVDR frameworks.
[120] Pharmaceutical Strategy for Europe Workshops March to June 2021 – Summaries (December 2021) Pharmaceutical Strategy for Europe Workshops March to June 2021 (europa.eu).
[121] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives, OJ L 354, 31.12.2008, p. 16.
[122] Commission Regulation (EU) 2022/63 of 14 January 2022 amending Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the food additive titanium dioxide (E 171), C/2022/77, OJ L 11, 18.1.2022, p. 1.
[123] A medicine becomes accessible once it has been authorised, is being marketed, and, if relevant, can be reimbursed in a Member State.
[124] See Appendix B: Areas where the current legislation has been effective (survey analysis).
[125] Article 14(9) of Regulation (EC) No 726/2004.

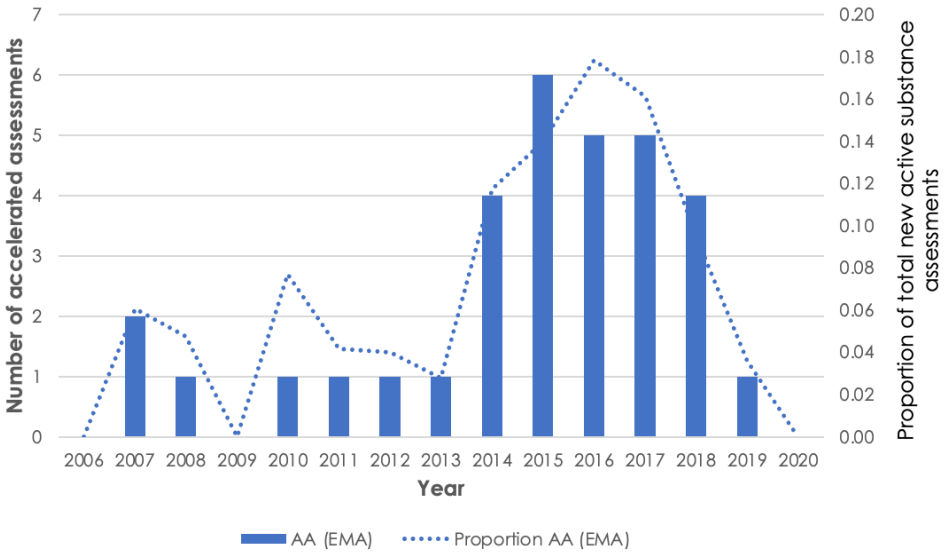



Figure 8: Number and proportion of accelerated assessments by EMA
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA

The 2004 revision aimed to increase access to innovative products. Based on the analysis of EMA's assessment times in days (yearly, 1995-2020), there has been an improvement inaverage assessment times between 2005 (380 days) and 2010 (270 days), which increased gradually over the next 10 years (340 days in 2020) (Figure 9). This suggests that the revisions improved timelines, for a period before other factors (e.g. resourcing, more complex dossiers) resulted in a reversal trend. Comparing with FDA's assessment times, EMA's average is shorter until 2015. After that, the situation reversed with the FDA taking 244 days on average compared with the EMA's 343.5 days. Whilst the difference is large, the indicators may not be fully comparable as the elements included in the assessment can vary[126]. The analysis also shows that, over time, average FDA assessment times have been more variable than the EMA's times.

Some industry stakeholders (eight of the sixty intereviwed) observed that accelerated approval pathways are not used as much as they are in the USA. According to the CIRS policy brief, 67% of new active pharmaceutical ingredients were approved through expedited approval procedures in the US, versus 14% in the EU[127].

[126] For example, the FDA time-data count from first application to approval even where initial applications may be refused and resubmitted several times, whereas the EMA counts time from the point of submission of the application to approval but only for the application that is ultimately approved.
[127] CIRS, 2021.

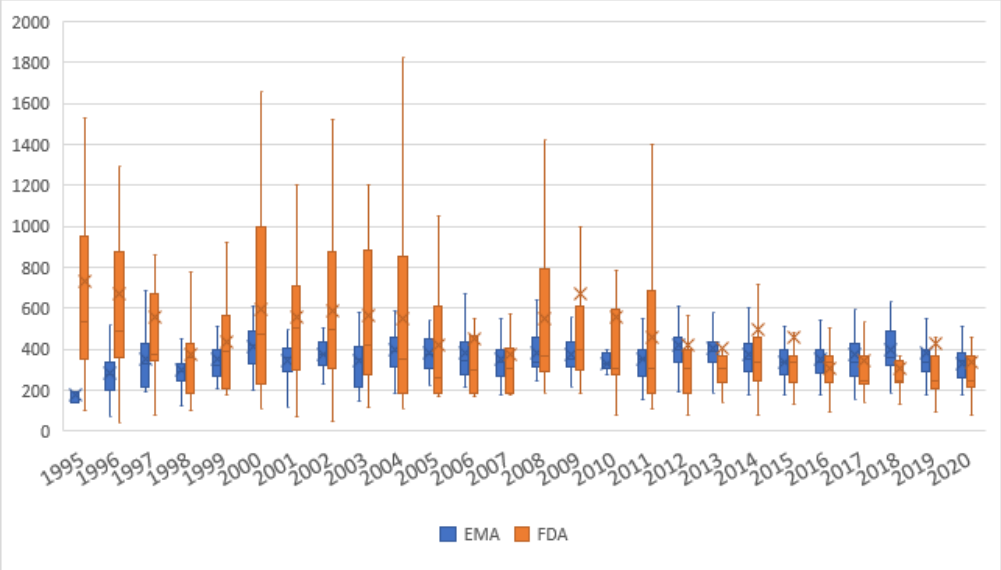



Figure 9: Total assessment times of new active substances/new molecular entities authorised by EMA and FDA in days (yearly, 1995-2020)
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA

On the basis of a a medicine's positive benefit-risk profile, the marketing authorisation – also in case of accelerated assessment or conditional marketing authorisation – ensures that medicines are safe, efficacious and of high quality.

The 2004 revision aimed to improve accessto centrally authorised medicines across the EU, even though the granting of a Union marketing authorisation does not oblige the marketing authorisation holder (MAH) to place that medicine on the market of all or most Member States. Contrary to the improvement in terms of authorised products the number of EEA countries in which a new chemical entity is launched has been steadily decreasing. Various studies have also shown that, even for products that have been approved through the centralised procedure, access remains uneven across the EU. The evaluation of the Orphan Regulation showed that, in the first three years after marketing authorisation, EU authorised orphan medicinal products (OMPs) reached, on average, fewer than six EU-12 Member States and that no medicine reached all Member States. A 2019 study in five European countries similarly found that in some countries less than a third of authorised OMPs were available to patients. Also, for other centrally authorised medicines, such as oncology medicines, substantial differences have been reported in availability and time to entry.

Crucially, however**, patient access to medicines is contingent on decisions post-authorisation**. Firstly, it requires a willingness by the MAH to place a product on a particular market, typically informed by expectations about a positive return on investment. Secondly, payers (health systems or insurers) need to agree to include the medicine into the package of reimbursed care.

This may depend on an assessment of the expected (relative) cost-effectiveness of the medicine by the public authorities and the outcome of price negotiations with the MAH. Such assessment procedures and outcomes may take months or even years[128] and strongly influence the time to launch.

The assessment of medicines' relative effectiveness and cost-effectiveness is outside the scope of the general pharmaceutical legislation. **HTA bodies and payers in Member**

[128] COM/2012/084 final.

**States** make decisions based on their national assessments of cost-effectiveness of a given medicine.

Whilst the legislation has led to improvements in the authorisation of medicines, the system has also become more complex over the years according to industry interviewees and delays in national pricing and reimbursement decisions were mentioned. According to healthcare payers in the public consultation and the interviews, the clinical data available in the marketing authorisation is often insufficient for HTA bodies for their assessment, in particular for medicines authorised with accelerated assessment or conditional marketing authorisation for faster access for patients in case of unmet medical need. While the general pharmaceutical legislation requires data for the assessment of the benefits and risks of a medicine, access to medicines may be delayed if the HTA bodies do not have relevant data for their assessment.

Medicines granted **conditional marketing authorisation** (CMA), thus on less compehensive clinical data, must fulfil post-marketing specific obligations for additional data. EMA's 10 year review of conditional marketing authorisations[129] concluded that 70% of the specific obligations were completed within the specified timelines. On average, a CMA is converted into a standard marketing authorisation within 4 years. A third of the requested data from clinical studies were more preliminary than phase III or uncontrolled single arm studies, or both. Two thirds were for open label studies. Out of the 77 studies requested, only nine — all oncology studies, not necessarily randomised — reported overall survival as the primary outcome, and not one reported quality of life. In a tenth of the cases, the deadline was extended by more than a year, due mainly to slow recruitment or difficulties in activating clinical sites.

Patient access can also be positively influenced by the entry of generics and biosimilars. Regarding **generic entry**, the **Orphan Regulation** lacks coherence with Directive 2001/83/EC. For medicines for rare diseases, generic companies can only submit an application for MA at the end of the 10-year market exclusivity period while for all other medicines, at the end of the market protection period generics can be placed directly on the market. This issue will be further considered in the on-going revision of the Orphan Regulation. Respondents to the targeted survey confirmed this view, especially civil society organisations (38%) estimated the legislation was "slightly" coherent). They identified incoherencies resulting in duplication of similar processes in the general legislation on unmet medical need. 35% of respondents to the targeted survey assessed the legislation as "moderately" consisent with specialised ones. In the public consultation concerns were shared on excessive data exclusivity due to the interplay between the general pharmaceutical legislation and the Orphan regulation. Some respondents suggested the orphan regulation would be better integrated in the general pharmaceutical legislation to also better address some issues arising from data exclusivity of old active substances. No specific concern of coherence were shared during the consultation activities on paediatric legislation.

The fact that **inequitable access is observed** even for centrally authorised medicines points towards 'downstream' factors beyond the authorisation process that affect whether and when products are placed on specific markets. Such factors relate significantly to the characteristics of national markets. Smaller countries and poorer countries tend to see fewer product entries. To illustrate, data provided by EFPIA member associations and IQVIA showed (Figure 10) that, whilst in Germany 133 out of 152 (88%) of all new medicines authorised between 2016 and 2019 were available to patients, small Member States such as

[129] Conditional marketing authorisation - Report on ten years of experience at the EMA (europa.eu).

the Baltic countries or countries with comparatively low prices, like Romania, had fewer than 50 of these available[130]. The difference is smaller when comparing the therapeutic availability (i.e. availability of the therapy - molecule) and not the product availability. The time to patient access is also significantly longer for most of these latter countries, at approximately two years or more in Romania compared to four months in Germany. Similar observations were made across different subsets of medicines, including oncology medicines and orphan medicines[131].

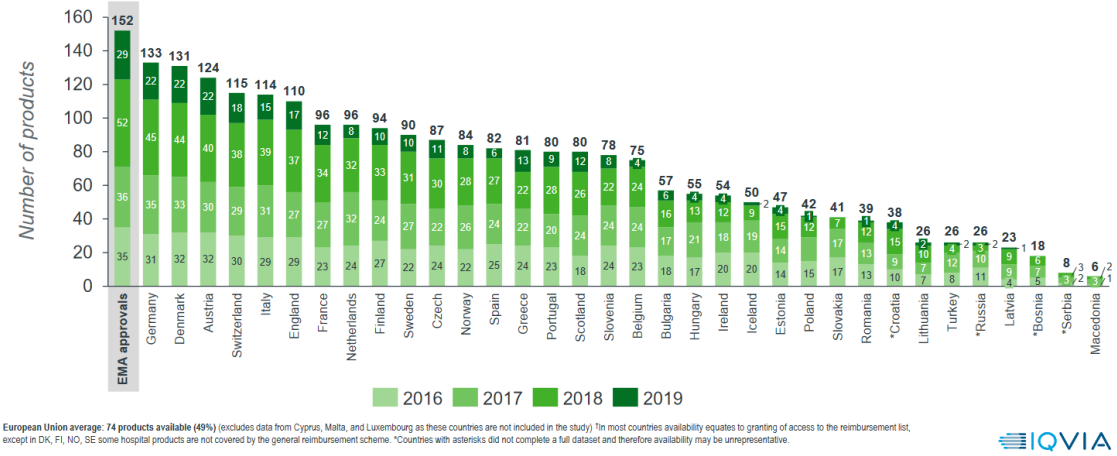



Figure 10: Availability of EU authorised medicines (2016-2019) and their availability in Member States by the end of 2020
Source: IQVIA

Collectively, these studies suggest that expanded access to the centralised procedure has not been an effective measure to improve access, because other factors, mentioned above, are much more relevant in influencing access. Hence, only 40-50% EU markets have access to innovative medicines.

**Medicines shortages** present a major problem for patient care. A recent study[132] considered how the EU legal framework has contributed to preventing and mitigating shortages, whilst assessing how this framework is consistent with and has been complemented by Member States' actions The current framework focuses on marketing authorisation holders notifying supply disruptions[133] and requires them and distributors to ensure appropriate and continued supply of the medicines they are responsible for[134]. Due to a lack of comparable data, it was not possible to asses the implementation and effectiveness of the provisions. Member States have transposed the supply requirement for MAH and distributors in different ways and at different levels of 'intensity', which have not been effective to ensure supply.

The outcome of the public consultation confirms the importance all stakeholders (in particular civil society and healthcare professionals) place on medicines shortages as a key issue impacting on access and ultimately public health. Healthcare professionals stress that the current legislation has not been effective as evidenced by rising shortage notifications. In the targeted survey, civil society, public authorities and health service stakeholders

[130] Newton et al., 2021.
[131] Oncology medicines and orphan medicines both fall within the mandatory scope of the centralised procedure and thus are authorised for marketing in all EU countries simultaneously.
[132] de Jongh et al., 2021
[133] Art. 23a of Directive 2001/83/EC.
[134] Art. 81 of Directive 2001/83/EC.

considered the security of supply of medicines and shortages to be an aspect that the legislation has been least effective in addressing.

Figure 11 presents an overview of the number of medicines shortages reported in the EU annually (total and average per Member State). It shows a strong increase in notifications over the last 10 years, suggesting an increasing disruption for patients and health systems. However, other factors contribute to the increase, e.g. more countries track and report shortages, and/or do so more effectively. Regardless, the increasing trend is clear. The implication is that, while the legislation helped generate more insight into the scale and prevalence of medicine shortages (through introduction of continuity of supply/ marketing notification requirements), it has not been sufficiently able to address their causes and to implement effective actions to prevent, mitigate or alleviate their impact.

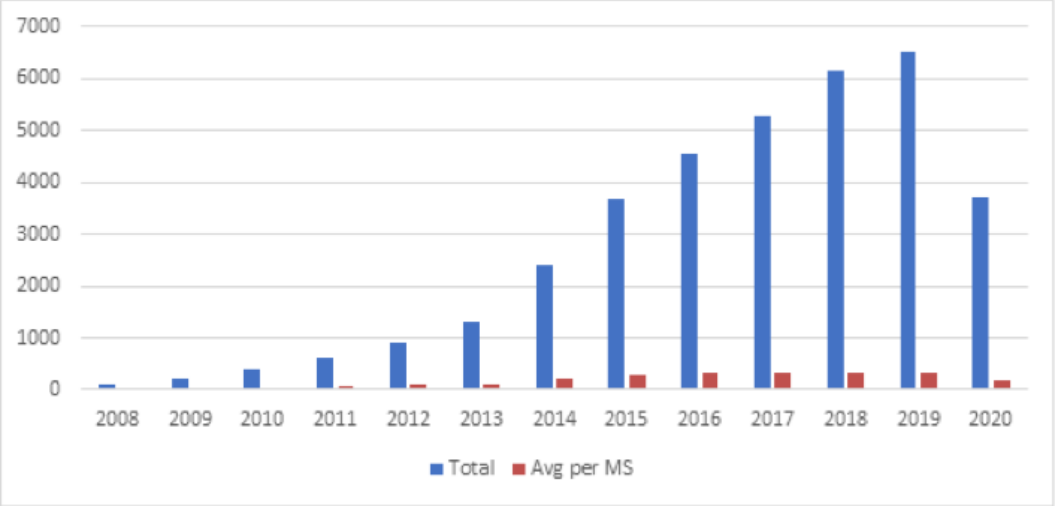
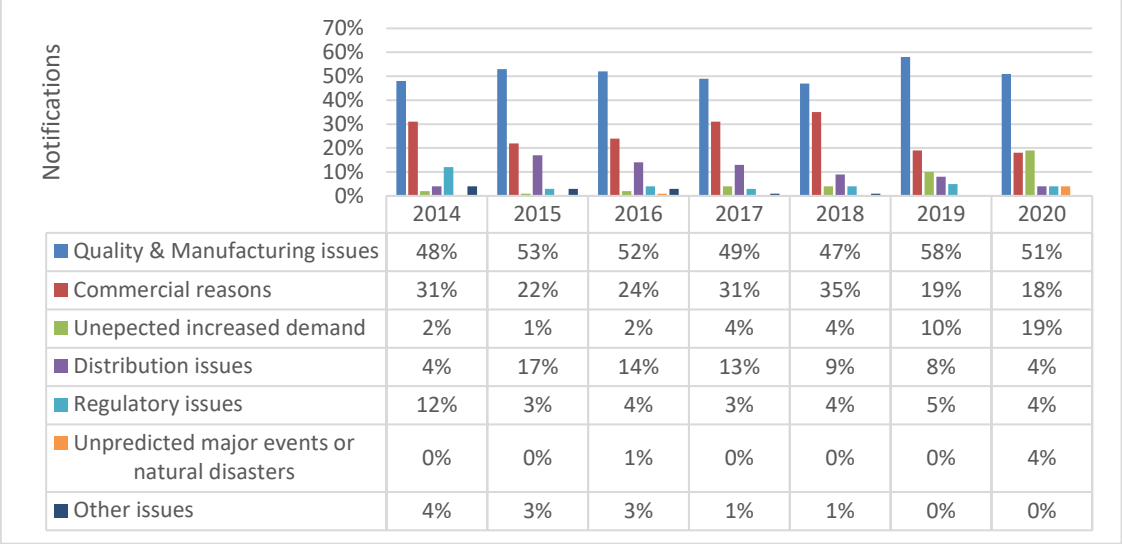



Figure 11: Total number of shortages reported across the EU
Source: Analysis of data from national shortage registries. Technopolis. The average number of countries reporting data on notifications from 2008-2010 is 2; from 2011-2013 is 7; and from 2014-2020 is 15.

The root causes of medicines shortages are divergent[135] (Figure 12). Quality and manufacturing issues, reflecting unforeseen problems with the quality of ingredients or processes that lead to distruptions in supply, recallsare the most common reasons. While the legislation has been successful in increasing the observance of good manufacturing and distribution practices (GMP/GDP) and the more comprehensive scrutiny of manufactured quality, this may have indirectly increased the number of shortages. While commercial issues have in the past been second as the root cause of shortages they have decreased, from around 30% of all causes in 2014 to 18% of the causes in 2020. Similarly, the proportion of notifications citing distribution issues as the root cause of shortages have declined over time. Instead, since 2019, unexpected increased demand became a major cause.

[135]de Jongh et al., 2021




| | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|---|
| Quality & Manufacturing issues | 48% | 53% | 52% | 49% | 47% | 58% | 51% |
| Commercial reasons | 31% | 22% | 24% | 31% | 35% | 19% | 18% |
| Unepected increased demand | 2% | 1% | 2% | 4% | 4% | 10% | 19% |
| Distribution issues | 4% | 17% | 14% | 13% | 9% | 8% | 4% |
| Regulatory issues | 12% | 3% | 4% | 3% | 4% | 5% | 4% |
| Unpredicted major events or natural disasters | 0% | 0% | 1% | 0% | 0% | 0% | 4% |
| Other issues | 4% | 3% | 3% | 1% | 1% | 0% | 0% |

Figure 12: Time trends in reported root causes of shortages (2014-2020)
Source: Analysis of data from national shortage registries. Technopolis

Stakeholders, particularly industry and NCAs, report that generic medicines are particularly at risk of shortages, given the higher relative fragility of their supply chains. Procurement practices have driven down the prices of generics to the extent that these products cannot be manufactured in the EU - profitably and suppliers need to be consolidated, sometimes to one global supplier.

Studies performed by pharmaceutical industry associations suggest that Asian producers of active pharmaceutical ingredients (APIs) hold a strong position in the large volume generic API market. Some of these APIs are no longer produced in the EU[136]. Industry reports that the EU has dependencies upstream in supply chains, for medicine precursors and intermediates[137]. In addition, some technologies, used upstream in the manufacturing chain of medicines, may no longer be available in Europe[138]. However, not every dependency on imports from third countries will automatically lead to a vulnerability that threatens the security of EU supplies. Due to the complexity of pharmaceutical supply chains further analysis of dependencies is necessary to identify specific vulnerabilities. In addition, diversification of supply chains can present important benefits to the EU's open economy and opportunities to strengthen security of supply.

#### *4.1.1.3 Affordability*

In the interest of public health, marketing authorisation decisions on medicinal products are taken on the basis of objective criteria of quality, safety and efficacy, to the exclusion of economic considerations. Decisions on setting of prices for medicines and their inclusion in the scope of national reimbursement schemes are a responsibility of the Member States[139].

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[136] Progenerica Study of 2020 Microsoft PowerPoint - Microsoft PowerPoint - 200929_Final Report_short_v04_en (progenerika.de) and SICOS study on vulnerabilities of supply chains Press-release-SICOS-Leem-Gemme-Etude-PwC_20211027-EN.pdf (cefic.org).
[137] IQVIA for EFCG study IQVIA for EFCG - Executive summary - EFCG (cefic.org); and ECIPE analysis for EFPIA, International EU27 pharmaceutical production, trade, dependencies and vulnerabilities: a factual analysis (efpia.eu).
[138] EU Fine Chemical Commercial KPI – executive summary, IQVIA, December 2020 https://efcg.cefic.org/wp-content/uploads/2021/06/20201211_IQVIA-for-EFCG_Executive-summary.pdf.
[139] Article 4 (3) Directive 2001/83/EC.

The general pharmaceutical legislation does not directly address affordability of medicines. Affordability was not among the objectives of the 2004 revision of the general pharmaceutical legislation. However, in the past years, the costs of medicines for health systems continue to rise impacting patient access.

**Pharmaceutical spending** is the third biggest cost element in healthcare spending, roughly responsible for 1/6 of healthcare spending. Spending in the retail pharmaceutical sector (on prescription medicine and non-prescription medicine but not on medicines consumed in healthcare settings) has remained stable over the last 20 years in EU27, at 17-21%, according to OECD Health statistics, pharmaceutical spending[140]. This is in line with the findings of a recent report that highlights that spending on pharmaceuticals has been growing more slowly than overall health spending in most countries, and below GDP growth[141]. Understanding the growing expenditures in hospital settings is more complex (due to lack and inconsistency of availability data, different tax and supply chain costs, leading to nominal list prices only), however, there are indications that this is driven by high cost speciality medicines[142].

In the consultations, regional public authorities noted that an assessment for better definition of 'innovative medicines' is needed, with **transparency of research and development (R&D) costs**. However, in interviews and in the workshop, industry stakeholders noted that transparency of R&D costs is not feasible as the methodology to calculate them would vary enormously and would contain sensitive information.

**Enabling access to affordable medicines** is among the areas where the legislation has been less effective and more needs to be done according to all stakeholder groups in the targeted survey and the public consultation[143]. The rising costs of medicines and affordability were key concerns for academics, healthcare professionals, public authorities and civil society stakeholders in the interviews[144]; they were open to any measures that could address these issues including incentives and new pricing models. The impact of the new HTA Regulation adopted in 2022 has yet to be seen.

Another angle supporting affordability relates to generic and biosimilar competition. Amongst other things generic/biosimlar entry is influenced by protection periods. The data and market protection provided by the general pharmaceutical legislation – together with patents, SPCs, and protection given to orphan and paediatric medicines – effectively prevent market entry for generic and biosimilar medicines. Several stakeholders perceived the protection periods as complex, suboptimal and referred to fragmentation. While fragmentation of the regulatory protection was phased out by 2016 as a result of the 2004 revision, the SPC system remains fragmented. Furthermore, where the intellectual property rights expire after the regulatory protection periods, access to generic or biosimilar medicines is delayed and affordability negatively impacted.

An analysis of a sample of products in France, Germany, Italy and Spain with protection expiry between 2016-2024 shows that two thirds of the products are protected by

[140] Analytical report, Figure AFF-3, Annex 10.
[141] IQVIA Institute, 2021
[142] Annual average growth in retail and hospital pharmaceutical expenditure, in real terms, 2008-2018. (OECD, 2020).
[143] See Appendix B: Tageted survey overview: Areas where the current legislation has been effective.
[144] Based on stakeholder interviews, 29% of academics (total interviewed = 14), 62.5% of healthcare professionals (total interviewed = 8), 44% public authorities (total interviewed = 48 ) and 75% of civil society representatives (total interviewed = 16).

intellectual property rights (patent and SPC) from generic competition, while one third of the products are protected by data and market protection[145].

The share of generics in total medicinal products sales revenue is modestly increasing in the EU (from 13% to 16%) between 2002-2020. The analysis shows the EU is on a similar trend as other comparator markets (Japan and USA). Competition from these products is expected to lower price levels and increase affordability of medicines[146]. An analysis of top selling medicine sales data indicates that branded product prices drop on average by one third of the price level prior to generic entry[147]. This is the highest level among comparator countries, and similar to that in Australia and Korea. The discount of the generic medicines (compared to the price level of branded equivalent prior to generic entry) is even larger in the EU and steadily increased since 2007 from 50% to 65%. However, the data also suggests that further efforts can be made - by Member States - to fully exploit the savings generated by generic competition, as there is variability in generic uptake at national level.

Stakeholders interviewed[148] agreed that the legislation has been beneficial for increasing competition in the EU by facilitating generics and biosimilar entry in the market. This has been also enabled by the Bolar exemption which has allowed generics and biosimilars to be brought on the market more quickly. However, according to interviewees, the benefits from the Bolar exemption can vary across MSs because of differences in how the exemption is interpreted and implemented[149].

#### *4.1.1.4 Accommodating innovation*

Developing new medicines is a very capital intensive, high-risk, high-gain business. Profits from new products and a supportive regulatory system with relevant incentives (e.g. intellectual property and regulatory protections) incentivise innovation. **Intellectual property rights**, i.e. patents and **supplementary protection certificates (SPCs)**, are key drivers of innovation, allowing return on R&D investment to be realised.

To take advantage of scientific and technological developments and to better accommodate innovation, the 2004 revision altered EMA's scientific committees to ensure relevant expertise, mandated EMA to provide scientific advice to marketing authorisation applicants and introduced a new pathway for biosimilar medicines.

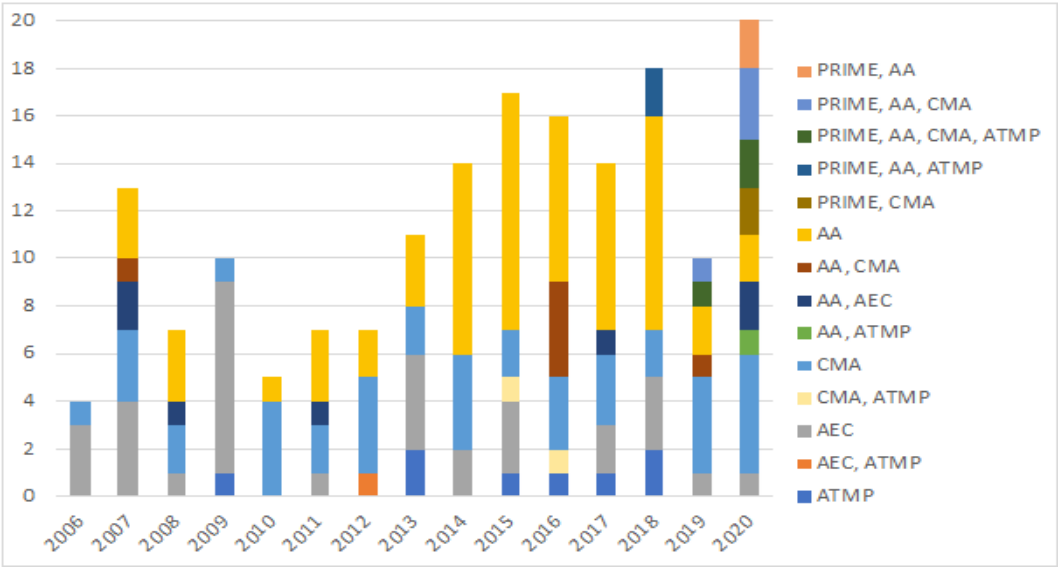
The interviews with stakeholders[150] confirmed that the general pharmaceutical legislation has provided a regulatory system which has facilitated innovation. The centralised procedure, the creation of the EMA, the scientific advice procedures and overall harmonisation of quality and manufacturing rules were cited as some of the main enablers accommodating innovation.

However, new types of medicines, approaches and processes may raise questions about whether they meet the medicinal product scope or definitions or whether they fully fit within the legislation, which can create unintended barriers to innovation, development, production or marketing authorisations. Challenges are particularly evident on advanced therapy

[145] This finding is line with that of the Copenhagen Economics study.
[146] Analytical Report, indicator AFF-6, Annex 10.
[147] Idem.
[148] 43% of academics (total interviewed = 14), 62.5% of healthcare professionals (total interviewed = 8), 29% public authorities (total interviewed = 48), 56% of civil society representatives (total interviewed = 16) and 53% of industry representatives (total interviewed = 60).
[149] CMS, 2007
[150] 36% of academics (total interviewed = 14), 50% of healthcare professionals (total interviewed = 8), 48% public authorities (total interviewed = 48), 94% of civil society representatives (total interviewed = 16) and 52 % of industry representatives (total interviewed = 60).

medicines, combined products (medicines used in combination with medical devices) and other novel technologies and approaches.

The **legislation has proven flexible enough to accommodate developments and innovations** in the pharmaceutical sector in the last two decades. There has been a growth in the number of innovative medicines authorised in the EU (Figure 13), including innovative medicines (e.g. ATMPs) and those addressing UMN (e.g. through PRIME[151] and conditional marketing authorisation (CMA) routes). However, it was the view of several stakeholders in the consultations[152] that the system has **not been fully able to accommodate other emerging technological developments,** as readily. These include, combined products/borderlines with medical devices or substances of human origin, digitalisation and new manufacturing methods. The creation of different committees for assessing ATMPs, orphan and paediatric medicines should facilitate pooling of expertise and thus contribute to ensuring safety and efficacy of such products. However, challenges related to the interaction and coordination between possibly 5 of EMA's scientific committees (CHMP, CAT, PDCO, COMP and PRAC) were identified[153] and different national implementations of the hospital exemption for ATMPs has given rise to public health concerns[154].




**ATMP = Advanced Therapy Medicinal Product; CMA = Conditional Marketing Authorisation; PRIME = Priority Medicine; AA = Accelerated Assessment; AEC = Authorisation under exceptional circumstances.**

Figure 13: The number of innovative medicines authorised by EC, 2006-2020

Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA

The lack of coordination and alignment of the CHMP and COMP processes with different timelines and data requirements was also shown by the **evaluation of the Orphan Regulation**. This may lead to delays in the assessment of the marketing authorisation[155]. Academic stakeholders highlighted that the legislation needs to promote more development of new paediatric indications where it currently focuses on repurposing of authorised adults' medicines for use in children.

[151] Defined in the Glossary.

[152] Based on stakeholder interviews, all healthcare professionals (n = 8), 69% of civil society representatives (total interviewed = 16), 29% of public authorities (total interviewed = 48), 24 % of industry representatives (total interviewed = 66) and one academic (total interviewed = 14).

[153] Orphan evaluation (SWD/2020/0163/final).

[154] Coppens et al, 2020

[155] Idem.

**Scientific and technology developments in the pharmaceutical sector** have disrupted the traditional model in which (most) activities are carried out by a single pharmaceutical company. These activities concern R&D, clinical development, manufacturing and marketing. The value chain of the pharmaceutical industry is now much more divided in tasks and specialisation, with academic institutions conducting basic research and usually small businesses taking scientific discoveries into product development. In the clinical development stage, costs sharply increase across the different phases of clinical trials, and usually this is the moment when small companies either licence out their product, partner with, or are acquired by large pharmaceutical companies. Large and well capitalised global companies have the means to conduct and finance late-stage clinical trials, experience in regulatory procedures and capacity to place a product on the market. A high concentration of large pharmaceutical companies is observed among the market authorisation holders of innovative products[156], but this can hide the original innovator. The 2004 revision aimed to encourage firms to increase their development efforts with harmonisation of the period of regulatory protection across the whole of the EU (8+2+1 system). This was expected to lead to increased R&D investment, more clinical trials in the EU and an expansion in the medicines pipeline. These three expectations have been met to some extent at least[157]. However, these effects cannot be solely attributed solely to the legislation or its revision.

While the legislation has been overall flexible to accommodate innovation, a broad range of stakeholders were of the opinion that the legislation has not been successful in increasing the **EU's regulatory attractiveness** in specific areas. These were related to a lack of adequate incentives for innovation by SMEs, academic/industry collaborations, innovation to address areas of unmet medical needs, biosimilar innovation, and antimicrobial innovation. These challenges are underpinned by several reasons which include complexity of disease pathologies, knowledge gaps in molecular and physiological elements of diseases, market failure, and high risk R&D. Prioritisation seems needed to balance investment in the development of highly innovative medicines to address unmet medical needs and investment in incremental innovation (i.e. medicines similar to pre-existing medicines). There is currently no distinction in regulatory incentives between different types of innovation. While out of scope of the general pharmaceutical legislation, there was also a broad consensus that health technology assessments (HTA) and pricing and reimbursement decisions are main drivers of innovation as these represent the return on investment into R&D.

Industry stakeholders[158] noted that the regulatory protection brought by the 2004 revision had improved the attractiveness of the EU's regulatory system globally. An international comparative legal analysis[159] confirmed the continuing relative advantage of the innovation incentives within the EU system as compared with those in operation in selected other regions, as did the international review reported by Copenhagen Economics (2018)[160]. Several stakeholders from patients' groups and academia[161] remarked on what they considered to be the overly generous provisions available within the EU, arguing it has favoured innovation over access. These stakeholder groups recommended the Commission to review the balance between innovation and access in the related Impact Assessment,

[156] European Medicines Agency, 2021a.
[157] Analytical report, indicators RI-8 and IEC-6, Annex 10.
[158] 167 out of 173 industry respondents open public consultation considered the current data and market protection period the most important incentives for innovation.
[159] Technopolis study 2022.
[160] Copenhagen Economics, 2018
[161] Views of nine civil society representatives (out of the sixteen interviewed) and of three academics (out of the fourteen interviewed.

suggesting there is scope to reduce innovation incentives, without damaging Europe's attractiveness globally, while also strengthening the rewards / obligations around access and affordability.

All stakeholder groups concurred that digitisation and emerging science and technology developments have not been adequately integrated in the current regulatory system. The majority of stakeholders see the need for improvement in the coherence of the general pharmaceutical legislation with the **EU digital agenda.** In particular, industry deems little coherence and public authorities medium[162]. There is a high level of fragmentation, lack of interoperability across the various databases and IT systems, lack of re-use of data for public interest - which is a general issue in the health sector. The general pharmaceutical legislation has no specific provisions supporting or facilitating the digitisation of the pharmaceutical sector and on certain aspects the lack of consideration for digital tools may have hindered its objectives with regard to innovation and reduction of administrative burden. As such, the general pharmaceutical legislation is not well aligned with the EU priority of "A Europe fit for the digital age,"[163] which negatively affects access to public information and transparency.

Most stakeholders[164] agreed that the legislation and related guidelines do not provide enough clarity for companies and national regulators when it comes to innovative combined products (i.e. medical devices that also contain medicines), use of real-world evidence for clinical trials and medicinal products consisting of or containing GMOs.

Similarly, radiopharmaceuticals have been cited during the consultation activities[165] as a key area where the legislation has not achieved a positive result in terms of facilitating innovation, with the lack of clarity in the regulatory framework for hospital preparations and lack of incentives for R&D in this area as main causes.

The 2004 revision introduced several new procedures to encourage pharmaceutical companies to pursue innovative products relevant to unmet medical needs with a strong public health benefit, including the conditional marketing authorisation (CMA).

However, the legislation has not fully managed to promote innovation in certain **areas of unmet medical need such as AMR**. AMR was not among the objectives of the previous revision of the pharmaceutical legislation and has become an issue of greater public health concern[166]. Bacteria and other microorganisms have become increasingly resistant to antimicrobial medicines, thus increasing mortality[167].The last entirely original class of antibiotic was discovered in the late 1980s[168]. Declining private investment, lack of innovation in the development of new antimicrobials, scientific challenges in finding new compounds, lack of profitability of antimicrobials are among the causes leading to fewer

[162] Academia considers the coherence high, though a reservation should be made for very few responses from academia in this regard.
[163] https://ec.europa.eu/info/strategy/priorities-2019-2024/europe-fit-digital-age_en.
[164] See Appendix B: Targeted survey overview: areas where the current legislation has been effective (survey analysis). Low score means that stakeholders ranked these topics, on average, below three (very small = 1, small = 2, moderate = 3).
[165] Based on the survey replies, views shared by 22 healthcare professionals out of the 77 respondents to the public consultation representing health services.
[166] https://www.who.int/news/item/17-01-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections
[167] Thompson, Tosin. "The staggering death toll of drug-resistant bacteria." Nature (2022).
[168] Plackett, Benjamin. "Why big pharma has abandoned antibiotics." Nature 586.7830 (2020): S50-S50.

new antibiotics reaching the market[169].Contrary to the veterinary medicines legislation, the general pharmaceutical legislation does not include specific provisions targeting AMR, based on considerations in the **EU Strategy on Antimicrobial Resistance**[170]. It currently lacks provisions to restrict and optimise use of antimicrobials and to promote development and the authorisation of new classes of antimicrobials.

Another objective of the legislation was to **attract R&D to the EU**. However, many contextual factors affect such anchoring within the EU. These include R&D capacity, market size, availability of public and private funding, tax system and incentives. While the growth in the pharmaceutical sector in the EU (as well as globally) has led to an increase in total R&D expenditure, doubling since 2000 to more than €40bn in 2019[171], it cannot be attributed to the implementation of the legislation. R&D investment in the EU has remained much lower than that in the US (€74 billion in 2019).

Funding instruments at EU level have worked synergistically with the general pharmaceutical legislation and have contributed to promote medical innovation and attract R&D to Europe. **Horizon Europe** (2021-2027)[172] is a key funding programme for EU research and innovation with dedicated instruments supporting basic research, EU-wide research collaboration and providing grants and investments to small innovative companies. The **Innovative Health Initiative** (IHI)[173] is a European public-private partnership between the EU, the pharmaceutical sectors and the life science industry (biopharmaceutial, biotechnology and medical technology sectors, incl. companies in the digital area). It co-funded by Horizon Europe and the health industry. IHI is based on an integrated, cross-sector approach between academia and industry to advance and accelerate medicine development. The partnership and its predecessor, the Innovative Medicines Initiative, can involve the participation of regulatory bodies, facilitating mutual learning.

The increase in R&D expenditure and introduction of revised procedures (e.g. PRIME, CMA) has led to an increase in the number of innovative medicines approved with a consistent rise year-on-year from 2012 onwards (Figure 13).

Still, despite a large amount of R&D in Europe concentrated in universities and public research organisations, translation of academic research and innovation to marketable medicines is suboptimal. Many academics work on developing cell and gene therapies for cancers and certain genetic diseases. However, academics do not necessarily have the required regulatory knowledge and capacity, are not very experienced with product development and have limited production capacity[174]. Moreover, sometimes guidelines and other regulatory standards are not available to support novel developments. Lastly, high-risk investments required for clinical trials are not always accessible. Collaborations between academics and industry can therefore provide an opportunity to advance research and bring medicines to market.

The number of applications marketing authorisation overall has increased across therapeutic areas (Figure 14). Since 2005, most therapeutic areas show a sustained increase in number

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169 https://www.efpia.eu/about-medicines/development-of-medicines/antimicrobial-resistance-amr/# and https://www.reactgroup.org/news-and-views/news-and-opinions/year-2021/the-world-needs-new-antibiotics-so-why-arent-they-developed/

170 EU One Health Action Plan against AMR (June 2017), https://ec.europa.eu/health/system/files/2020-01/amr_2017_action-plan_0.pdf.

171 Analytical report, indiator RI-8, Annex 10.

172 Horizon Europe | European Commission (europa.eu).

173 Innovative Health Initiative | IHI Innovative Health Initiative (europa.eu).

174 KWF, 2021

of authorised medicines following the expansion in the scope of the CP. A proportionately larger expansion (467%) in the number of authorisations of cancer medicines (antineoplastics) and immunomodulating agents, compared with the growth in all other therapeutic areas, likely reflecting the expansion in investments in oncology and ATMPs.

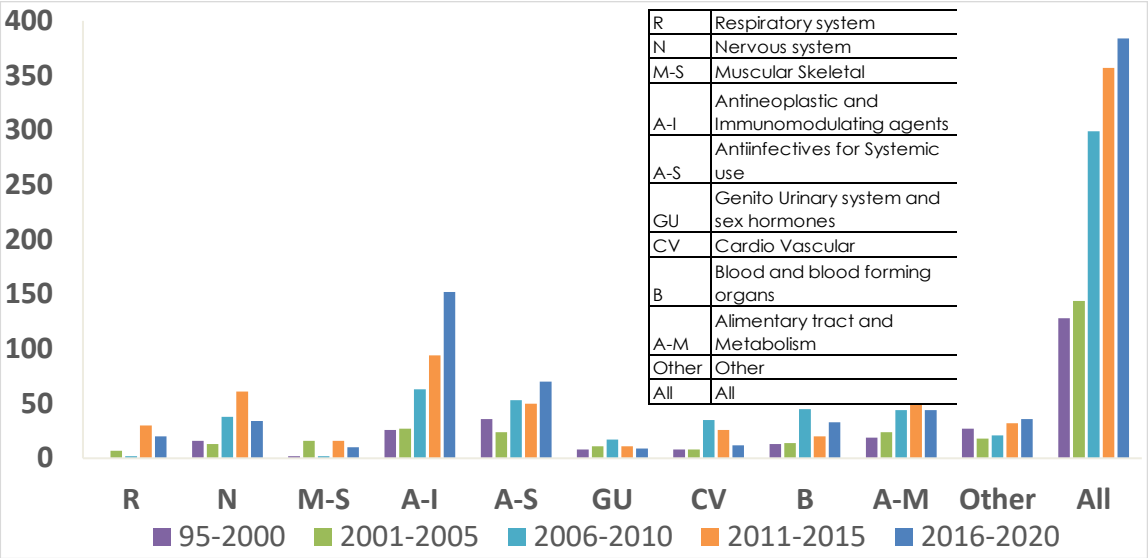


Figure 14: Number of EC authorised medicinal products by anatomic / therapeutic classification

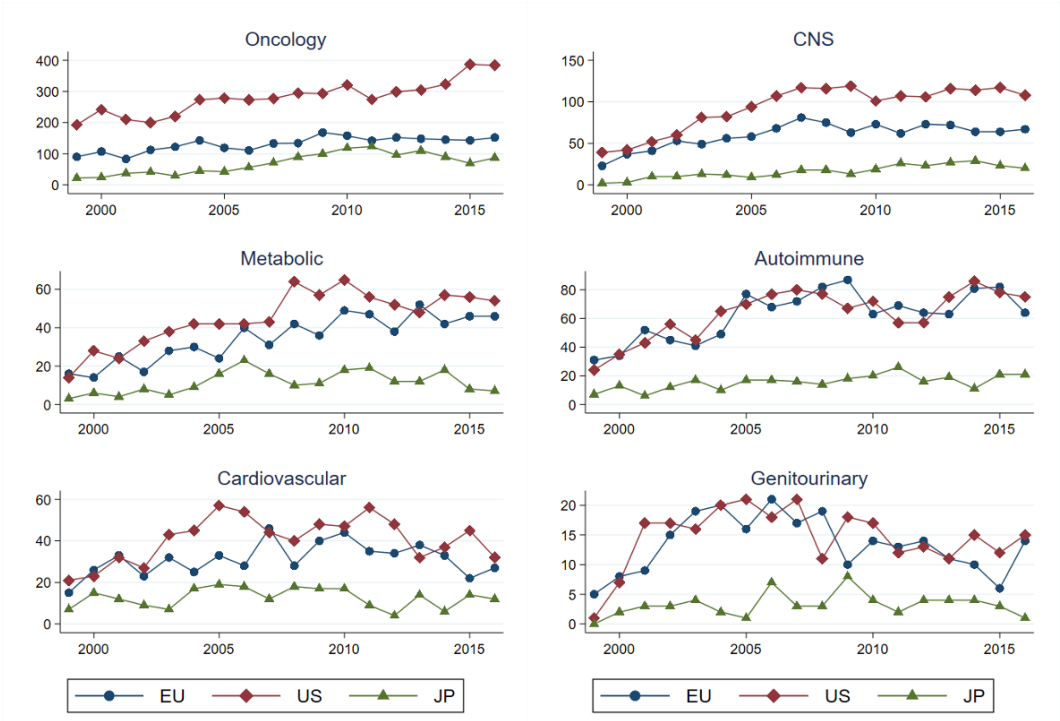


Figure 15: Trends in the number of new candidate medicinal products (pipeline) per year, by therapeutic area
*Source: Informa Pharmaproducts and FDA databases*

The number of new candidate medicinal products has increased steadily over time in all therapeutic areas, perhaps with the exception of genito-urinary medicines (Figure 15). The trends are broadly consistent across the EU, US and Japan, suggesting that the EU market functions in line with other international regions despite the different governance structures. However, there are no evident discontinuities in the EU trend data around the timing of the implementation of the 2004 revision. This suggests the legislation has not boosted

incentives substantially in the EU, nor has it hampered industry ambitions and competitiveness.

The general pharmaceutical legislation has few provisions on **digitisation**[175]. Though not a legal requirement, most applications under the CP are submitted electronically and some NCAs accept/require electronic information/applications[176]. Still, industry stakeholders find that digitisation is not adequately accommodated; while public authorities, academia and civil society have a more positive view. Specific suggestions from position papers shared in the public consultation by medical devices industry respondents also included the creation of standards for clinical trials e-signatures and more digitisation to assist medication management at hospitals. Real world evidence[177] and big data have not been used to their full potential, neither artificial intelligence and machine learning, though initiatives are ongoing, namely the proposed **European Health Data Space**[178].

While the **General Data Protection Regulation (GDPR) and EU Data Protection Regulation** allow the (further) processing of sensitive personal data for scientific purposes or for reasons of public interest in the area of public health, industry and public health authorities found nevertheless the coherence moderate with the general pharmaceutical legislation. In the targeted survey, 26% of industry respondents assessed it as "slightly" coherent while 24% of public authorities respondents rated it as "moderately" coherent. There is uncertainty on the extent to which private companies and universities can further process sensitive personal data for scientific purposes[179] and the application of the GDPR varies between Member States[180].

*4.1.1.5 Ensure competitive functioning of the single market*

The intervention reduced the administrative burden for generic medicines and the introduction of the Bolar exemption was expected to speed up market entry of generic medicines, while the other measures of this strand aimed to reduce the costs for generic medicines, improving their access. These measures were also expected to further harmonise the marketing authorisation procedure and reduce market barriers, ensuring the **competitive functioning of the single market**.

The market for generic and biosimilar medicines has increased in the evaluation period from 13% to 16% in terms of sales revenue and from 25% to 40% in sales volume[181].The total

[175] E.g requirement for marketing authorisation holders and Member States to electronically submit information on suspected adverse reactions to the EU database on adverse reactions (Eudravigilance).

[176] Procedural guidance on eSubmissions can be found in the Heads of Medicines Agencies and EMA websites: https://www.hma.eu/human-medicines/cmdh/procedural-guidance/esubmissions.html and https://esubmission.ema.europa.eu/index.htm.

[177] Flynn, Robert, et al. "Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?." Clinical Pharmacology & Therapeutics 111.1 (2022): 90-97.

[178] COM(2022) 197 final EUR-Lex - 52022PC0197 - EN - EUR-Lex (europa.eu).

[179] Dept for Digital, Culture, Media and Sport, Data a New Direction (2021), available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1022315/Data_Reform_Consultation_Document__Accessible_.pdf.

[180] NIH, Implications of GDPR for US-EU Cooperation in Biomedical Science: Observations from the US National Institutes of Health (2019). Available at: http://www.iscintelligence.com/archivos_subidos/robert_eiss_gdpr_us-eu_cooperation_in_biomedical_science_isc_gdpr_seminar_19_nov_2019.pdf.

[181] Section on access and indicator AFF-4 of Analytical report.

European biosimilar market has reached €8.8 billion in 2021[182] while the generics market was valued at €67 billion for 2021[183].

The vast majority of biosimilar medicines fall within the mandatory scope of the centralised procedure. The EU has been an early adopter of biosimilar medicines and delineated an authorisation pathway (for biosimilars) much before any other country. The biosimilar pathway is also a success according to industry, increases competition with the originator and facilitates access (of biosimilar medcines) for patients.

Generic medicines dominate the MRP and DCP (around 65% of procedures). Since 2005, between 954 and 1152 procedures were finalised every year; in 2020 around 1 600 generic products were authorised across the EU[184].

Inquiries into the **competition between originator and generic/biosimilar medicines** show that originator undertakings sometimes use various practices aiming at preventing or delaying generic entry (e.g. patent filing strategies, patent disputes and oppositions, settlement agreements with generic companies, interventions before competent authorities and life cycle strategies for follow-on products)[185]. These practices are not as such illegitimate, but in specific cases they attract the scrutiny of competition authorities[186]. While there is agreement across the various stakeholder groups – in the targeted survey and in interviews – that competition is suboptimal, many stakeholders[187] agreed that the legislation has been beneficial for increasing competition in the EU pharmaceutical sector by facilitating the market entry of generic and biosimilar medicines, particularly through the Bolar exemption.

In terms of coherence, the general pharmaceutical legislation, which seeks to safeguard public health, is in line with **EU competition legislation,** whose primary objective is protecting consumer welfare. For example, Articles 101 and 102 TFEU facilitate competition based on price (allocative efficiency). They prohibit originators from abusing dominant positions (acquired largely from exclusivity rights) to impede the subsequent entry of generic or biosimilar medicines. Merger controls (and to a lesser extent Articles 101 and 102 TFEU) also provide scope for protecting competition based on innovation (dynamic efficiency).

*The EU's leading role on biosimilars*

Biosimilar medicines have since 2005 an abbreviated registration process complemented by guidelines. Between 2006 and 2021, 84 biosimilar medicines were authorised in the EU[188]. The EU accounted for around 70% of the world's biosimilar medicine authorisations in the 5-year period 2006-2010 and in 2016-2020, still accounted for the largest share of authorisations (30%)[189]. In

[182] Troein et al., 2021
[183] Market Data Forecast, 2022
[184] MRFG and CMDh statistics: No Slide Title (hma.eu), CMDh statistics (hma.eu).
[185] Final Report, Pharmaceutical sector inquiry, European Commission, Competition DG available at: https://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf, COM(2019) 17 final: https://ec.europa.eu/competition/sectors/pharmaceuticals/report2019/report_en.pdf.
[186] See e.g. Commission Decision of 15 June 2005 in case COMP/AT.37507 – Generics/AstraZeneca, Commission Decision of 19 June 2013 in case COMP/AT.39226 – *Lundbeck*, Commission Decision of 9 July 2014 in case COMP/AT.39612 – *Servier*, Commission Decision of 10 December 2013 in case COMP/AT.39685 – *Fentanyl*.
[187] Based on stakeholder interviews, 62,5% of healthcare professionals (total interviewed = 8), 56% of civil society representatives (total interviewed = 16), 29% of public authorities (total interviewed = 48), 53% of industry representatives (total interviewed = 66) and 43% of academics (total interviewed = 14).
[188] GaBI, 2022
[189] Troein et al., 2021

comparison, the FDA only approved its first biosimilar medicine in 2015, and has since granted 29 approvals for biosimilar medicines with only 18 having been launched on the US market[190].

However, uptake (and access) of biosimilar medicines is not uniform across Member States. On a per capita basis, central and eastern European markets lag behind western European countries[191]. Uptake is affected by factors such as historic usage of protected brands, lack of clarity on the scientific foundation for interchangeability of biosimilars with their originators, national policies on interchangeability and lack of confidence in biosimilar medicines among healthcare professionals and patients[192]. There may be additional costs for biosimilar medicine manufacturers to develop the same relationships with prescribers, key opinion leaders and patients as originators (to encourage prescribing), and for post-launch studies to assuage healthcare professionals' concerns as regards comparability of the biosimilar medicine and the originator[193]. These factors may also influence the uptake of biosimilar medicines.

The EC has actively promoted biosimilar medicines' uptake through its Project Group on Market Access and Uptake of Biosimilars consisting of Member States, EEA countries' representatives, and other stakeholders such as patient organisations, healthcare professionals and experts. In addition, Member States have provided targets and incentives for biosimilar medicines' uptake, e.g. France has set a target of 80% biosimilar penetration by 2022[194]. About a dozen countries in Europe, including Germany, France and the UK, offer incentives to prescribe biosimilar medicines[195].

Biosimilar entry creates competition, broadening patients' access to advanced treatments at more affordable prices and alleviating healthcare costs. In Germany, the waiting time for patients with rheumatoid arthritis to be treated with a biologic has been reduced from 7.4 years to 0.3 years after the introduction of biosimilar medicines[196]. Biosimilar medicines are typically cheaper by 20% compared to originator products[197]. One study estimated the impact of biosimilar entry in terms of healthcare systems savings between 2007 and 2020 for eight EU countries (France, Germany, Italy, Poland, Romania, Spain, Sweden, and the UK), ranging from €11.8 billion to €33.4 billion[198]. Savings from biosimilar medicines are smaller compared to generic medicines at least in part because of the higher development and manufacturing costs as well as greater regulatory requirements to obtain marketing authorisation, which create barriers to market entry for competitors[199].

Generally, only one Union marketing authorisation is granted to an applicant for a specific medicinal product, however, the applicant/holder can obtain a **duplicate Union authorisation** for the same medicinal product *where there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients, or co-marketing reasons*[200]. MAHs have been making use of this exception to obtain a duplicate authorisation for the first own generic/biosimilar product on the basis that its inaugural launch into the market can improve availability because it

[190] GaBI, 2021
[191] Troein et al., 2021
[192] Druedahl et al., 2022
[193] Mestre-Ferrandiz et al., 2016
[194] Haustein et al., 2012
[195] Arad et al., Realizing the benefits of biosimilars: what the U.S. can learn from Europe, Duke MargolisCenter for Health Policy, April 2021.
[196] Guntern, 2021
[197] Chen et al., 2021
[198] Haustein et al., 2012
[199] Ferrario et al., 2020
[200] European Commission, 2019

usually increases accessibility. Still, this behaviour may have hindered competition from generic or biosimilar medicines.

### *4.1.2 Efficiency*

#### *4.1.2.1 Types of costs and benefits*

The revision addresses several aspects in the development, production, distribution and use of medicines, some of which have anyway occurred (at least partly). The situation before and after 2004 revision is compared, taking into account general market developments, whenever appropriate. The evidence for the size of costs and benefits has been gathered from various sources: interviews, surveys and data analysis.

The 2004 revision were not accompanied by a comprehensive *ex ante* impact assessment, and as such the evaluation has sought to define the main types of direct and indirect costs and benefits, retrospectively. The following table, lists the main types of costs or benefits identified for each of the main stakeholder groups:

| Actors | Type of cost / benefit | Direct impacts |
|---|---|---|
| Innovator industry | Pre-marketing costs (e.g. R&D) | A mixture of cost savings (reflecting improved harmonisation and centralisation) and cost increases |
| | Post marketing costs | Cost increases associated with the strengthening of the EU-wide pharmacovigilance system |
| | Market access benefits | Earlier access |
| | Market protection benefits | Higher protection level |
| Generic industry | Market access benefits | Simplified multi-country access, earlier biosimilar authorisation |
| | Market protection benefits | Delayed entry but more innovation creates more business opportunities for generic companies |
| Wholesalers | Distribution costs | Harmonisation facilitating cross-border trade resulting in lower costs |
| EMA | Regulatory costs | Expansion in scope of activities creating a higher volume of work, resulting in higher operating costs |
| NCAs | Regulatory costs | Generally higher costs, some savings due to fewer authorisation procedures nationally |
| Health systems: healthcare providers, patients, carers, citizens. | Quality of MPs (benefits) | Measures generally result in higher quality / efficacy of products |
| | Availability of MPs (benefits) | National health systems and patients have access to a larger number of innovative medicines |
| | Costs of MPs | Some products have longer market protection, which may result in higher prices |
| | Information on MPs (benefits) | More and better information available, more informed decision making by reimbursement agencies and prescribers |
| | Environmental impact of MPs (benefits) | Improved transparency around the environmental risks of specific products / APIs, facilitating improved environmental management |

Table 2: Cost/benefit and potential direct impacts, by stakeholder group

Costs and benefits were identified and measured comparing the situation post 2004 revision with the pre 2004 situation, taking into account general market developments, when appropriate. Given the long period of time since the implementation of the 2004 revision, most stakeholders were unable to provide quantitative estimates of the costs and benefits associated with those changes. Therefore, the cost-benefit analysis relied on quantitative

estimates provided by a small number of organisations that directly experienced those changes and on limited historical data. This limited number of observations was augmented by several studies and presentations. However, data are scarce and only large estimated ranges could be identified.

| Stakeholders | Cost | Benefits |
|---|---|---|
| Citizens and consumers, health systems | Increased pharma expenditure due to strengthened exclusivities | 25-30 new innovative medicines, in total; producing 170,000-210,000 QALYs in total; which amounts to €4.8bn-€17.2bn in monetised benefits |
| Businesses | Additional investments in IT systems to cope with expanded data requirements on safety and manufacturing – 250M€<br><br>Higher costs due to data requirements for new and current marketing authorisations; additional costs for legal departments<br><br>€50m-€100m p.a., €750m-€1,500m in total | Cost savings due to the harmonisation and streamlining of procedures associated with the introduction of the DCP and the substantial reduction in the use of the mutual recognition procedure<br><br>CP: €4.8m p.a., DCP: €36m p.a.<br><br>Eliminating the need for further (after the first) renewals at 5-yearly cycles €23m p.a. |
| EMA | Higher staff and evaluation costs for EMA €2.5m-€3.1m p.a | |
| NCAs | higher inspection costs for national competent authorities €8m-€25m p.a | Cost savings for national competent authorities due to streamlining / harmonisation of national authorisation procedures (switch to DCP away from MRP) €20m-€40m pa |

Table 3: Summary of estimated costs and benefits

#### *4.1.2.2 Stakeholder impact*

***Citizens and health care systems***

Citizens expect continued patient access to new and essential medicines. The authorisation of products is an inherenet element to meet this objective, but not sufficient as the authoristaion is an intermediate step before real patient access happens. The expansion of the scope of the centralised procedure and the extension of the regulatory protection period have contributed to an increase in the number of marketing authorisations of innovative medicines in Europe. The number of newly authorised medicines increased in the period following the introduction of the revisions, with the number of applications and authorisations almost doubling in the next 10 years - from around 35 in 2005 to around 70 in 2015[201]. The same has happened in respect to the number of medicines with new active substances (NAS) increasing from around 20 peryear to around 30 per year. This growth in the number of medicines and NAS is partly a reflection of changes in the scope of the centralised procedure, but it also reflects wider trends, with increasing demand for new medicines globally and an expansion in R&D investment by pharmaceutical companies across the world[202].

Notwhitstanding the increased number and sales of generics in the EU and in the authorisations of innovative medicines, there is still an issue of access to medicines across EU countries, not all EU citizens have equal access (see Section 4.1.1.1 for more details).

[201] In 2021, EMA recommended 92 medicines for marketing authorisation. Of these, 54 had a new active substance which had never been authorised in the European Union (EU) before. (European Medicines Agency, 2021a).

[202] This OECD report reviews the important role of medicines in health systems, describes recent trends in pharmaceutical expenditure and financing, and summarises the approaches used by OECD countries to determine coverage and pricing. (OCDE, 2019).

There is no simple means by which to estimate the numbers of additional new medicines authorised and launched on the market that are attributable to the 2004 revision, however, there is a clear discontinuity in the EMA trend data with the 3-year averages declining around 10% per year across the period 2001-2005 and then growing around 20% per year from 2006-2009. The US FDA authorisation data exhibits a similar trend, but with a 3-year delay. Within the period, the EU changes from authorising 5-10 fewer products each year to authorising 5-10 more than the FDA. The trend data suggest the US regulatory system had adjusted by 2010 with the FDA once again authorising more innovative medicines annually than the EU. The two regions' 3-year averages mirrored one another through to 2016, after which there was a marked divergence in outputs between the regions with authorisations in the US growing strongly while the EU recorded a period of low or no growth in product authorisations. From this perspective, the analysis assumed the 2004 revision have led to the authorisation of an additional 25-30 innovative medicines in total across the 4-year window between 2006 and 2009.

Working with this estimate, it was assumed that those 25-30 new medicines will have been approved for sale in the EU and that each will have delivered 10 years of additional benefits to health services and patients. The analysis of IQVIA sales data for the period 2009-2021 calculated an average annual sales income of €22.7m across all innovative medicines and all EU markets. Using this average of sales, the calculated, combined EU sales for these additional products falls in the range €570m-€680m. Based on the number of additional products and EU sales, the estimation is that the 2004 revisions were associated with an additional 170 000-210 000 QALYs[203] across the period. The estimated monetary value of the 2004 revision would fall in the range €4.8bn-€17.2bn.

The **impact of the regulatory data and market protection is quite significant**, with an estimate that 1/3 of all centrally authorised innovative medicines benefit from the 10 or 11 years protection[204]. This is a sizeable reward for innovators, allowing sufficient duration to recover R&D investment and support additional investment in innovation benefiting society as a whole. In the absence of regulatory protection, some products would still have an SPC protection, but less than 10 years. And for half of the products currently benefitting from regulatory protection, there would be no protection at all, offering little to no incentive to invest in R&D, submit a market authorisation application and launch the product on various markets.

On the other hand, this **regulatory protection delays generic/biosimilar entry, and creates an increased expense to public health systems**. Although this is an expected and assumed effect of the regulatory protection that is tolerated to promote innovation, the legislation was designed with targeted features to facilitate entry of generics/biosimilars into the market (i.e. the Bolar exemption and the biosimilars regulatory pathway).

**For national health technology assessment bodies** and **health payers**, the introduction of the CMA proved problematic, with substantial additional costs associated with the subsequent assessment of the relative cost-effectiveness of these newly authorised medicines.

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[203] This is based on a median ICER of €33,000 / QALY which was calculated using a basket of 11 medicines and the ICERs presented in the NICE HTA assessment reports. Using the WHO guidelines on valuing a QALY (1-3 GDP/Capita) http://www.who.int/choice/cost-effectiveness/en/, as recommended in the Better Regulation Toolbox (tool #32), and using an average GDP/capita for the EU of €27,810 (Eurostat Statistics Explained, 2021).

[204] The other 2/3 has a longer protection than 10 or 11 years, thanks to patent and SPC protection, or orphan market exclusivity.

***Businesses***

The 2004 revisions introduced a **harmonised system of regulatory data protection for innovative medicines** (8 years of data protection, with additional 2 years of market protection + possibility of additional 1 year market protection for new indications with significant clinical benefit) that stakeholders[205] viewed positively, with the new arrangements bringing greater clarity, harmonisation and predictability as compared with the previous situation, where there was a variety of different national policies in place.

The baseline situation was defined by the pre-revision Directive 2001/83/EC, which required Member States to grant a period of six years of data exclusivity for most pharmaceuticals from the date of the first market authorisation, and 10 years for biotech and other high-tech medicinal products[206]. The Directive allowed Member States to define a period of ten years for all pharmaceuticals if they considered it was "in the interest of public health." Belgium, France, Germany, Italy, the Netherlands, Sweden, and the United Kingdom did so. The other eight Member States implemented the 6-year period as their default term, using the 10-year period selectively. The 2004 revision turned the 6-year and/or 10-year period into the 8+2 arrangements. These changes became applicable across all 15 Member States and the 13 central and eastern European countries that joined the Union after May 2004. The latter typically had no specified period of data exclusivity, prior to this. While more than half the EU would have seen an enhancement in the standard period of regulatory protection, most innovative medicines – even nationally authorised – would have been granted 10 years protection rather than 6 years.

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The interviews and surveys revealed that adjustment costs for businesses[208] mainly related to the need to invest in upgraded IT systems. Based on the data received in the survey, the estimated one-off adjustment costs are at €250 million[209].

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[205] 167 out of 173 industry respondents open public consultation considered the current data and market protection period the most important incentives for innovation.

[206] Adamini et al., 2009

[207] The other 2/3 has a longer protection than 10 or 11 years, thanks to patent and SPC protection, or orphan market exclusivity.

[208] (one off) adjustment costs relate to the changes that companies had to make in order to provide the information for the additional inspectiongs introduced with the 2004 revision.

[209] Five businesses estimated their one-off costs, which ranged from €25,000 to €15m, or 0.1-1% of annual sales. The median figure was around 0.5%. Applying this 0.5% to the EU pharma industry output in 2005 (c.

Industry also incurred ongoing additional administrative costs associated with several new measures, including, for example, the expansion in the scope of the centralised procedure[210]. The biggest additional costs however related to the post-market authorisation phase, with substantial additional reporting introduced to strengthen pharmacovigilance. Industry respondents were not able to provide specific estimates for these individual elements though. For originators, the additional costs amounted to ca. 5-10% increase in the overall companies' regulatory costs. For the generics industry, the greater detail in the regulatory dossier increased the costs associated with variations to marketing authorisations. The major drivers of the ongoing costs for the distribution industry are related to the need to control, record, and validate all the elements in storage and distribution systems. These ongoing additional costs are estimated at €200m a year or €3bn over 15 years in current prices. Adjusting this for inflation would suggest a total adjustment cost of €2bn-€2.3bn. No significant, quantifiable indirect costs for industry have been identified.

As regards benefits, there were efficiency gains for companies in the guise of faster and more consistent assessment procedures (through the CP) and increased harmonisation of the decentralised procedures. For industry, however, the most significant efficiency gain relates to the withdrawal of the obligation to renew marketing authorisations every five years. The overall estimated amount of savings is around €300m-€375m over the past 15 years.

The abolition of the 5-year renewal of marketing authorisations led to an estimated cost reduction of €23m per year, covering the MAs authorised via the centralised procedure and nationally authorised. This has resulted in an estimated reduction of around 150 renewals of EU marketing authorisations annually over the period, and 1 350 national renewals. The stakeholder consultation confirmed that these changes have benefited the generics industry in particular. This has resulted in a saving of around €6.8m p.a. in fees and staff costs for the 150 renewals of Union marketing authorisations, and around €16.2m for products authorised by Member States, where the dossiers were less complex and renewal fees are lower.

There are also small cost savings for businesses, due to faster approval procedures, through the expansion of the centralised procedure and the harmonisation of decentralised procedures (DCP). Based on the average number of new applications these savings are estimated at €40m per year across the period, with 90% of those savings being realised by the generics industry (c. €36m per year).

The revision of the legislation might have encouraged and rewarded an increase in R&D, through the extension of the regulatory protection period across all Member States, the expansion of scientific advice, the additional data protection for new indications or the introduction of new assessment procedures designed to keep pace with the evolution in medical science. Feedback from stakeholders suggests that these multifaceted changes would likely have been lost in a broader set of market pressures affecting the global research-intensive pharmaceutical industry.

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€150bn according to EFPIA statistics), we arrive at an estimated gross cost of around €750m. There would have been a benefit to companies from implementing these new IT systems, and as such we have assigned a part and not all those costs to the 2004 revision. We have no feedback as to the appropriate fraction, so we have assumed one third, or €250m, as a conservative estimate of the one-off costs for EU industry adjusting to the requirements of the legislation.

[210] The revisions also included changes to the submission documents primarily the introduction of the environmental risk assessment (ERA), and the need to improve the readability of the content of the package leaflet and label, requiring greater detail on manufacturing value chains and sites.

EU statistics[211] broadly mirror the trends in the statistics for the US and other competitor regions, with no evident discontinuities in trends in the years following the implementation of the 2004 revision. The exception is biosimilar medicines, where the EU regulatory system's early response has underpinned a comparative advantage. Data show that the EU accounted for around 70% of the world's biosimilar medicine authorisations from 2006 to 2010. This 5-year period accounted for the largest share of authorisations (30%), albeit India and China have registered stronger growth and have bigger pipelines[212].

In summary, it is estimated that the overall costs of the revisions to the EU pharmaceutical industry amounts to €1bn-€1.3bn. While this is a significant sum viewed in isolation, it amounts to around 0.5% of the EU industry's c. €200bn annual economic output and less than 0.05% of the total output over the 15-year period since 2004[213].

***Public authorities***

***The European Medicines Agency***

The 2004 revision led to a substantial increase in the work of the EMA, related to the expansion in the scope of the centralised authorisation procedure, an intensification of the provision of scientific advice and greater support for a wider range of coordination and development activities with respect to the regulatory network and international cooperation. The Agency's annual expenditure increased from €96m in 2004 to €266m in 2014, reflecting in part the further enlargement of the EU (10 countries joined on 1 May 2004) and the incorporation of these countries' national competent authorities within the EMA structures, and the intensification and transfer of authorisation activities from Member States[214].

The EMA annual budget show steady year-on-year growth across the 10 years to 2014 and beyond[215]. The distribution of activities has remained broadly stable over time, split 35% on staff costs, 25% on buildings and 40% on operations. Operational expenditure (mainly consisting of expenditure for meetings (c. 4%) and evaluations [c. 35%]) for EMA increased from €39m in 2004[216] to €168m in 2020[217], while staff expenditure increased from €32m to €115m in the same period. Both types of expenditure rose much faster than inflation in these years. The increase in real terms was thus around €190m in the period 2004-2020.

This increase may be partly, attributed to the 2004 revision. In the absence of these additional EMA-led procedures, businesses would have continued to make use of national procedures. This means that the expenditure for NCA-led authorisations are lower due to expansion of the centralised procedure. It is assumed that these national savings largely mirror the extra costs for the EMA. There may be economies of scale, however, the amount to which these Member State savings and EU costs differ proved difficult to assess, as the data collection has not resulted in clear indications from stakeholders about either the savings or the costs. Given the intensification of support and coordination that accompanied the transfer of activities from the national regulators to the EMA, it is estimated that around 20-25%, or €40m-€50m, of the real-terms increase in EMA's expenditure is related to the 2004 revision. Given the substantial increase in EMA's costs over time, and the need to

[211] E.g. BERD, medicines pipeline.
[212] Troein et al., 2021
[213] EFPIA & PWC, 2019
[214] Increased activities due to the expansion of scope of the centralised procedure, new specialised frameworks on paediatric medicines and ATMPs, as well as further responsibilities on pharmacovigilance.
[215] European Medicines Agency, n.d.-b
[216] European Medicines Agency, 2005
[217] Samassa, 2021

make assumptions about attributable impacts, an average annual additional cost in the range: €2.5m-€3.1m has been put forward.

***National authorities***

Most NCAs provide resources to the EMA through the release of staff to work within its main committees and working parties, supporting both the assessment of applications and post-authorisation activities (e.g. variations, renewals, translations, etc.). The expansion in the scope of the work of the EMA has resulted in a reduction in activities relating to national authorisations and a switch of the work in support centralised procedures.

Only two NCAs[218] attempted to quantify the changes to their costs due to the 2004 revisions. Several other NCAs reported increases in national costs relating to the expansion of centralised activities in general and in particular the additional enforcement obligations due to the strengthened pharmacovigilance system, however, these stakeholders were not able to quantify those additional costs. Some public authorities and industry representatives[219] are of the view that they are not adequately remunerated for the services provided to the EMA. A revision of the EMA fee framework is currently ongoing and as part of it, NCAs costs are being taken into account to calculate revised, cost based fees and remuneration amounts.

Feedback from stakeholders overall, revealed a positive balance of opinion: the costs of the revisions are judged to have been proportionate to the benefits. The overall positive opinion as to the cost-effectiveness of the legislative changes, looks different across stakeholders. Industry and public authorities are strongly positive on the overall balance of costs and public health benefits, whereas health systems and – in particular – patient groups are slightly negative overall. The latter consider the legislation has been strongly beneficial to industry, with the revision offering valuable incentives that have supported investment in innovative medicines but have increased prices for those products. They are very much less positive about the balance of costs and benefits from the patient's perspective, expressing concerns about affordability, uneven access, unmet medical need, and medicines shortages. For this group, the perceived health impact is relatively small as compared with the (indirect) costs of the 2004 revision and the substantial number of remaining challenges.

#### *4.1.2.3 Simplification and burden reduction*

The preceding paragraphs have detailed three areas of simplification and burden reduction that have been achieved following the implementation of the 2004 revision:

- Cost savings for industry, especially the generics industry, due to the harmonisation and streamlining of procedures associated with the introduction of the DCP and the substantial reduction in the use of the MRP;

- Cost savings for industry, especially the generics industry, due to the switch to – as a general rule – a single renewal of a MA 5 years after the original authorisation, eliminating the need for further renewals at 5-yearly cycles; and

- Cost savings for NCAs due to the streamlining and harmonisation of national authorisation procedures (switch to DCP away from MRP).

[218] Out of twenty-seven survey replies from public authorities.

[219] Views collected from six public authorities in interviews (out of forty-eight) and from three industry represntatives in survey responses (out of one-hundred-thirteen).

Recognising the results achieved, opportunities remain for further reductions of administrative burden, e.g. streamlining of changes to marketing authorisation (variations)[220] which was also mentioned by industry and medicines authorities in stakeholder consultations. The stakeholder consultations revealed widespread concerns across stakeholders from industry and regulators over the under-exploitation of digitisation within the EU medicines regulatory system and the related problem of duplicative activities there may be areas where further harmonisation and digitisation of regulatory processes could deliver savings.

In carrying out the evaluation and the analysis of costs and benefits, elements of the general pharmaceutical legislation that posed an administrative burden or were overly complex have been identified.

The 2004 revision introduced new measures, designed to improve the **effectiveness of the regulatory system**, that brought additional costs for some stakeholder groups. From the consultations and interviews, the following elements were identified as the main sources of additional costs:

- Changes to documentation requirements, including environmental risk assessments;
- Increased transparency and harmonisation of key documents, i.e. publication of European public assessment reports (EPARs), summary of product information (SmPCs) and package leaflet;
- Harmonised application of good manufacturing practice (GMP) for active substances;
- Improved pharmacovigilance by more frequent submission of periodic safety update reports (PSURs); and
- Reinforcement of inspections and increased coordination by introducing new tools (EudraGMDP).

For **industry**, the major administrative burden relates to the additional post-market authorisation procedures that have to be followed to support a more robust pharmacovigilance system.

For **public authorities**, the major additional costs were associated with the expansion in the scope of the centralised procedure and the general intensification of the work of the EMA committees. This however is largely driven by increasing applications. There have also been challenges with the growing numbers of advanced therapy medicines and more complex products that require relatively greater scientific effort to review and often entail assessments and advice from multiple committees.

*4.1.2.4 The costs of partially meeting or not meeting some of the objectives*

The 2004 revision has achieved its objectives to a large extent and as such there have been no substantial costs incurred by any stakeholder groups associated with a failed or partially achieved objective.

There are challenges around access and affordability in the broadest sense, where the 2004 revision did little to improve the effectiveness of the general pharmaceutical legislation in ensuring access to medicines for all. While it was not a specific objective of the previous revisions, there are widespread concerns that medicines shortages have become a bigger

[220] COM(2021)497 final

problem over time. Shortages were seen as a large cost to public health and for day-to-day operations. Pharmacists in particular argued that the legislation lacks flexibility to allow them to handle shortages, which creates inefficiencies. It was estimated by some interviewees that pharmacists spent 6 hours every week to deal with medicine shortages, though the average in Portugal can be as high as one day per week spent on this task[221].

For public authorities and civil society organisations, the high price of medicines arising from what they perceive to be the misuse/abuse of incentives was cited as a cost to healthcare systems, in particular for small countries.

## 4.2 How did the EU intervention make a difference?

Evidence from literature and stakeholder consultations suggest that the objectives could not reasonably be better achieved at national level and that the EU is the appropriate level of intervention. The general pharmaceutical legislation has brought value in ensuring the quality, safety and efficacy of medicines and the functioning of the single market through common principles and regulatory approach, harmonised rules and requirements for the authorisation fo medicines[222].

Higher availability of medicines leads to better access for patients throughout the EU. It enables more competition both among innovative medicines and generic and biosimilar competitors after protection expiry. Patients thus benefit from safe, effective medicines of good quality and from higher availability of medicines across the EU (i.e. more medicines authorised irrespective of the authorisation procedure). The centralised procedure and its expanded scope have increased the availability of innovative medicines, in particular for smaller Member States[223].

Coordinated actions at EU level have benefitted industry as well. The common principles, harmonisation, centralised or coordinated assessments, authorisations and mutual recognition between Member States have led to easier interactions with medicines authorities as well as easier and faster authorisation of medicines. As an example, the decentralised procedure allows authorisation in several Member States through the same procedure without requiring a national marketing authorisation to rely upon saving at least 180 days. Stakeholder groups, including industry and public authorities, highlighted the added value of EU-level coordination and cooperation to develop best practices. The increased cooperation between Member States and between public authorities as well as the successful collaboration of EMA with NCAs has led to the optimisation of resource use for industry and medicines authorities[224].

The EU general pharmaceutical legislation provides a simplified framework for medicines that is easier to navigate in and less costly for industry than 27 national frameworks. Some industry stakeholders, in particular SMEs and generic companies, highlighted the added value of also having the decentralised procedure and mutual recognition procedure in

[221] Technopolis study 2022b.

[222] E.g. documentation requirements and assessment criteria, specific authorisation procedures, harmonised requirements for authorisation of manufacturers and distributors and for manufacturing and distribution, harmonised requirements for active substances and their manufacturing and mutual recognition of inspection outcomes.

[223] Smaller Member States would not have the resources or expertise to assess all the innovative medcines authorised through the centralised procedure.

[224] The pan-EU SPOR (Substance, Product, Organisation and Referential) data management serices was mentioned as an example of a valuable source for promoting exchange of medicinal product information across Member States.

addition to the centralised procedure allowing flexibility to get approval of medicines at national level.

For medicines authorities, the evidence shows there is EU added value in the reduction of duplication of assessments and inspections through mutual recognition and coordinated procedures[225]. The centralised procedure also allows medicines authorities to rely on the collective expertise of the Network, which is particularly important in very specialised or new fields with few available experts[226].

Among stakeholders, there was consensus that the legislation has struck the right balance between action at EU level and national action. In the targeted survey, stakeholders indicated this to be the case from a moderate to large extent (Table 4). Respondents considered that in the absence of coordinated action at EU level, it would have been difficult for Member States to put in place appropriate harmonised measures. Industry stakeholders also highlighted the EU as a global leader in establishing the first science-based regulatory framework for authorisation of high-quality, safe and effective biosimilar medicines.

| Please provide your view on the balance of EU level actions and national actions arising from the legislation. | All stakeholders average score | Individual stakeholders average score | | | | | Agreement between stakeholders |
|---|---|---|---|---|---|---|---|
| | | Industry | Civil Society | Public Authorities | Academic | Health Services | |
| To what extent has the legislation struck the right balance between action at EU level and national level? | 3.3 | 3.2 | 2.8 | 3.37 | 3.7 | 3.3 | High |
| To what extent has the EU intervention in the context of the COVID crisis struck the right balance between action related to the legislation at EU level and national level? | 3.8 | 4.22 | 3.7 | 3.6 | 3.9 | 3.6 | High |
| In the absence of EU level action, to what extent would member states have had the ability to put in place appropriate measures? | 2.4 | 2.3 | 1.75 | 2.7 | 3.0 | 2.5 | High |

Table 4: Overview for the evaluation criterion 'EU added value' summarising the overall average view for all stakeholders, per stakeholder group, and the level of agreement across the stakeholder groups.
*Source: Targeted survey data (Technopolis study, 2022)*

Concerning **proportionality and subsidiarity** it can be argued that EU actions in the pharmaceutical area do no go beyond what is necessary to achieve the objectives of the Treaty[227]. The EU sets a general regulatory framework, allowing Member States to be involved in the assessment of innovative medicines for the EU, to authorise medicines for their own territory – through the non-centralised procedures, to be responsible for manufacturers and distributors based in their own territory and to be involved in the pharmacovigilance of medicines marketed in their territory. At the same time, the general pharmaceutical legislation fully respects the Member States' exclusive competence in the organisationof health services, including pricing and reimbursement of medicines.

During consultation activities (incl. interviews) stakeholders commonly cited the creation of the EMA as one of the biggest achievements of the legislation. Stakeholders regarded **EMA**

[225] OECD (2021), International Regulatory Co-operation, OECD Best Practice Principles for Regulatory Policy, OECD Publishing, Paris, https://doi.org/10.1787/5b28b589-en.
[226] Idem.
[227] Legislation regulating medicines is based on Articles 114 and 168(4)(c) of the Treaty on the Functioning of the European Union (TFEU). As a shared competence with Members States and in line with the principle of subsidiarity, Article 168(4)(c) of the Treaty allows the Union to set measures establishing high standards of quality and safety for medicinal products. The authorisation of medicines is fully harmonised at EU level. EU action takes advantage of the single market (Article 114) to achieve a stronger impact as regards access to safe, effective and affordable medicines, as well as the security of supply across the EU.

**as a key actor in the unification and coordination of the regulatory system across the EU,** which provides a valuable exchange of experience and access to a wide range of scientific and technical expertise that would not be available in one country or region alone. Thus, **the pooling and coordination of scientific resources under a common set of rules and practices** has helped foster a common understanding across Member States of high standards of medicines evaluation and approval and handling of safety concerns consistently. Stakeholders frequently pointed out that since the establishment of EMA, **transparency on how the regulatory system works and decisions are made has greatly improved** – thus building trust and consistency across the EU regulatory system. EMA publications of European public assessment reports (EPARs) and guidance documents were cited as a reason for the increased flow of transparent information. Industry stakeholders highlighted EMA's clear guidance on pre-authorisation and post-authorisation procedures for medicines as particularly valuable for facilitating regulatory processes. Moreover, EPARs have had wider impact in facilitating approval of medicines outside the EU (e.g. Africa, Asia, South America).

### *4.2.1 Added value of the EU intervention in the context of the COVID-19 crisis*

During the COVID-19 crisis, EU action proved to be of particularly high added value. Throughout the consultations conducted, all stakeholders highlighted the right balance between the action at EU and Member States' level (Table 4).

There is consensus that EU level action **enabled quicker and concerted action** compared to what Member States would have been able to achieve independently. Stakeholders commonly cited[228] this was made possible because of **regulatory flexibilities and optimisations** enabling resources, capacities and expertise to be rapidly mobilised across EU. For example, the Commission granted a temporary derogation from certain rules for clinical trials of medicines involving GMOs, in particular the environmental risk assessment[229], amended the variation regulation to facilitate the adaptation of COVID-19 vaccines[230] and allowed labelling flexibilities, remote processes for source data verification, audits and monitoring[231]. These measures helped to accelerate the development and approval of vaccines and to coordinate equitable access to vaccines in all Member States.

The pandemic provided a good example of how the legislation enabled Member States to **work together, learn from each other and coordinate efforts**. For example, public authorities cited multinational work sharing activities such as assessments of COVID-19 vaccines as an EU value add – especially for less experienced Member States.

Stakeholders' feedback, and especially interviewed academic researchers, highlighted that the creation of an an emergency task force at EMA, EU-wide adoption of accelerated assessments and rolling review played an important role in fast approval and access to medicinal products for COVID-19. These **EU-level mechanisms prevented duplication of**

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[228] Based on the Evaluation Workshop and Interviews, 50% of healthcare professionals (n = 8), one civil society representative (total interviewed = 16), 42 % of industry representatives (total interviewed = 60) and 21% of academics (total interviewed = 14).

[229] Regulation (EU) 2020/1043.

[230] Commission Delegated Regulation (EU) 2021/756 of 24 March 2021 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.

[231] Notice to Stakeholders - Questions and Qnswers on regulatory expectations for medicinal products for human use during the covid-19 pandemic, Brussels, 30 September 2021 https://ec.europa.eu/health/system/files/2021-09/guidance_regulatory_covid19_en_0.pdf

**efforts and enabled timely availability of the right expertise**, which particularly benefited smaller Member States[232].

Table 5 shows that EU authorisation of COVID-19 vaccines took place only a few weeks after authorisation in the USA and earlier than in Japan.

| COVID-19 vaccine name | EU (conditional marketing authorisation) | USA (Emergency Use Authorisation) | Japan (Special Approval for Emergency) |
|---|---|---|---|
| Comirnaty | 21/12/2020 | 11/12/2020 | 14/02/2021 |
| Spikevax | 06/01/2021 | 19/12/2020 | 21/05/2021 |
| Vaxzevria | 29/01/2021 | n/a | 21/05/2021 |
| Jcovden | 11/03/2021 | 27/02/2021 | n/a |
| Nuvaxovid | 20/12/2021 | n/a | 18/04/2021 |

Table 5: Comparison of authorisation dates for COVID-19 vaccines in the EU, USA and Japan.
Source: COVID-19 Track Vaccines (COVID19 Vaccine Tracker, n.d.) and EMA (European Medicines Agency, n.d.-c).

Civil society stakeholders mentioned that EMA played a central role in **supporting Member States to communicate the risks and benefits of vaccines** through various activities such as public stakeholder meetings, media engagement activities and issuing regular pandemic safety updates with accompanying visuals to explain regulatory concepts[233]. This helped build public confidence in COVID-19 vaccines and uptake by European citizens.

There was consensus across stakeholders that EU-level cooperation was very important for **quick coordinated action to ensure medicines supply chains continued to function** during the pandemic. Health services highlighted the creation of the EU Executive Steering Group on Shortages of Medicines as an important enabler for the **increased collaboration and data sharing** across Member States to prevent and mitigate supply shortages[234] Furthermore, EU-level guidelines on the optimal and rational supply of medicines to avoid shortages during the COVID-19 outbreak[235] and the reinforcement of EMA's mandate[236] were cited as being valuable to Member States. These guidelines helped promote cooperation between Member States, thus preventing stockpiling and encouraging sharing of essential medicines during the pandemic. Moreover, the guidelines to establish 'green lanes' were seen[237] as instrumental in facilitating the cooperation between Member States to order to prevent shortages across the EU.

[232] For example, industry highlighted the EU added value of leveraging and consolidating scientific expertise across EU to provide rapid interactive scientific advice. This promoted use of best methods and study designs for developing COVID-19 medicinal products. Thus, ensuring the development of high-quality, safe, and effective vaccines for European citizens.
[233] Cavaleri et al., 2021
[234] This steering group, along with other ad hoc structures and processes established during the pandemic, has been codified in Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices, PE/76/2021/REV/1, OJ L 20, 31.1.2022, p. 1
[235] Communication from the Commission Guidelines on the optimal and rational supply of medicines to avoid shortages during the COVID-19 outbreak 2020/C 116 I/01, OJ C, C/116, 08.04.2020, p. 1, CELEX: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020XC0408(03))
[236] Regulation (EU) 2022/123
[237] Based on interviews, views expressed by one civil society representative and one healthcare professional.

### 4.3 Is the intervention still relevant?

The general pharmaceutical legislation has delivered positively on the four main objectives of the 2004 revision, as the analysis shows in section 4.1. Despite the progress made, these objectives remain highly relevant today.

#### *4.3.1 Ensure quality, safety and efficacy of medicines*

The EU has a recognised robust regulatory framework to authorise safe, efficacious medicines of high quality. The framework has responded well to the need to incentivise development of **innovative medicines.** However, it has been less relevant to ensure development and authorisation of medicines addressing unmet medical needs and antimicrobial resistance (see Section 4.1.1.4) [238].

Scientific and technological developments challenge the current framework with new products combining medicines with technologies regulated under other frameworks, e.g. medical devices with articifical intelligence, creating uncertainty about the applicable framework. Another area where the current framework is not adapted to concerns the new platform technologies[239]. Stakeholders from industry, civil society, healthcare professionals and public authorities are therefore calling for adaptations.

Despite the introduction in 2004 of a requirement for environmental risk assessment in the application for marketing authorisation, the environmental impact of medicines continues to be a relevant concern in the EU, as residues of medicines are detected in the environment[240]. According to the public authorities the relevance of the environmental risk assessment is low to moderate in minimising the environmental impacts. The general pharmaceutical legislation cannot stand alone in this respect and the environmental impact has to be addressed also through measures on waste and chemicals.

#### *4.3.2 Enable access to medicines*

While the EU regulatory framework has responded well to the need to make medicines available in the Member States through a robust and flexible authorisation system, the general pharmaceutical legislation has limitations to ensure that authorised medicines are launched in the Member States and thus in ensuring equitable access to all citizens across the EU. Accelerated assessment, conditional marketing authorisation and compassionate use programmes contribute to earlier access to medicines. However, external factors such as national decisions on pricing and reimbursement and market size, are of higher relevance when it comes to access to medicines.

An important aspect in terms of access to medicines and on which political focus[241] has increased in recent years is the **affordability of medicines**. The EU pharmaceutical

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[238] E.g. there are only currently 43 antimicrobials in development and in the evaluation period 25 new antimicrobials have been authorised in the EU, cf. case study 1 on AMR (Technopolis study report 2022).

[239] When a certain process /method is used to manufacture specific individualised treatments, i.e. adjustments to the medicine are made based on the characteristics of the patient or the causing pathogen.

[240] Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee European Union Strategic Approach to Pharmaceuticals in the Environment COM/2019/128 final.

[241] As demonstrated by the Council conclusions on strengthening the balance in the pharmaceutical systems in the European Union and its Member States (OJ C, C/269, 23.07.2016, p. 31, CELEX: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52016XG0723(03)).

legislation has limitations in delivering on affordability of medicines, as its scope is the authorisation of medicines. Factors outside EU competence, such as a Member State's health budget and negotiating power, have greater influence. Still, the legislation impacts on costs of development, authorisation, manufacture, distribution and supervision of medicines as well as on generic and biosimilar competition and hence on the affordability of medicines. As the analysis shows[242], the 2004 revision reduced some administrative costs. However, overall costs for the pharmaceutical industry and for healthcare systems were not reduced, Although the revision has facilitated competition from generic and biosimilar medicines, leading to cheaper medicines.

In the evaluation period, the evidence shows that the number of shortages has increased and there has been an increased reporting of shortages (see Section 4.1.1.2). The current framework was not specifically designed to mitigate or prevent shortages and rather focuses on notifying supply disruptions; it is thus not surprising that the majority of stakeholders rated the relevance of the legislation in maintaining security of supply of medicines as low.

Stakeholders representing civil society, academia, health services and public authorities find access, affordability and shortages among the areas least addressed by the general pharmaceutical legislation; more than half of the respondants in these stakeholder groups found that the legislation is not at all or slightly relevant in ensuring access to affordable medicines and 80% of health service respondents found that the legislation is not at all or slightly relevant in maintaining security of supply of medicines in the EU.

### *4.3.3 Ensure the competitive functioning of the EU internal market*

The general pharmaceutical legislation is relevant to the functioning of the EU internal market. The full harmonisation of authorisation and post-authorisation requirements, including regulatory protection periods, provides a level-playing field for all actors. It provides measures to ensure competition such as the pathways for market authorisation, including for generic, biosimilar and over-the-counter medicines, though the time of competition from generic or biosimilar medicines is also governed by patent and supplementary protection certificates. Importantly, the actual market launch of products depends on businesses decisions and on national pricing and reimbursement schemes.

### *4.3.4 Ensure attractiveness in the global context*

The 2004 revision further ensured a coherent and attractive regulatory system for developing pharmaceuticals in light of scientific and technological developments and the EU enlargement.

The USA has the largest share of the global market for pharmaceuticals, more than three times the size of the EU market, the second largest. A 2021 comparison of six regulatory agencies - US, EU, Japan, Canada, Switzerland, Australia - found that all new active substances (NAS) authorised by the six agencies are first submitted to the FDA (USA) and on average only a few days later to the EU (with the EU being the second choice jurisdiction)[243]. Submissions to the other agencies occurred 63-150 days later on average compared to the US.

[242] See Annex 13.
[243] CIRS, 2021

The **time needed for the assessment of the marketing authorisation application** is another important factor for regulatory attractiveness. Figure 16 presents additional results[244]. Data from 2011 to 2020 shows that the FDA had the shortest median approval time overall (273 days in the first five year period falling to 242 in 2026-2020). In 2020, the median approval time in the EU was 182 days greater than in the US. These results suggest that shorter approval times may result from more NAS going through expedited processes in the US than in the EU.

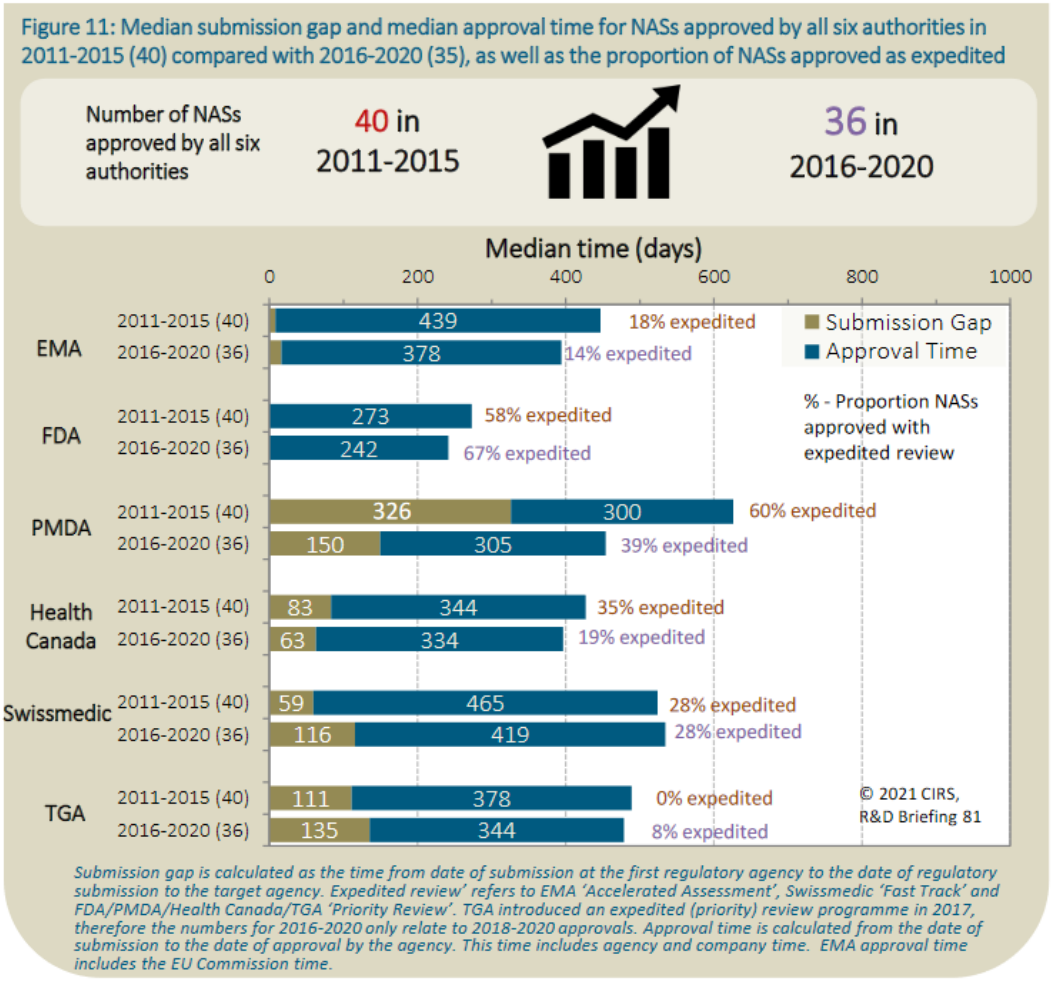


Figure 16**:** New active substance median approval time for six regulatory authorities in 2011-2020

Source: Centre for Innovation in Regulatory Science annual analysis of new active substance approvals by the EMA, FDA, the Japan Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, Swissmedic and the Australian Therapeutic Goods Administration (TGA). Approval TMP by the agency. This time includes agency and company time. EMA approval time includes EC time. N1 = median approval time for products approved in 2020; (N2) = median time from submission to the end of scientific assessment for products approved in 2020.

Several industry participants[245] (including those in the EU) in the stakeholder consultations (interviews and survey) confirmed that the FDA is a preferred jurisdiction for developers. This can be due to differing data requirements for filing, greater opportunity for direct

[244] Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time. N1 = median approval time for products approved in 2020; N2 = median time from submission to the end of scientific assessment for products approved in 2020.

[245] Views of nineteen industry representatives (out of the sixty interviewed and the one hundred and thirteen industry replies to the survey).

interaction on scientific advice and need to interact with multiple EMA committees (e.g. up to five bodies[246] for ATMPs targeting rare diseases). In addition, some lack of coordination between the EMA committees CHMP, PDCO, COMP and CAT, has been identified[247].

It was a common view in the consultations that complexities also arise from the links between the general pharmaceutical legislation and other EU legislation. it can make the EU less attractive for developers, in particular for SMEs and companies that are not familiar with the EU system. For example, public authorities and industry interviewees observed that medical devices, clinical trials and medicines are regulated by different regulations and implemented by different competent authorities, making it difficult to coordinate approaches and navigate the system. In Japan and the USA, separate regulations also apply to these areas, but the same competent authority is in charge of them.

The targeted survey showed a high agreement among industry, public authorities and health service stakeholders that the current legislation has provided an attractive and robust authorisation system for medicines[248]. In particular, the centralised assessment system (CP route) allowing developers to access the EU market on the basis of a single marketing authorisation (MA), increases the EU's attractiveness as as market and location for pharmaceutical development and manufacturing. According to industry interviewees, the EU has also been a global leader in setting up a process for licensing biosimilars, which encourages innovation and filing in the EU compared to other jurisdictions. Besides the market size, there are several factors influencing developers' strategies as to when and where they apply for MA. These include the level of regulatory flexibility or specific local epidemiological situations. In terms of **pharmaceutical R&D**, the EU has a strong second position globally (after the US), especially together with the UK and Switzerland. The EU's biopharmaceutical industry R&D expenditure has continuously grown in the last decades and only US firms spend more in comparison. Between 2005 and 2019, employment in the EU pharmaceutical industry increased from 636 763 in 2005 to 795 000 (estimated), and employment in pharmaceutical R&D increased from 100 636 to 118 000 (estimated)[249].

Figure 17 presents a time-series analysis of medicines approved in the EU either developed in the EU or elsewhere. It suggests that the legislation and the 2004 revision had a positive impact on the relative attractiveness of the EU. A trend analysis on the number of EU approved medicines - novel, new molecular entities; and all products, including biosimilars and other generics - was carried out to understand whether the reformed regulatory environment in the EU following the implementation of the 2004 revisions had provided an advantage to pharmaceutical companies based in the EU as compared to their competitors located elsewhere and looking to sell into Europe.

The analysis[250] did not support the hypothesis that the 2004 revision (expansion of the CP, greater harmonisation of processes and procedures, etc.) might have given advantage and

[246] COMP, CAT, SAWP, CHMP and PRAC.
[247] SWD(2020) 163 final.
[248] See Appendix B: Targeted survey overview - areas where the current legislation has been effective.
[249] EFPIA. (2021). The Pharmaceutical Industry in Figures. www.efpia.eu. For pharmaceutical industry data includes Iceland (since 2017), Turkey (since 2011), Croatia and Lithuania (since 2010), Bulgaria, Estonia and Hungary (since 2009), Czech Republic (since 2008), Cyprus (since 2007), Latvia, Romania & Slovakia (since 2005), Malta, Poland and Slovenia (since 2004); For pharmaceutical R&D Data includes Iceland (since 2017), Greece & Lithuania (since 2013), Bulgaria and Turkey (since 2012), Poland (since 2010), Czech Republic, Estonia and Hungary (since 2009), Romania (since 2005) and Slovenia (since 2004) Croatia, Cyprus, Latvia, Malta, Serbia, Slovakia: data not available.
[250] See Annex 13.

boost the competitiveness for EU industry in comparison with international competitors. However, the analysis (ran for all competing regions) suggests that any additional burden that may have been introduced by the 2004 revision, such as ERAs and improved pharmacovigilance and manufacturing practices, did not disadvantage EU-based pharmaceutical companies when compared with their international competitors, either within the EU or when exporting to other regions. The stakeholder consultations with industry suggest that overall, the various revisions resulted in a net increase total regulatory costs, estimated at 5-10% of regulatory costs. The analysis found a small increase in the average number of annual approvals pre and post implementation for EU origin medicines and medicines that originated with businesses located outside the EU. This does not rule out the possibility that the regulatory environment improved, to the benefit of both EU and non-EU industry.

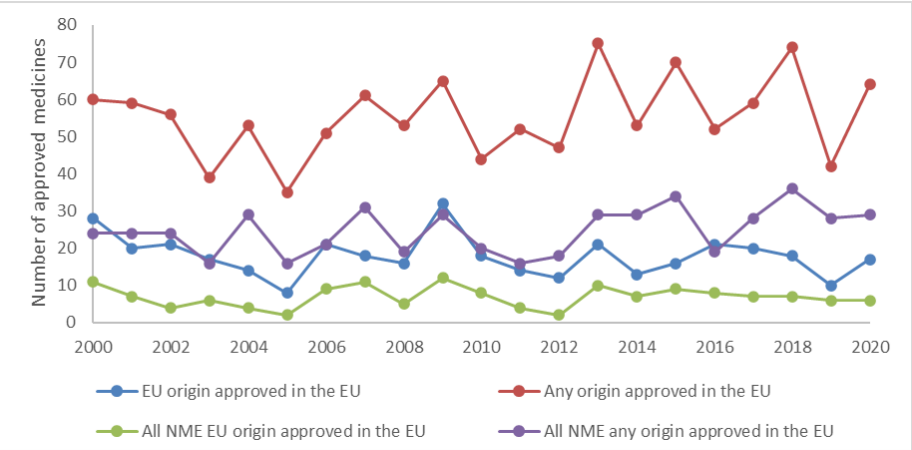


Figure 17: EU-origin medicines and any-origin medicines approved in the EU, split by all medicinal products and new active substances only
Source: Pharmaprojects, 2000-2020, from Pharma Intelligence study team analysis.

The landscape for **pharmaceutical manufacturing** has also changed in last decades. Production of less complex products, such as small chemical molecules and traditional vaccines, has moved to the Asian continent, in particular to China and India for off-patent medicinal products[251]. In the EU, small and large companies have shifted production focus to more complex, biological products (e.g. cell-based products), which require high-tech infrastructure, skilled work force and sophisticated processes. This has led to some companies offering contract manufacturing services as alternatives to in-house manufacturing and consolidated the EU as an important location for high-tech pharmaceutical manufacturers.

The EU has a large trade surplus in pharmaceutical products and is a leading exporter in developed markets. Between 2010 and 2019, there was a 78% increase in the value of EU27 exports of pharmaceutical products to other EU27 countries and third countries[252]. While the overall figures are positive for the EU, there is no obvious effect of the 2004 revision on the EU pharmaceutical industry's trade data. Other factors such as stable political and business environment, availability of skilled workers and existing infrastructure also play a role in EU's competitiveness, while high manufacturing standards and robust enforcement of good manufacturing practices increase the quality of EU produced medicines, which contributes to investments in manufacturing.

[251] Progenerika, 2020
[252] Guinea & Espés, 2021

*The EU's manufacturing capacity for exporting vaccines: COVID-19*

The Comirnaty mRNA vaccine is an example of the EU's manufacturing capacity underpinning a global leading role in exporting high-tech vaccines. BioNTech, the German biotechnology company that developed the technology behind Comirnarty, partnered up with Pfizer, headquartered in the US with production facilities in the EU, to advance and scale-up human clinical testing and manufacturing capacity. By March 2021, after receiving conditional marketing authorisation from the Commission in December 2020[253], the BioNTech/Pfizer collaboration had already produced over 70 million vaccine doses in Germany and Belgium, positioning the EU in the second place in manufacturing of COVID-19 mRNA vaccines, only behind the US.

Through the export authorisation mechanism, the EU became the global leader in vaccines exports in 2021, supplying to the UK, Canada, Mexico, Japan, and many other countries. As of March 2022, the EU had nearly 40% of the global share of vaccine exports, as outlined below.

Table 6 - Total number of vaccine doses exported by producing economy

| Producing economy | Number of doses (million) | Share of world exports | Exports as share of total supply |
|---|---|---|---|
| European Union | 2,276.20 | 39.70% | 64.80% |
| China | 1,869.10 | 32.60% | 32.10% |
| United States of America | 859.1 | 15% | 58.40% |
| Korea, Republic of | 235.8 | 4.10% | 91.10% |
| India | 134.7 | 2.30% | 5.70% |
| Russian Federation | 100.2 | 1.70% | 35.80% |
| South Africa | 91.2 | 1.60% | 87.00% |
| Japan | 67 | 1.20% | 99.80% |
| Other | 105.9 | 1.80% | |

Source: World Trade Organization. WTO-IMF Covid-19 Vaccine Trade Tracker.

Alongside measures to simulate innovation in medicines and to harmonise requirements and coordinate assessments within the EU regulatory system, the **simplification and reduction of administrative burden** linked to the authorisation and monitoring of medicines and companies in the EU contributes to the attractiveness of this framework in a global context. Although authorisations were granted in the EU after those in US, many innovative medicines were authorised[254], regardless of where they were developed. In this respect, the general pharmaceutical legislation remains relevant, though external factors, such as the global development of medicines or market size play an equally important role in the attractiveness of the EU as a medicines market.

[253] Product information for Comirnaty, Union Register of medicinal products for human use https://ec.europa.eu/health/documents/community-register/html/h1528.htm.

[254] Around 60-80 medicines are authorised through the centralised procedure every year, see section 4.1.1.1, Figure 1, though not all of these are innovative; in 2020, positive EMA opinion was given for 39 new active substances, 22 for medicines for children and 3 for ATMPs, cf. EMA Annual Report 2020.

### *4.3.5 Megatrends*

It has almost been 20 years since the last comprehensive revision of the general pharmaceutical legislation and its provisions are not future-proofed. The 14 megatrends identified by the EC Joint Research Centre[255] should be considered in terms of their impacts on the legislation. Out of these 14 megatrends, four trends are likely to strongly shape the future of health in Europe and thus to impact all concerned stakeholders.

*Megatrend 1 and 4: Shifting health challenges, climate change and environmental degradation*. This overarching topic includes trends ranging from the digitalisation of society to demographic changes or environmental challenges. Even though science and technology enable us to live longer, the rise of new diseases due to anthropogenic causes and demographic changes will create a new burden for public health. The COVID-19 crisis best pictures this situation. The impact of changing climate patterns on public health is another example. It is therefore crucial to create a more agile and flexible legislative framework ready to adapt to future challenges and to simultaneously maintain its objectives in terms of research and innovation.

*Megatrend 2: Accelerating technological change and hyperconnectivity.* Increasing technological developments are changing the way we live, but also the nature and speed of new discoveries. In the field of public health, there are new ways to generate health data at individual level to develop more personalised treatments based on patients' needs and genetic profile. Technological changes are fundamental in the area of research and innovation to maintain scientific developments, especially in areas of unmet need. There is also great potential in connecting datasets and using advanced analytics. Administrative burden and inefficient procedures could be improved through the use of technological tools.

*Megatrend 3: Increasing demographic imbalances*. The global population is growing and age structures becoming more imbalanced. Especially in Europe, population is ageing and birth rates are declining. This shift recalls the fundamental need to guarantee a high level of health protection for the people of Europe, particularly through quick access to innovative, safe and efficacious products and increased market surveillance.

# 5 WHAT ARE THE CONCLUSIONS AND LESSONS LEARNED?

## 5.1 Conclusions

New, innovative medicines are essential for providing new opportunities to treat or prevent diseases. The EU pharmaceutical legislation has established a framework that encourages the development of such medicines, while ensuring high standards of quality, safety and efficacy, and enabling the internal market to function smoothly.

The evaluation shows that the general pharmaceutical legislation is a successful EU intervention. It achieved progress on its high level objectives. The needs, problems and the initial objectives of the legislation and of its revision remain relevant.

The EU general pharmaceutical legislation has set up a robust and flexible authorisation system which benefits from harmonised processes through the centralised procedure for innovative medicines requiring pooled European scientific expertise. In parallel, it allowed for the co-existence with decentralised procedures at national level, available for smaller

[255] The Megatrends Hub | Knowledge for policy (europa.eu).

companies and generic companies with distinct business models. In addition, post-marketing monitoring and reinforced inspections of manufacturing and distribution created a consistent system along the lifecycle of medicines. The system designed at EU level has allowed for safe, efficacious and high quality medicines.

The system includes a predictable incentives framework (8+2 years of regulatory protection period) that has kept Europe an attractive market for medicine developers and has allowed innovative medicines to be available to the different national health systems. However, innovative medicines may not always be accessible to patients and their benefits may not commensurate with their costs for healthcare systems. In addition, the analysis shows that the protection period directly influences market entry of generic and biosimilar medicines (in cases where no longer protection period apply due to patents), affecting affordability of medicines and Member States' health budgets. The Bolar exemption has allowed quicker generic entry, but since the implementation of the exemption varies, so do the benefits. The creation of an authorisation pathway for biosimilars in Europe before any other jurisdictions, has made Europe a leader in this space, allowing the launch of biosimilar medicines on the EU market and thereby increasing access for patients, choice for health services and providing cost savings for national health system. Yet, there is room for further improving the uptake of biosimilar medicines across Member States.

It is important to note however that the increased number of innovative medicines does not lead to equitable access to those across Member States. The legislation was not able to steer market launch decisions of companies and access to medicines primarily in smaller Member States and those with lower per capita healthcare budgets. Access thus remains a real problem for many across the EU. There are however clear limitiations what the general pharmaceutical legislation can achieve, as companies make commercial decisions on market launch and pricing and reimbursement remains within the remit of the Member States.

The European pharmaceutical industry sector remains second behind the US even though revenues have increased. Similarly, R&D investment has increased in absolute terms but not as fast as in the US or China recently. The US remains the jurisdiction of choice for filing marketing authorisation applications for new active substances but the EU is the second destination for filing and most substances are being authorised in the EU less than 1 year after the FDA.

The legislation is well-framed, internally coherent and has clear EU added value. However, its coherence with other legislation has become a challenge in a fast-changing EU regulatory landscape. Emergence of new technologies and borderline cases (that potentially sit between two or more legislations) cause inconsistencies and uncertainties such as the coverage of GMO requirements, environmental challenges and new manufacturing methods.

Overall efficiency was challenging to assess quantitatively. Most stakeholders were unable to provide quantitative estimates of the costs and benefits associated with the 2004 revision. Where available, data is scarce and much of the relevant data is not available in literature. There were cost savings associated with the harmonisation and streamling of procedures (for industry and NCAs) and through switching to a single MA renewal after 5 years. Age-standardised mortality rates have improved in all EU countries in the period since 2007[256], albeit with significant variations in improvements across Member States and the regulatory system will have been an important contributor, by driving innovation in new medicines as well as ensuring the safety, quality and efficacy of medicines. Based on additional products coming on the market and EU sales, it was estimated that the 2004 revision were associated

[256] Santos et al., 2020

with an additional 170 000-210 000 QALYs across the evaluation period (based on a median ICER of €33 000 / QALY) and total additional public health benefits monetised at €4.8bn-€17.2bn. With the upper bound of additional costs estimated at €1.8bn, the 2004 revisions have delivered a positive overall social return.

## 5.2 Lessons learned

The objectives of the general pharmaceutical legislation remain valid. As shown in the analysis, the last review of the general pharmaceutical framework in 2004 provided an appropriate regulatory framework for ensuring access to high quality, safe and efficacious medicines to all Member States. Furthermore, the introduction of the accelerated assessment procedure and the conditional marketing authorisation procedure facilitated faster authorisation and access to medicines of major public health interest, therapeutic innovation and targeting unmet medical needs.

The evaluation findings indicate that while the legislation has been overall flexible to accommodate innovation, it has not been successful in specific areas. These were related to a lack of adequate incentives for innovation by SMEs, academic/industry collaborations, innovation to address areas of UMN and antimicrobial innovation. The reasons are manifold (e.g. market failure, complexity in disease pathologies, knowledge gaps in molecular and physiological underpinnings of diseases, high risk R&D).

Alongside the initial objectives which remain relevant, new objectives will need to be considered in the legislation and new approaches are needed to address the remaining challenges. There is limited readiness and adaptability of the legislation to respond to technological developments, for example, in new manufacturing methods, and rapidly increasing presence of digitisation in new tools generating (real world evidence) evidence for regulatory decision-making and for the development of medicines.

Continued relevance also involves providing targeted incentives to the development of medicines that respond to high unmet medical needs, for example for therapies against antimicrobial resistant infections. AMR has become an issue of greater public health concern requiring further action. The recognition of the increasingly complex and advanced therapies as medicines within the legislation is also important to ensure continued relevance of the legislation to permit authorisation of those products in a streamlined manner for the benefit of patients.

Not all objectives have been fully met through the 2004 revision of the legislation, notably the aim to ensure equitable access to medicines for patients in all EU Member States has had the least success. Affordability was not among the objectives of the 2004 revision of the general pharmaceutical legislation. Furthermore, pricing and reimbursement decisions are a national competence. However, in the past years, the costs of medicines for health systems continue to rise affecting patient access and country differences in terms of availability of medicines are of great concern. The impact of the new HTA Regulation adopted in 2022 has yet to be seen but it is expected to improve the availability innovative health technologies through joint clinical assessments, joint scientific consultations and voluntary cooperation.

As regards the implementation of the legislation at national level, differences have been noted across Member States in the implementation of Directive 2001/83/EC. Examples include in particular the implementation of the "Bolar" provision, the hospital exemption, the assessments of medicines containing or consisting of genetically-modified organisms (GMOs) and the provisions related to medicines shortages.

Improved coherence with other specialised health legislations is required to remove uncertainty and improve consistency of interpretation. In addition, improved coherence with other wider EU legislations is required to reduce tensions and improve synergies, increasing the likelihood of positive impact in terms of public health, environmental sustainability, digitalisation, etc. This will ensure a systemic fit of the general pharmaceutical legislation in the wider EU policy framework.

Several lessons have been learned from the recent experience of medicine developers and public authorities having acted under the pressure of the ongoing COVID-19 pandemic. It also highlighted factors causing shortages such as over-reliance on one or very few foreign suppliers for some essential APIs. The actions taken during the pandemic have shown that there is room for flexibility to adapt regulatory processes and accelerate product development and authorisation processes, including the use of remote processes for source data verification, virtual audits and monitoring. This would reduce administrative burden for developers and release capacity for regulatory authorities. Collaboration between industry and regulators during the pandemic on the development of COVID-19 vaccines and therapeutics as well as on stocks and shortages demonstrated that different interests can be usefully aligned. EMA has also adapted to respond to the scientific, regulatory and operational challenges which can serve as a blueprint not only for future emergencies but for a more fit for purpose system. It is however noted that EMA and the network of national competent authorities have limited resources and its expertise and capacity need to be expanded in order to progress complex dossiers at pace and keep up global attractiveness, and do so without compromising safety, efficacy and quality of authorised medicines.

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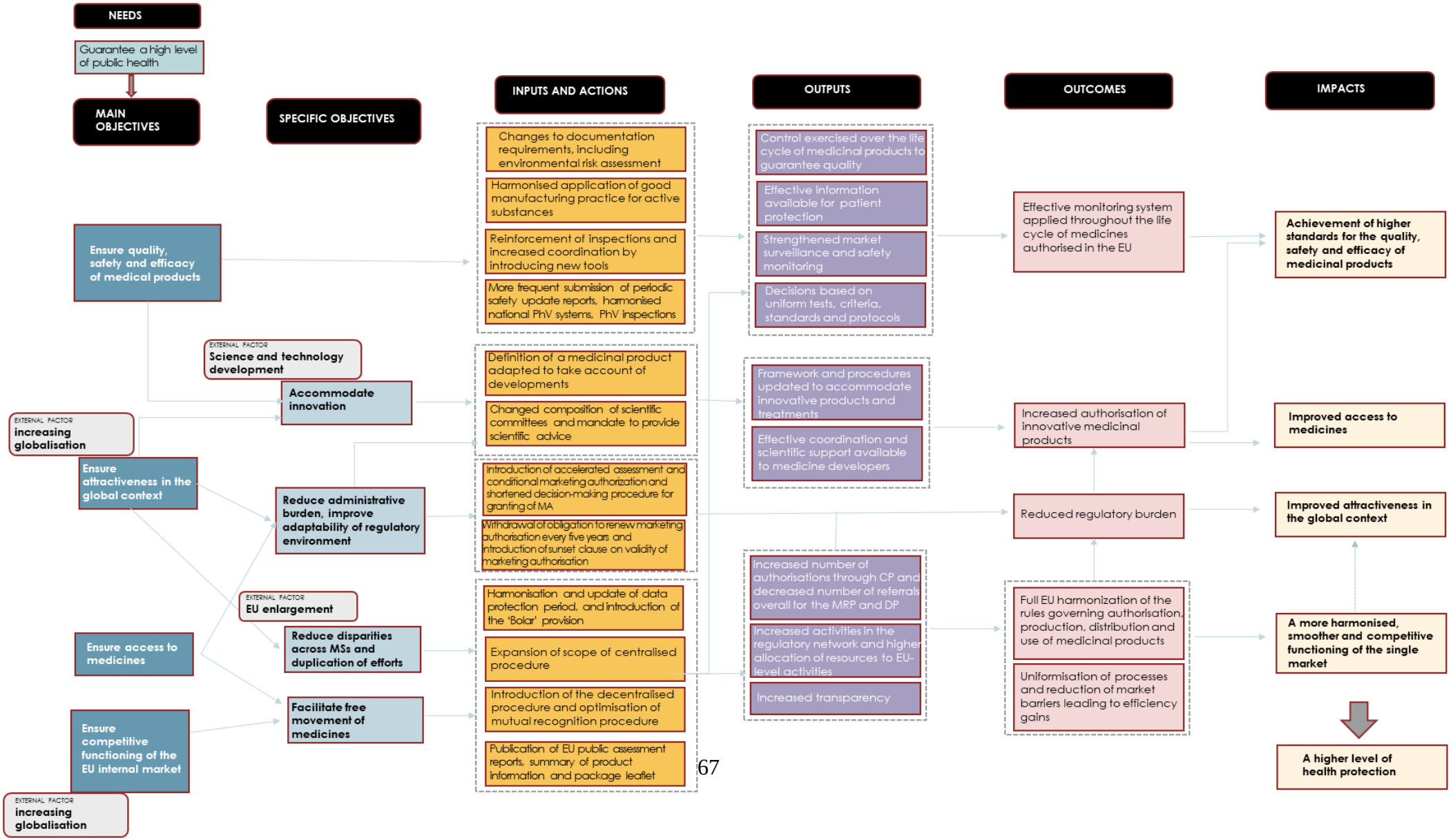
# 7 APPENDIX A: INTERVENTION LOGIC



# 8 APPENDIX B: TARGETED SURVEY OVERVIEW – AREAS WHERE THE LEGISLATION HAS BEEN EFFECTIVE

| To what extent has the legislation been effective in contributing to the following objectives? | All stakeholders average score | Individual stakeholders average score | | | | | Agreement between stakeholders | Ranked Effectiveness |
|---|---|---|---|---|---|---|---|---|
| | | Industry | Civil Society | Public Authorities | Academic | Health Services | | |
| Safeguard public health | 3.7 | 4.4 | 3.5 | 4.0 | 3.5 | 3.3 | Low | most effective |
| Provide an attractive and robust authorisation system for medicines | 3.8 | 3.9 | | 3.8 | | 3.8 | High | most effective |
| Provide resources and expertise to ensure timely assessment and authorisation of medicines at all times | 3.44 | 3.3 | | 3.5 | | | High | |
| Enable timely access to medicines for patients and health systems | 2.9 | 3.2 | 2.8 | 3.1 | 2.7 | 2.8 | High | |
| Enable access to affordable medicines for patients and health systems | 2.4 | 3.0 | 2.0 | 2.3 | 2.1 | 2.7 | Low | least effective |
| Minimise inefficiencies and administrative burden of regulatory procedures | 2.8 | 2.3 | | 3.0 | | 3.1 | Low | |
| Provide harmonised measures for an improved functioning of the internal market for medicines | 2.9 | 2.7 | 2.60 | 3.5 | 2.8 | 2.8 | Med | |
| Ensure quality of medicines including through manufacturing rules and oversight of manufacturing and supply chain | 3.9 | 4.4 | 3.7 | 4.2 | 3.9 | 3.5 | Low | most effective |
| Enhance the security of supply of medicines and address shortages | 2.3 | 2.9 | 1.80 | 2.4 | | 2.0 | Low | least effective |
| Provide clear and appropriate responsibilities to all actors throughout the lifecycle of medicines, including post-marketing obligations and oversight | 3.6 | 3.6 | | 3.7 | | | High | |
| Ensure a competitive EU market for medicines | 2.8 | 3.1 | 2.2 | 3.0 | | | High | |
| Improve competitiveness of EU pharmaceutical industry on the global market | 2.7 | 2.4 | | 3.1 | | | Low | |
| Facilitate generic/biosimilar product entry to markets | 3.3 | 3.6 | 2.7 | 3.3 | 3.3 | 3.44 | High | |
| Enable progress in science, technology and digitisation for the development of high quality, safe and effective medicines | 3.2 | 3.0 | 3.0 | 3.2 | 3.1 | 3.6 | High | |
| Accommodate innovation for the development of complex and combination medicinal products | 3.0 | 2.9 | 2.7 | 3.2 | 2.9 | 3.3 | High | |
| Accommodate innovation for medicine manufacturing | 3.1 | 3.2 | | 3.2 | 2.9 | 8 | High | |
| Attract pharmaceutical developers from outside the EU | 2.7 | 2.7 | | | | | High | |
| Reduce the environmental footprint of medicines | 2.5 | 3.1 | 2.2 | 2.3 | | | Low | least effective |

## 9 APPENDIX C: EVALUATION MATRIX

An evaluation matrix was developed to provide a framework for answering the evaluation questions. The matrix cross-references evaluation questions to the relevant judgement criteria, indicators and data sources. The indicators aim to compare periods before and after the 2004 revision of the general pharmaceutical legislation was implemented.

The indicators followed by a star (*) are explained in details in the analytical report (Annex 10). These cover parameters and areas such as new marketing authorisations (number, type of medicine and approval times), access and affordability (medicine prices), clinical trials, medicine shortages in Member States (number and cause) and non-compliance with good manufacturing procedure (GMP).

| ***Evaluation question*** | ***Sub-questions*** | ***Judgement Criteria*** | ***Indicator*** | ***Data sources*** |
|---|---|---|---|---|
| ***EFFECTIVENESS*** | | | | |
| 1. To what extent have the actions envisaged by the general pharmaceutical legislation contributed to achieving the following objectives? | 1.a. To safeguard public health. | ***For all Effectiveness questions:***<br><br>Degree to which quantitative indicators show positive trend over time. This is corroborated with qualitative information (where available). | Number of innovative medicines*; Number of medicines authorised*; Time from start of Phase1 to completion of Phase 3 clinical trials*; Sales volumes of antibiotics*; Adverse reaction data trends (EudraVigilance). | Desk research; Mini case studies; Stakeholder views including targeted survey, interviews and stakeholder workshops. |
| | 1.b. To build an attractive and robust authorisation system for medicines. | | Number of USA-origin medicines approved in the USA, of Japan-origin medicines approved in Japan, of Switzerland-origin medicines approved in Switzerland*; Number of USA-, Japan-, Switzerland- medicines approved in the EU*; Transition success rate (%) of candidates | Desk research; Mini case studies; Stakeholder views including targeted survey, interviews and stakeholder workshops. |

| *Evaluation question* | *Sub-questions* | *Judgement Criteria* | *Indicator* | *Data sources* |
|---|---|---|---|---|
| | | | from Phase 3 to approval*; Speed of approval for authorised medicines*; EMA assessment times including accelerated assessments.* | |
| | 1.c. To give patient timely access to medicines. | | Number of approved medicines with zero sales volume in EU countries*; Time from authorisation to non-zero sales volume reported for authorised medicines in individual EU countries*; Number of market withdrawals*; Time from market authorisation to market withdrawal*. | Desk research; Mini case studies; Stakeholder views including interviews and stakeholder workshops. |
| | 1.d. To minimise inefficiencies and administrative burden of regulatory procedures. | | Number of lead and co-lead assessments by national regulatory authorities (rapporteurs and co-rapporteurs)*; EMA assessment times including accelerated assessments*. | Desk research; Stakeholder views including targeted survey, interviews and stakeholder workshops. |
| | 1.e. To provide harmonised measures for an improved functioning of internal market for medicines. | | Number of medicines authorised*; Number of lead and co-lead assessments by national regulatory authorities (rapporteurs and co-rapporteurs)*; Employment in the pharmaceutical industry*; GVA contribution of the pharmaceutical industry*; Revenue generated by pharma | Desk research. |

| *Evaluation question* | *Sub-questions* | *Judgement Criteria* | *Indicator* | *Data sources* |
|---|---|---|---|---|
| | | | companies*. | |
| | 1.f. To ensure the quality of medicines including through manufacturing rules and supply chain oversight. | | Change of root cause reported for medicines*; Number of non-compliance of GMP, stratified by countries*. | Literature review; Mini-case studies; Stakeholder views including targeted survey, interviews and stakeholder workshops. |
| | 1.g. To create an integrated lifecycle model with clear and appropriate responsibilities including post-marketing obligations and oversight. | | Number of medicines authorised*. | Mini-case studies; Stakeholder views including targeted survey, interviews and stakeholder workshops. |
| | 1.h. To create a competitive market for medicines in the EU, including taking into account market effects impacting on affordability. | | Number of EU-origin medicines approved in the EU*; Number of USA-, Japan-, Switzerland origin medicines approved in the EU*; Volumes and values of EU import/export of APIs, vaccines, finished pharmaceutical products and antibiotics*; Net price of selected group of medicines (e.g., representative sample or essential medicines list) in individual countries*; Rate of generics/biosimilars entry and uptake*; Average price discount (%) of generics/biosimilars over originator*; Number of authorised medicines per class, therapeutic area*; Number of pipeline products per class, therapeutic area*; Sales volume | Desk research; Mini-case studies; Stakeholder views including stakeholder workshops. |

| *Evaluation question* | *Sub-questions* | *Judgement Criteria* | *Indicator* | *Data sources* |
|---|---|---|---|---|
| | | | of antibiotics*. | |
| | 1.i. To make it easier to place generic/biosimilar products on the market. | | Rate of generics/biosimilars entry and uptake*; Time to entry after IP protection expires*. | Desk research; Stakeholder views including targeted survey and interviews. |
| | 1.j. To enable innovation for the development of high quality, safe and effective medicines in a way that harnesses the benefits of digitisation and emerging science and technology. | | Number of antibiotics approved per year*; Number of antibiotic medicine candidates in the R&D pipelines*; Number of candidates entering Phase 1 clinical trials*; Transition success rate (%) of candidates from Phase 1 to Phase 2 to Phase 3 to clinical trials to approval*; Number of clinical trials with digital end points, real world data, complex trial design. | Literature review; Desk research; Mini cases studies; Stakeholder views including targeted survey, interviews, stakeholder workshop. |
| | 1.k. To ensure openness to cutting-edge products and integrated therapies. | | Number of medicines authorised*. | Desk research; Mini cases studies; Stakeholder views including targeted survey, interviews. |
| | 1.l. To improve competitiveness of EU pharmaceutical industry on the global market. | | Number of EU-origin medicines approved in one or more non-EU countries*; Value of medicine exports EU to USA and USA to EU; EU to Japan and Japan to EU; EU to Switzerland and Switzerland to EU*; Revenue generated by pharma companies*; Volumes and values of EU import/export | Literature review; Desk research; Stakeholder views including stakeholder workshop. |

| *Evaluation question* | *Sub-questions* | *Judgement Criteria* | *Indicator* | *Data sources* |
|---|---|---|---|---|
| | | | of APIs, vaccines, finished pharmaceutical products and antibiotics*. | |
| | 1.m. To enhance the security of supply of medicines and address shortages. | | Trend of shortage duration for medicines in shortage*; Trend of volume drop for medicines in shortage (critical, severe, moderate)*; Number of third-country API sites, stratified by geography*; Number of EU-registered API sites, stratified by MS*. | Desk research; Mini case studies; Stakeholder views including stakeholder workshop. |
| | 1.n. To reduce the environmental footprint of medicines. | | Concentrations of pharmaceutical residues in the environment*; Emission intensity/absolute emissions of GHG by the pharmaceutical industry*. | Literature review; Desk research. |
| 2. How do the achieved results and impacts compare with the expected ones? | 2.a. To what extent the results of the legislation meet the need of stakeholders? | | Comparison of available indicators with stakeholder views. | Desk research; Stakeholder views including targeted survey, interviews, stakeholder workshop. |
| 3. Which were the key contributing and hindering factors in achieving the intended objectives? | 3. a To what extent has the type of legislative act, i.e. a Directive, been a contributing or hindering factor in achieving the intended objectives? | | Comparison of available indicators with stakeholder views. | Desk research; Stakeholder views including targeted survey, interviews, stakeholder workshop. |
| | 3.b. To what extent has Directive 2001/83/EC been transposed by Member States in a way that allows the effective | | Qualitative evidence based on expert legal opinion and stakeholder views. | Desk research; Stakeholder views and expert legal opinion including targeted survey, |

| *Evaluation question* | *Sub-questions* | *Judgement Criteria* | *Indicator* | *Data sources* |
|---|---|---|---|---|
| | implementation; which are the factors hampering the implementation; to what extent are these factors influenced by regional and national conditions? Are there any unexpected or unintended effects that occurred and which drove or hindered progress? | | | interviews. |
| 4. To what extent is the general pharmaceutical legislation relevant to position the EU regulatory system in an international context, including the attractiveness of the EU system for developers compared to other jurisdictions? | 4.a. To what extent non-EU based sponsors conduct trials in the EU?<br>To what extent non-EU based sponsors apply for marketing authorisation in the EU? | | Number of USA-, Japan-, Switzerland-origin medicines approved in the EU*; Number of clinical trials performed in different geographies*; Overall Likelihood of Approval (LOA) from Phase 1*; Time from start of Phase1 to completion of Phase 3 clinical trials*. | Desk research; Stakeholder view including targeted survey, interviews. |
| ***EFFICIENCY*** | | | | |
| 5. What have been the main costs (e.g. implementation costs, authorisation costs, life cycle management, staff time etc.) to implement and apply the general pharmaceutical legislation for the different actors concerned (e.g. Commission, Member States, industry, patients, researchers, etc.)? What were the factors driving these costs? | 5.a. What have been the main costs (per stakeholder category) implications of the legislation? | The implications of the legislation can be monetised in an attributable way. | Cost per product development and implementation steps. | Literature review; Stakeholder view including targeted survey and stakeholder workshops. |
| | 5.b. What have been the cost drivers? | Views on relevant drivers and their contribution to overall costs. | Top cost elements. | Literature review; Stakeholder view including targeted survey, interviews, stakeholder workshops. |
| 6. What social, environmental and economic benefits has the general pharmaceutical legislation achieved for the different stakeholders and what is the corresponding monetised value, where possible and | 6.a. What have been the social benefits of the legislation? | Degree to which quantitative indicators show favourable trend over time and this is corroborated with qualitative | Net price of selected group of medicines (e.g., representative sample or essential medicines list) in individual countries*; Ratio of net price of medicines | Desk research; Mini case studies; Stakeholder view including interviews. |

| *Evaluation question* | *Sub-questions* | *Judgement Criteria* | *Indicator* | *Data sources* |
|---|---|---|---|---|
| relevant to estimate? | | information (where available) | to GDP per capita in individual countries*; Expenditure on medicines in total healthcare spending in individual countries; Rate of generics/biosimilars entry and uptake*; Change in unmet healthcare needs. | |
| | 6.b. What have been the economic benefits of the legislation? | Degree to which quantitative indicators lead to favourable trend over time | Employment in the pharmaceutical industry*; GVA contribution of the pharmaceutical industry*; Revenue generated by pharma companies*; Foreign direct investment in the pharmaceutical sector. | Desk research. |
| | 6.c.. What have been the environmental benefits of the legislation? | | Concentrations of pharmaceutical residues in the environment*; Emission intensity/absolute emissions of GHG by the pharmaceutical industry*; Residues of pharmaceuticals in the environment and emissions from manufacturing plants. | Literature review; desk research. |
| 7. To what extent were the general pharmaceutical legislation's costs proportionate to its benefits (i.e. positive outcomes)? | 7.a. What is the scale of the significant and monetisable costs and benefits, applying the principle of proportionate analysis?<br>What is the ratio of those significant costs and benefits?<br>What is the balance of those | The extent to which the model result in positive outcomes | Partial cost benefit analysis considering monetisable costs and benefits and accompanying multi-criteria analysis to assess the balance when including non-monetisable aspects. | Literature review; Desk research; Stakeholder view including targeted survey, interviews, stakeholder workshop. |

| *Evaluation question* | *Sub-questions* | *Judgement Criteria* | *Indicator* | *Data sources* |
|---|---|---|---|---|
| | costs and benefits when including non-monetisable aspects? | | | |
| 8. What have been the costs of partially meeting or not meeting some of the objectives and requirements of the general pharmaceutical legislation? | 8.a. What share of the total costs can be attributed reasonably to each of the specific objectives of the legislation?<br>What is the scale / value of the benefits associated with each specific objective and attributable to the legislation?<br>What have been the total costs of meeting each of these specific objectives, jointly and severally? | The cost and benefit items can be attributed to objectives and these can be aggregated | Cost-Benefit model integrating the share of costs and value of benefits for each objective and jointly. | Literature review; desk research; Stakeholder view including targeted survey, interviews, stakeholder workshop. |
| 9. Which elements of the general pharmaceutical legislation pose an administrative burden or are overly complex? What are the administrative costs for the different actors? Which provisions could be further simplified? | 9.a. Which are the burdensome or complex aspects of the legislation? | The degree to which stakeholders can point to attributable administrative burden. | Top 5 'burdens' overall and by key stakeholder group. | Literature review; Stakeholder view including targeted survey. |
| | 9.b. What is the level of costs corresponding to these aspects? | The degree to which administrative burden can be quantified by stakeholders. | Median value of costs associated with the principal direct costs for each key stakeholder group | Literature review; Desk research; Stakeholder view including targeted survey. |
| ***COHERENCE*** | | | | |
| 10. To what extent has the general pharmaceutical legislation responded to the needs and problems concerning medicines for the 2004 revision? | 10.a To what extent definition of new therapies and new forms of administration routes enabled innovation? | Degree to which quantitative indicators show favourable trend over time and this is corroborated with qualitative information (where available). | Speed of approval for authorised medicines*; Number of authorised medicines per class, therapeutic area*; Number of pipeline products per class, therapeutic area*. | Desk research; Stakeholder view including targeted survey, interviews. |

| *Evaluation question* | *Sub-questions* | *Judgement Criteria* | *Indicator* | *Data sources* |
|---|---|---|---|---|
| | 10.b. To what extent the new pathway for biosimilars responded to the needs? | | Rate of generics/biosimilars entry and uptake*; Time to entry after IP protection expires*; Average price discount (%) of generics/biosimilars over originator*. | Desk research;, Stakeholder view including targeted survey, interviews. |
| 11. To what extent are the general pharmaceutical legislation's objectives and required actions relevant today to address the current needs and problems and expected scientific and technological developments related to medicinal products in the EU? | 11.a. How have the needs and problems identified for the 2004 revision evolved since then? | Degree to which quantitative indicators show identifiable trend over time. | Overall Likelihood of Approval (LOA) from Phase 1*; Number of grants and value of grant funding by country and/or funding body*; Amount of private R&D investment in the sector*; Number of medicines authorised*; Speed of approval for authorised medicines*; Share of EU population with access to medicines sold on the market*; Net price of selected group of medicines (e.g., representative sample or essential medicines list) in individual countries*; Ratio of net price of medicines to GDP per capita in individual countries*; Expenditure on medicines in total healthcare spending in individual countries*. | Desk research; Stakeholder view including stakeholder workshop. |
| | 11.b. What are the current needs and problems related to the use of medicinal products and how will they evolve (e.g. fulfilling unmet medical need, access to affordable medicines, security | Views on relevant needs and problems corroborating quantitative trends of indicators | Analysis of the current level of indicator available from the comparative analysis of the European pharmaceutical legislation and contrast those | Desk research; Stakeholder view including targeted survey, interviews, stakeholder workshop. |

| *Evaluation question* | *Sub-questions* | *Judgement Criteria* | *Indicator* | *Data sources* |
|---|---|---|---|---|
| | of the supply chain, adaptation of the regulatory framework to scientific and technological developments)? | | with stakeholder view. | |
| 12. To what extent is the general pharmaceutical legislation relevant to health crises resilience and responsiveness? What are the lessons learned from the COVID-19 pandemic? | 12.a. To what extent is the general pharmaceutical legislation relevant to health crises resilience and responsiveness? | The degree to which stakeholders and experts can point to relevant examples. | Examples of application of the legislation during crises management and response. | Literature review; Mini case studies; Stakeholder view including, interviews, stakeholder workshop. |
| | 12.b. What are the lessons learned from the COVID-19 pandemic? | The degree to which stakeholders can articulate learnings. | Qualitative assessment based on stakeholder view. | Literature review; Stakeholder view including interviews, stakeholder workshop. |
| ***COHERENCE*** | | | | |
| 13. To what extent is the general pharmaceutical legislation coherent internally? Have the different elements of the legislation have operated together to achieve all the objectives of the legislation in a coherent way? Which are the reasons for the perceived tensions between innovation, access and affordability and which are the factors influencing them? ***(Internal coherence)*** | 13.a. To what extent is the EU legislation coherent and different elements operate in synergy to achieve all of its objectives?<br><br>Are there tensions between the objectives linked to innovations, access and affordability of medicines? If yes, what are those? How could these be resolved? | The degree to which (positive or negative) interdependencies of the elements of the general pharmaceutical legislations can be identified and where needed resolved. | Qualitative assessment based on expert legal opinion (analysis of potential overlaps, contradictions, or other inconsistencies between its provisions/requirements; analysis of whether its provisions adequately fulfil its objectives) and stakeholder view on issues and solutions (especially Member State authorities in charge of the implementation and enforcements of this legislation at national level). | Literature review; Mini case studies; Stakeholder view including interviews, stakeholder workshop. |

| *Evaluation question* | *Sub-questions* | *Judgement Criteria* | *Indicator* | *Data sources* |
|---|---|---|---|---|
| | | | | |
| 14. The general pharmaceutical legislation has strong links with lex specialis pharmaceutical legislations. To what extent has the general pharmaceutical legislation created an effective and coherent link with the specialised pharmaceutical frameworks that is not hampered by undue complexity? ***(external coherence I)*** | 14.a. Are there overlaps, inconsistencies or ambiguities between the legislation and lex specialis pharmaceutical legislations?<br><br>Is there unnecessary complexity in the system due to the way the legislation is drafted there?<br><br>Are there ways the legislations could be better streamlined? | The degree to which interdependencies of the general pharmaceutical legislations and specialised pharmaceutical frameworks can be identified and where needed resolved | Qualitative assessment based on axpert legal opinion (analysis of potential inconsistencies between the general pharmaceutical legislation and the *lex specialis* pharmaceutical laws of core obligations using a table of comparison and possible legal solutions). | Literature review; Mini case studies; Stakeholder view including interviews, stakeholder workshop. |
| 15. To which extent is the general pharmaceutical legislation dependent on the implementation of the linked legislation in achieving its objectives? In particular, the link with the non-pharmaceutical legislations and non-pharmaceutical policies should be explored. ***(external coherence II)*** | 15.a What are the potential links between the pharmaceutical legislation and other EU legislations and policies along the pharmaceutical chain (e.g. development, placing on the market, use, waste management and/or emissions in the environment)?<br><br>To what extent is the intervention coherent with international obligations? including the SDGs?<br><br>Are these other legislations (designed at different times with different purpose under different competencies) essential for the pharmaceutical legislation achieve all of its objectives?<br><br>Do these other legislations | The degree to which (positive or negative) interdependencies of the general pharmaceutical legislations and other EU legislations can be identified and their effects assessed | Qualitative assessment based on expert legal opinion.<br><br>Note: An in-depth legal analysis is not feasible, however, there is already a vast amount of literature available which would guide the evaluation, meaning a legal analysis would only be needed to debunk or prove a specific inconsistency. | Literature review, Stakeholder view including interviews, stakeholder workshop. |

| *Evaluation question* | *Sub-questions* | *Judgement Criteria* | *Indicator* | *Data sources* |
|---|---|---|---|---|
| | hinder the pharmaceutical legislation to achieve any of its objectives? | | | |
| ***EU ADDED-VALUE*** | | | | |
| 16. What has been the added value resulting from the EU intervention in the legislation of pharmaceuticals compared to what could have been achieved at international, national or regional level without such intervention? | 16.a. What has been the added value of the EU legislation compared to international actions alone? compared to EU national actions alone? compared to EU regional actions alone? | The degree to which additional value can be identified as a result of the implementation of the general pharmaceutical legislation | Qualitative assessment based on expert legal opinion and stakeholder view. | Literature review; Stakeholder view including interviews, stakeholder workshop. |
| 17. To which extent did the general pharmaceutical legislation strike the right balance between action at EU level and national action? Is it a proportionate response to the problem? | 17.a To what extent has the EU legislation been applied in a balanced and proportionate way to problems arising? | The problems and related national/EU actions can be assessed along the same metric/scale and their relationship assessed. | Number of MA via the CP versus MRP or DCP*; Number of lead and co-lead assessments by national regulatory authorities (rapporteurs and co-rapporteurs)*. | Literature review; Desk research, Stakeholder view including interviews, stakeholder workshop. |
| 18. What has been the added value resulting from the EU intervention in the context of the COVID crisis (e.g. providing strategic priorities for action, a common framework for action, etc.)? | 18.a. In what way has the EU intervention added value to the COVID response? | The degree to which added value through quantitative indicators can be attributed to EU action and corroborated by qualitative information for the ongoing crisis. | Number of clinical trials conducted and number of medicines authorised relevant for COVID medicine (therapeutic categorisation)* | Literature review; Desk research; Mini case studies; Stakeholder view including interviews, stakeholder workshop. |
| 19. To which extent did this EU intervention strike the right balance between action at EU level and national action? Is it a proportionate response to the pandemic? | 19.a. To what extent has the EU intervened in a balanced and proportionate way with respect to national actions during the | The degree to which EU actions and national actions can be disentangled. | Qualitative assessment based on expert legal opinion and stakeholder view. | Literature review; Mini case studies; Stakeholder view and expert legal opinion including interviews, stakeholder workshop. |

| *Evaluation question* | *Sub-questions* | *Judgement Criteria* | *Indicator* | *Data sources* |
|---|---|---|---|---|
| | COVID crisis? | | | |

## 10 APPENDIX D: OVERVIEW OF BENEFITS AND COSTS

Table 22 Overview of costs and benefits identified in the evaluation

| | | Citizens/Consumers | | Businesses | | Administrations | | Society | |
|---|---|---|---|---|---|---|---|---|---|
| | | Quantitative | Comment | Quantitative | Comment | Quantitative | Comment | Quantitative | Comment |
| **Costs and Benefits of 2004 revision of Pharmaceutical Legislation (millions of Euro)** | | | | | | | | | |
| **Direct costs** | | | | | | | | | |
| **Direct Compliance costs** (adjustment costs) | **one-off** | | | €250m | Additional investments in IT systems to cope with expanded data requirements on safety and manufacturing, estimated at 0.1-1% of sales. Using the 0.5% median value gives a gross figure of €750m for the EU industry overall. However, the new iT systems have provided wider benefits / productivity gains, so the attributable cost is assumed to be lower (1/3 of gross costs) | | | | |
| **Direct compliance costs** (adjustment costs) | **recurrent** | | | €50m-€100m p.a., €750m-€1,500m in total | Higher costs due to data requirements for new and current marketing authorisations; additional costs for legal departments | | | | |
| **Enforcement costs:** (costs associated with activities linked to the implementation of an initiative such as monitoring, inspections and adjudication/litigation) | **recurrent** | | | | | EMA: €2.5m-€3.1m p.a., NCAs: €8m-€25m p.a. | Higher staff and evaluation costs for EMA; higher inspection costs for national competent authorities | | |
| **Direct benefits** | | | | | | | | | |
| **Health impacts** | **recurrent** | 25-30 new innovative medicines, in total; producing 170,000-210,000 QALYs in total; which amounts to €4.8bn-€17.2bn in monetised benefits, using WHO guidelines | The additional number of new products has been estimated based on a comparison between EMA and FDA authorisations over time; the QALYs are based on estimated average EU | | | | | | |

| | | Citizens/Consumers | | Businesses | | Administrations | | Society | |
|---|---|---|---|---|---|---|---|---|---|
| | | Quantitative | Comment | Quantitative | Comment | Quantitative | Comment | Quantitative | Comment |
| | | on valuing QALYs | income and a median ICER | | | | | | |
| **Compliance costs: lower costs marketing authorisations** | **recurrent** | | | CP: €4.8m p.a., DCP: €36m p.a. | Cost savings due to the harmonisation and streamlining of procedures associated with the introduction of the DCP and the substantial reduction in the use of the mutual recognition procedure | | | | |
| **Compliance costs: Lower costs marketing authorisations** (lower regulatory costs) | **recurrent** | | | €23m p.a. | MA holders benefited from the switch to a single renewal of a MA 5 years after the original notice of authorisation, eliminating the need for further renewals at 5-yearly cycles, and removing the need for renewals by generics companies | | | | |
| **Enforcement** | **recurrent** | | | | | €20m-€40m pa | Cost savings for national competent authorities due to streamlining / harmonisation of national authorisation procedures (switch to DCP away from MRP) | | |
| **Environmental damage** | **recurrent** | | | | | | | 0 | The 2004 revision has not contributed to reducing the environmental footprint. |

**Table 6** Simplification and burden reduction (savings already achieved)

| | Citizens/Consumers/Workers | | Businesses | | Administrations | | Society | |
|---|---|---|---|---|---|---|---|---|
| | Quantitative | Comment | Quantitative | Comment | Quantitative | Comment | Quantitative | Comment |
| **Title**[257]*: (i) direct compliance cost savings (for example adjustment cost savings, administrative cost savings, savings from regulatory charges)* | | | | | | | | |
| **Recurrent savings (MAHs)** | | | CP: €4.8m p.a., DCP: €36m p.a. | Cost savings due to the harmonisation and streamlining of procedures associated with the introduction of the DCP and the substantial reduction in the use of the mutual recognition procedure | | | | |
| **Recurrent savings (MAHs)** | | | €23m p.a. | MA holders benefited from the switch to a single renewal of a MA 5 years after the original notice of authorisation, eliminating the need for further renewals at 5-yearly cycles, and removing the need for renewals by generics companies | | | | |
| **Recurrent savings (enforcement)** | | | | | €20m-€40m pa | Cost savings for national competent authorities due to streamlining / harmonisation of | | |

[257] Each simplification/saving should be included on a separate line.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | national authorisation procedures (switch to DCP away from MRP) | | |

***PART II: <u>Potential</u> simplification and burden reduction (savings)***

*Identify further potential simplification and savings **that could be achieved** with a view to make the initiative more effective and efficient without prejudice to its policy objectives[258].*

| | Citizens/Consumers/Workers | | Businesses | | Administrations | | [Other…] _ specify | |
|---|---|---|---|---|---|---|---|---|
| | Quantitative | Comment | Quantitative | Comment | Quantitative | Comment | Quantitative | Comment |
| **Description:** Our evaluation consultations revealed widespread concerns across industry and regulators about the under-exploitation of digitalisation within the EU pharma regulatory system and the related problem of duplicative activity. As such, there may be areas where further harmonisation and digitalisation of regulatory processes could deliver savings, however, these are contingent on future revisions and operational enhancements being implemented. As an aside, we note that the EMA strategy indicates there are >80 people working on digital transformation and its annual financial accounts show it is investing €5m-€15m a year in new ICT systems. The wider literature on ICT productivity suggests that a 10% increase in ICT investment should produce a productivity gain of around 0.6%[259] | | | | | | | |
| **Recurrent** (MAHs) | | | €9.6m p.a. | There are opportunities for substantial further digitalisation across the EU pharma regulatory system to increase efficiency and duplicative activity | | | | |
| **Recurrent** (EMA) | | | | | €2.1m p.a. | There are opportunities for substantial further digitalisation across the EU pharma regulatory system to | | |

[258] This assessment is without prejudice to a possible future Impact Assessment.

[259] https://www.sciencedirect.com/science/article/abs/pii/S0167624513000036.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | increase efficiency and duplicative activity | | |
| **Recurrent** (NCAs) | | | | | €12m p.a. | There are opportunities for substantial further digitalisation across the EU pharma regulatory system to increase efficiency and duplicative activity | | |

# Annex 11: Impact analysis of all policy measures

## Table of Contents

## A.1. Introduction

This appendix provides an assessment of the likely impacts of each of the 77 policy measures considered as part of the impact assessment study.

The presentation also includes the 10 pivotal policy measures that were identified from within the 77 measures, based on the initial assessment of the long list, as being of critical importance for the revisions to the legislation, and which have therefore been looked at in more depth. The pivotal measures are also presented in the main report of the study supporting the IA and the accompanying Staff Working Document. The assessment of the remaining policy measures is only presented here in the appendices.

For ease of reference, Table 1 presents the titles and reference number for each of the long list of 77 measures that have been assessed by the study team, the results of which are presented in some detail over the next 70 pages.

The measures are organised by policy block (e.g. antimicrobial resistance [AMR]), with the different combinations of policy elements set out under each of the three policy options. The tabular presentation allows the reader to more readily understand the different combinations of policy elements that have been brought together for each policy block, and with the common elements being tagged as such. For example, under the 'incentives for innovation' Policy Block, policy element C.1.1. is the same as policy element B.1.1. and C.1.8. is the same as B.1.8 and so on.

Option C is the most comprehensive of the three policy options and is expected to become the preferred option, having been able to strike the best balance between encouraging further innovation, supporting a strategic industry, while promoting improvements in access, affordability and environmental impact. The 77 measures are considered from the perspective of the current baseline and the specific policy option. The pivotal measures are listed in **bold**, to distinguish them visually from the other policy measures some of which may yet be included in the Commission's final proposals for the revisions.

Appendix B presents a similar overview of the 30+ horizontal measures that have been identified as a possible means by which to streamline the regulatory system in order to speed up assessments and otherwise reduce administrative burden. These measures would apply in principal to any of the three policy options, and have therefore been presented once only. The initial assessment of the long list of horizontal measures has been used as the basis for selecting a series of 10 pivotal horizontal measures, which are looked at in more depth and have been the subject of our cost-benefit analysis.

*Table 1 Principal policy elements considered under each of the three policy options*

| Option A | Option B | Option C |
|---|---|---|
| **Incentives for innovation, in particular to address unmet medical needs (UMNs)** | | |
| A.1.1. PRIME remains under the current scheme (i.e. not included in the legislation).<br>A.1.2. Establish a non-binding system for scientific assessment of evidence for repurposing<br>A.1.3 Add a special incentive bonus (+1 year): of regulatory (data) protection for products with a demonstrated ability to address an UMN<br>A.1.4. Special incentive bonus: if data package includes | B.1.1. Codification of PRIME in the legislation<br>B.1.2. Establish a binding system for scientific assessment for repurposing<br>B.1.3. Obligation for MAHs to include a new indication when supported by scientific evidence | C.1.1. As B.1.1 Codification of PRIME in the legislation<br>C.1.2. As B.1.2 Establish a binding system for scientific assessment for repurposing |

| Option A | Option B | Option C |
|---|---|---|
| comparative trial with standard of care (+6 months) | B.1.4. Reduce duration of incentives for originators from 8+2 to 6+2 years<br>B.1.5. Medicines with demonstrated ability to address UMN get +2 years data protection.<br>B.1.6. Breaking market protection in case of urgency<br>B.1.7. Require transparency on any relevant public contribution or funding<br>B.1.8. Give regulators the possibility to impose a post authorisation obligation for additional studies | C.1.3. Additional data protection period for the new evidence generated to support repurposing<br>**C.1.4. Reduce duration of incentives for originators from 8+2 to 6+2 years (but with +2 years for launch in all markets [C.4.3.])**<br>**C.1.5 As B.1.5 Medicines with demonstrated ability to address UMN get +1-year data protection.**<br>**C.1.6. Same as A.1.4. Incentive bonus: if data package includes comparative trial (+6 months)**<br>**C.1.7 Transparency on public contribution to clinical trials.**<br>C.1.8 As B.1.8. Allow regulators to impose a post authorisation obligation for additional studies<br>C.1.9. Breaking market protection in case of urgency |
| **AMR specific** | | |
| A.2.1. Harmonisation of summary of product characteristics for nationally authorised antimicrobials to support prescription practices.<br>A.2.2 Transferable voucher independent and in addition to data/market protection for antimicrobial products<br>A.2.3. Consider adapted system for authorisation of phage therapies and other alternative products | B.2.1 Make central procedure mandatory for new antimicrobials.<br>B.2.2. PRIME like support scheme, including rolling review<br>B.2.3. Optimise package size<br>B.2.4. Stricter rules on disposal<br>B.2.5. Tighten prescription requirements<br>B.2.6. Mandatory use of diagnostics<br>B.2.7. Pay or play model<br>B.2.8. Establish a monitoring system for consumption and use and the environment<br>B.2.9. same as A.2.3 | C.2.1. Novel antimicrobials fall in the CAP mandatory scope<br>C.2.2. PRIME like support scheme, including rolling review<br>C.2.3 Require companies to develop AMR lifecycle management plan<br>C.2.4. same as B.2.3: Optimise package size<br>C.2.5. same as B.2.5: Tighten prescription requirements for antimicrobials<br>**C.2.6. Transferable voucher independent and in addition to data/market protection for antimicrobial products.**<br>C.2.7. Consider adapted system for authorisation of phage therapies and other alternative products |

| Option A | Option B | Option C |
|---|---|---|
| **Future proofing** | | |
| A.3.1. Maintain current exemptions from the scope of the legislation – add some clarifications/conditions<br>*GMO OPTIONS*<br>A.3.2. Clinical trials: a risk-based approach is applied to determine when a specific GMO assessment is required.<br>A.3.3. An environmental risk assessment continues to be performed (by EMA) in the context of the marketing authorisation procedure. | B.3.1. Adapted regulatory framework for certain categories of novel products/technologies<br>*GMO OPTIONS*<br>B.3.2. same as A.3.2 but for clinical trials: Where required, the assessment of the GMO aspects of investigational medicinal products is performed at Member State level<br>B.3.3. Adapt certain definitions, including that of medicinal product and *delink scope from industrial process*.<br>B.3.4. Create a central *classification mechanism* for advice on whether products are medicines or not | C.3.1. Adapted regulatory framework for certain categories of novel products/technologies<br>C.3.2. Clinical trials: a risk-based approach is applied to determine when a specific GMO assessment is required.<br>C.3.3. Same as B.3.3. Adapt certain definitions, including that of medicinal product and *delink scope from industrial process.*<br>For specific cell-based (ATMP) medicinal products [*-link with revision of BTC legislation*]:<br>C.3.4. adapted regulatory requirements to facilitate production in the hospital setting<br>C.3.5. less complex cell-based medicinal products to be defined on the basis of clear risk-based approach<br>C.3.6. Introduction of a regulatory sandbox environment, in the context of complex/cutting-edge 'medicinal product'<br>C.3.7. Same as B.3.4. Create a central [i]*classification mechanism* for advice on whether products are medicines or not. |
| **Access** | | |
| A.4.1. Facilitate 'multi country packs' with labelling to allow their placing on the market in several Member States.<br>A.4.2. Milestone incentive – +6 months data protection if product marketed in all MS within 6 years.<br>A.4.3. (non-regulatory option) Voluntary reporting of market launches within 2 years of centralised authorisation.<br>A.4.4. Promote placing on the market in all Member States within 5 years | B.4.1. Conditional marketing authorisation: more powers to regulators to enforce obligations for post-market evidence generation.<br>B.4.2. Require MAHs to notify regulators of their market launch intentions.<br>B.4.3. Obligation to place a centrally authorised medicine on the market in the majority of Member States within 5 years<br>B.4.4. Requirement to MAH applying for MRP/DCP to include small markets | C.4.1. Conditional marketing authorisation: UMN incentives are only granted upon switching to standard MA.<br>C.4.2. same as A.4.1. Facilitate 'multi country packs' with labelling to allow their placing on the market in several Member States.<br>**C.4.3. 2 years of protection conditional to launch of all EU markets within 2 years**<br>C.4.4. same as B.4.4.: Requirement to MAH applying for MRP/DCP to include small markets |
| **Competition: generic, biosimilar entry** | | |
| A.5.1. New simpler regulatory pathway for generics<br>A.5.2 No change to current situation and no restriction on duplicate marketing authorisations. | B.5.1. same as A.5.1. New simpler regulatory pathway for generics<br>B.5.2. Interchangeability of biosimilars with their reference product will be generally recognised | C.5.1. same as A.5.1. New simpler regulatory pathway for generics<br>C.5.2. same as B.5.2. Interchangeability of biosimilars with their reference product will be generally recognised |

| Option A | Option B | Option C |
|---|---|---|
| | B.5.3. Broaden Bolar exemption<br>B.5.4. Extend Bolar exemption beyond generics<br>B.5.5. Specific (regulatory) incentive for a limited number of first biosimilars<br>B.5.6.a. Reforming the duplicates regime: No auto-biologicals.<br>B.5.6.b. Duplicates restricted to cases of IP protection or co-marketing | C.5.3. same as B.5.3. Broaden Bolar exemption<br>C.5.4. same as B.5.4. Extend Bolar exemption beyond generics<br>C.5.5. same as B.5.6.b Duplicates restricted to cases of intellectual property protection or co-marketing |
| **Security of supply** | | |
| A.6.1. Encourage use of HMA/EMA guidance definitions<br>A.6.2. Notifications two months in advance<br>A.6.3. Marketing authorisation offered to another MAH before a permanent withdrawal<br>A.6.4. Use of the Falsified Medicines Directive (FMD) system to monitor shortages<br>A.6.5. EU coordination to exchange information on supply and supply chains | B.6.1. Introduce an EU definition of a shortage<br>B.6.2. Increase notification period to 6 months in advance<br>B.6.3. Shortage prevention and mitigation plans added to GMP for all medicines<br>B.6.4. Stockpiling requirements for MAHs and wholesalers for critical medicines<br>B.6.5. Introduce an EU shortage monitoring system<br>B.6.6. Require specific penalties for breaking supply obligations.<br>B.6.7. Expanded requirements for key suppliers and back-ups to diversify supply chain<br>B.6.8. Increase transparency of the supply chain, including active supply sites. | **C.6.1. Introduce an EU definition of a shortage**<br>**C.6.2.a. Withdrawals: Increase notification period to 12 months**<br>**C.6.2.b and at least 6 months in advance for all shortages (non-withdrawal).**<br>**C.6.2.c Introduce a common template for reporting withdrawals and shortages.**<br>**C.6.3. Stockpiling requirements for MAHs for unfinished critical medicines, as appropriate**<br>**C.6.4. same as A.6.3 Marketing authorisation offered for transfer to another MAH before a permanent withdrawal**<br>**C.6.5. MAHs to have shortage prevention and mitigation plans for all medicines**<br>**C.6.6. Monitoring remains at MS level, with information exchange based on national monitoring, using a common format**<br>**C.6.7. Same as B.6.7. Expand requirements to diversify supply chains.**<br>**C.6.8. Establish a mechanism of information exchange to identify bottlenecks / vulnerabilities**<br>**C.6.9. same as B.6.8. B.6.8. Increase transparency of supply chains** |
| **Quality and manufacturing** | | |

| Option A | Option B | Option C |
|---|---|---|
| A.7.1. Strengthen enforcement by introducing harmonised system of sanctions.<br>A.7.2. Inclusion of the information on the sustainability performance of supply chains actors by using international standards in the application dossiers.<br>A.7.3. Adaptation of legislation/inclusion of specific provisions covering new manufacturing methods | B.7.1. Improve oversight of supply chains *by modifying the provisions on inspections*<br>B.7.2. Reinforcing Member States GMP and GDP inspections capacity by setting up a mandatory joint audit scheme.<br>B.7.3. Stronger overall responsibilities of MAH over the entire supply chain.<br>B.7.4. same as A.7.3. Adaptation of legislation/inclusion of specific provisions covering new manufacturing methods | C.7.1. Strengthen the oversight of the sites within a supply chain *by extending the scope of mandatory inspections and modifying provisions on inspections*<br>C.7.2. Stronger EMA role in oversight of coordination of inspections, including in setting up multinational inspection teams.<br>C.7.3. same as B.7.2. Reinforcing Member States GMP and GDP inspections capacity by setting up a mandatory joint audit scheme.<br>C.7.4. same as A.7.3. Adaptation of legislation/inclusion of specific provisions covering new manufacturing methods |
| **Address environmental challenges[ii]** | | |
| A.8.1. No change<br>A.8.2. Obligation to include information on sustainability performance of supply chain using international standards | B.8.1. Include assessment of the environmental risk of manufacturing into ERA, including main supply chain actors (API, raw materials).<br>B.8.2. Strengthen the ERA requirements and conditions of use for medicines<br>B.8.3. Include the AMR aspects in GMP to address environmental challenges. | **C.8.1. Include assessment of the environmental risk of manufacturing into ERA, including main supply chain actors (API, raw materials).**<br>**C.8.2. same as B.8.2. Strengthen the ERA requirements and conditions of use for medicines**<br>**C.8.3. Advisory role of EMA on ERA and green manufacturing aspects and quality (e.g. with relation to generics)**<br>**B.8.4. Include the AMR aspects in GMP to address environmental challenges.** |
| **COVID-19 lessons learnt to be applied during and beyond crises** | | |
| A.9.1. No further changes apart from the extension of the EMA mandate | B.9.1. Refusal of immature applications<br>B9.2. Codification of rolling reviews for UMNs | C.9.1. same as B.9.1. Refusal of immature applications |

## A.2. The baseline situation

### *A.2.1. Policy Block A (Baseline): support for innovation, including unmet medical needs*

Table 2 presents a qualitative assessment of the likely future impacts of the current regulatory arrangements on innovation. It acknowledges that the current system – the baseline – has been a catalyst for innovation over the past 15 years and would be likely to continue to encourage innovation going forwards, were it to continue unchanged from its present arrangements. In simple terms, the table presents a dynamic view of the baseline situation.

*Table 2 Baseline situation: assessment of future impacts of current incentives for innovation*

| **Assessments of innovation related sub-themes** |
|---|
| 1. Incentives |
| The current system provides incentives for innovation in terms of data (8 years) and market protection (2 years) to give time to developers to recoup their investment by delaying the entry of generics or biosimilars. These are without prejudice to intellectual property (IP) protection and specific rewards and market exclusivity for orphan and paediatric indications.<br>The evaluation found the expanded scope and harmonised incentives of the current regulatory system had contributed to the growing numbers of applications for new medicines received by the EMA. Feedback from originators underlines support for the status quo and the relevance of current incentives, while other stakeholder groups and especially the representatives of generic companies and patients' groups see the current arrangements as favouring one particular model of innovation, and to a degree that is not optimal over other important objectives are considered (e.g. patients' access to affordable medicines).<br>We identified several factors that present challenges for the current arrangements' ability to continue to encourage innovation to the extent that it has done in the past. These issues largely revolve around the exciting advances in science and technology and the increasing numbers of more complex medicinal products and a greater diversity of manufacturing methodologies. These trends are largely to the cost and time of making and assessing applications, rather than acting as a brake on innovation, however, it is conceivable that the current system is feeding forward into developers' planning and causing originators to look at less ambitious candidates or even to look to other regulatory systems in the first instance.<br>Another external factor includes the increasing cost of medicines research, with statistics showing a long-run decline in research productivity overall (based on average success rates across phases of development), albeit these data point to an improvement in regulatory submission success rates. This trend is possibly driven in part by regulators' encouragement of and reward for increasingly risky or aspirational research.[1]<br>Given the long-run nature of medicines development cycles, we assume historical growth rates – in the numbers of innovative medicines – will continue to hold in the medium term but may start to slow slightly in the longer term. In 2021, the EMA approved 92 new medicines and 53 new active substances[2]. As such, EU health care systems and patients would continue to see an expanding pool of novel medicines and treatment options in the next five years with some fall off in the rates |
| 2. Expedited regulatory schemes |
| The current legislation successfully introduced several new schemes such as conditional marketing authorisation (CMA) and accelerated assessment (AE) to allow earlier authorisation of innovative products of major interest for public health. These regulatory pathways have supported the authorisation of more innovative medicines, and these expedited schemes have been given a further boost by the EMA's introduction of the Priority Medicines Scheme (PRIME), which is outside the legislation currently, but is nonetheless attracting a growing number of applications for promising medicines that address unmet medical needs.<br>Our consultations confirmed the added value of these expedited regulatory schemes from an innovation perspective, with originators expressing strong support for the retention or enhancement of these existing pathways. By contrast, while national competent authorities and health payers acknowledge the potential boost to innovation, there was a concern that these expedited pathways were being used more for the convenience of industry and less for public health. Health payers and HTAs argued that the CMA had encouraged early submission of immature applications, and that the resulting conditional authorisations were difficult to assess in terms of cost-effectiveness – against standard treatments – and that there was a hardening of attitudes towards these regulatory pathways, with approvals for reimbursement become less likely in the absence of supporting evidence.<br>Analysis of EMA statistics show increasing numbers of applications and authorisations running through these expedited schemes, especially CMAs and PRIME, many of which relate to major innovations relating to unmet medical needs.<br>We would expect this expansion in interest and activity to continue over the next 5-10 years – and possibly intensify – even within the current regulatory system.<br>There is a good pipeline of novel medicines in development, driven in part by more specific regulatory actions in the EU and the US, and relating to rare diseases and paediatric medicines in particular.[3] There is a substantial and growing interest across all stakeholder groups in addressing a number of key aspects around unmet medical needs, whether that is coming from patients groups and health systems or regulators and payers wanting to |

[1] For a trend analysis, see exhibit 27 of 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022.

[2] https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2021_en.pdf

3 https://invivo.pharmaintelligence.informa.com/-/media/supporting-documents/in-vivo-issue-pdfs/iv2003_lrs.pdf

| Assessments of innovation related sub-themes |
| --- |
| frame a coherent definition / set of criteria or major public private research initiatives seeking to develop breakthroughs around specific UMNs, such as the €2.4bn Innovative Health Initiative (IHI) supported by Horizon Europe. Perhaps most critical, there is evident growth in investment in cell and gene therapies, and the EMA and other regulators are handling a growing number of CGT / ATMP applications. This next wave of pharma technology has the potential to improved research productivity, accelerate innovation, expand treatment options and address UMNs and all within the existing regulatory arrangements.[4] |
| 3. Repurposing |
| There is an extended length of (market) protection available for new indications/repurposed medicinal products, whereby the 8+2+(1) major development would be maintained<br>The current legislative arrangements include a special incentive that encourages and rewards originators for identifying opportunities to extend the use of existing medicines to include new indications. This is used largely with newer medicines and is used less often with off-patent or off-label products, which is the main focus of concerns to promote repurposing.<br>While repurposing was one aspect where all stakeholder groups judged the current arrangements to have been less effective in driving a significant change in behaviour, the EMA annual reports and statistical highlights show the number of extensions of indications recommended is increasing over time: 51 recommendations in 2017, 65 in 2018, 60 in 2019, 83 in 2020 and 80 in 2021.[5]<br>From this perspective, the current arrangements are likely to see a growing number of extensions, however, the commercial uncertainty around repurposing suggest the current level of incentives are unlikely to result in a substantive change in the underlying level of repurposing of medicines. This may be the case for older medicines in particular, where there is a weaker business case for extensions, as products near the end of the patent or regulatory protection periods, and paradoxically where there is a greater likelihood that wider health benefits have been identified through off-label uses of existing medicines.<br>Originators are motivated to apply for extensions to new indications in the early years following the original marketing authorisation, taking advantage of the 8+2+1 incentive, however the incentive is not always strong enough to offset the costs / risks associated with repurposing medicines as they approach the end of the period of IP or regulatory protection.<br>For novel medicines, a continuation in the expansion in the numbers of new medicines being submitted to the EMA for assessment – and the growing number of positive opinions – is likely to continue to drive, indirectly, an expansion in the numbers of new indications / variations extensions applied for.<br>The current regulatory arrangements are therefore likely to accommodate an increase in demand for extensions of existing medicines to new conditions, which will continue to expand treatment options for patients. Support for repurposing will remain quite limited. |

Table 3 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories. For most impact types, we have concluded that the baseline policy option would be likely to have a largely neutral effect. That is, there would be no substantive change, positive or negative, in impacts over time. We foresee several areas of positive impact that reflect the current regulatory arrangements past successes, relating primarily to the realms of research and innovation, treatment options for patients and support to Europe's research-intensive pharmaceutical industry. There are many exciting new developments already in progress, around advanced therapies, novel products, next generation manufacturing, real-world evidence, and more. The current regulatory system has not impeded these global developments, and as such, one could expect the current regulation to continue to accommodate this progress and the benefits that will follow from it.

The current arrangements have not been particularly influential in changing behaviour around repurposing, albeit we would expect the gradual increase in the number of extensions to continue. In terms of the downside, the current system's expedited pathways are causing difficulties for health technology agencies nationally, which struggle to determine the cost-

[4] https://www.marketwatch.com/press-release/europe-cell-and-gene-therapy-market---size-by-type-by-distribution-channel-and-forecast-till-2022-2031-2022-03-22

[5] https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines/medicine-evaluation-figures#annual-medicines-highlights-(2015-2021)-section

effectiveness of new medicines with only limited data, and where there is less likelihood that these innovative treatments will be approved for reimbursement and where they are there may be less good treatment outcomes for patients as a higher proportion of expedited medicines prove to be less effective than had been anticipated.

*Table 3 Baseline – Summary assessment of incentives for innovation*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Incentives | +++ | +/- | +/- | +/- | +/- | +++ | +/- | ++ | +/- |
| Expedited pathways | ++ | +/- | +/- | +/- | +/- | + | - | - | +/- |
| Repurposing | +/- | +/- | +/- | +/- | +/- | +/- | +/- | + | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### *A.2.2. Policy Block B (Baseline): Antimicrobial Resistance (AMR)*

As noted in the problem analysis, the EC has several flagship projects underway that aim to restrict and optimise the use of antimicrobials, which are encompassed by the EU One Health Action Plan against AMR (June 2017)[6] built on 3 main pillars:

- Making the EU a best practice region
- Boosting research, development and innovation
- Shaping the global agenda

The Commission has also adopted the first deliverables of the plan, for example the EU Guidelines on the prudent use of antimicrobials in human health.

These commitments are underlined by the EC 2020 Pharmaceutical Strategy, which highlights the importance of AMR in the context of unmet medical needs, and presents two flagship initiatives in the field of AMR: (i) a public procurement mechanism to generate pull incentives; (ii) a role for the new Health Emergency Response Authority (HERA) in the process of promoting investment and coordinating research, development, manufacturing, deployment and use of novel antibiotics; and it furthermore commits to (iii) Review the pharmaceutical legislation with the aim of restricting and optimising the use of antimicrobial medicines.

From the perspective of the EU general pharmaceutical legislation, the baseline is clear: the current legislation includes no special incentives or obligations for the development of or prudent use of antimicrobials. As such, we see no change in impact (across the different impact dimensions) if the current scenario were to continue.

While the current legislation is silent on AMR, statistics show that the problem is wide ranging and expected to worsen without further interventions by governments and health systems around the world.

- The social costs of AMR are high and increasing
  - It is estimated that each year about 670,000 infections occur, and that 33,000 Europeans die as a consequence of antibiotic-resistant bacteria. With the burden

[6] https://ec.europa.eu/health/antimicrobial-resistance/eu-action-antimicrobial-resistance_en

being highest in the elderly and infants[7]. It is also estimated that AMR costs the EU €1.5bn per year in healthcare costs and productivity losses.

- The use of antimicrobials in Europe is reducing overall but with substantial unevenness across the EU
  - Stewardship measures are expected to continue to restrict and optimise the use of antimicrobials overall, however, there is considerable variability in stewardship policies and practices across the EU.
- The global AM pipeline is much weaker than other therapeutic areas

The development challenge is widely documented, with a weak global pipeline that is not expected to be rebuilt without substantive public support, as there are evident and growing market failures, with an evident gap between the typical cost and scale of the scientific challenge involved in developing new antimicrobials and the typical income and profit that can be derived from sales of these products. Global efforts to reduce use is increasing this gap between costs and benefits.

- The WHO Global Observatory on Health Research and Development monitors antibacterial products in development, and its April 2021 dashboard[8] shows that as of September 2020, there was a total of 41 antibiotics and 27 non-traditional antibacterial agents in clinical development globally. Those 68 products are distributed across the three phases of clinical trials. Overall, the WHO concludes that the clinical pipeline and recently approved antibiotics are insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance.
- We would expect to see increasing support for innovation and novel antimicrobials, through major public research programmes, such as Horizon Europe, and other regulators' actions (FDA), which should help to sustain and possibly improve the global pipeline, from its admittedly weak status currently.

### A.2.3. *Policy Block C (Baseline): Future Proofing*

To regulatory system needs to be adaptive to adequately protect public health[9]. Exclusions exist to limit the scope of what medicinal products fall within the pharmaceutical legislation (currently there are seven product categories excluded from the scope). However, novel medicines, approaches and processes which do not naturally meet the scope or definitions or which the legislation does not fully fit can therefore find themselves unregulated or subject to unintended barriers.

Our consultations and desk research suggest that advances in science and technology have led to several regulatory challenges:

- Delays and inefficiencies due to uncertainty around the most appropriate regulatory pathway(s) resulting in applications being assessed in several committees rather than

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[7] Cassini, A., Högberg, L. D., Plachouras, D., Quattrocchi, A., Hoxha, A., Simonsen, G. S., Colomb-Cotinat, M., Kretzschmar, M. E., Devleesschauwer, B., Cecchini, M., Ouakrim, D. A., Oliveira, T. C., Struelens, M. J., Suetens, C., Monnet, D. L., Strauss, R., Mertens, K., Struyf, T., Catry, B., … Hopkins, S. (2019). Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *The Lancet Infectious Diseases*, *19*(1), 56–66. https://doi.org/10.1016/S1473-3099(18)30605-4

[8] https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antibacterial-products-in-clinical-development-for-priority-pathogens

[9] Klein, K., Stolk, P., de Bruin, M. L., & Leufkens, H. (2021). Regulatory density as a means to refine current regulatory approaches for increasingly complex medicines. *Drug Discovery Today*, *26*(10), 2221–2225. https://doi.org/10.1016/J.DRUDIS.2021.04.005

one, additional external advice being sought, and applicants being asked to clarify evidence or resubmit applications. The problem is exacerbated by the fact that each committee's mandate is narrow, fitting to the scope of the framework under which is set up, and there is a lack of coordination/consultation between the committees.

- Legislative barriers within regulatory pathways and processes due to definitions and guidance that do not apply to changing technology and heterogenous interpretation of such guidance by member states.
- Several new technologies, product combinations and innovative processes are causing uncertainty regarding their inclusion within the scope of the legislation in part as a result of the narrowness of current definitions and uncertainty on which legislative framework is most appropriate. For instance, certain technologies can also be subject to other EU legal frameworks that provide for safety, quality and efficacy requirements such as those for medical devices, substances of human origin, etc.

Challenges are particularly evident around these key areas:

1. Gene Therapy medicinal products:
   - Advanced therapy medicinal products (ATMPs): ATMPS are highly innovative and complex medicines based on genes, tissue or cells. Classification of these complex products can be complicated due to difficulties to distinguish between different biological subcategories.[10] These classification challenges are further complicated by the blood, cells, tissue (BTC) legislation where there are difficulties distinguishing between BTC and medicines because of (a) different criteria set in the general pharmaceutical legislation (industrial process, intention to put on market, hospital exclusion) and in the ATMP regulation (substantial manipulation, non-homologous use) as well as (b) lack of coordination between authorities/advisory bodies in relevant sectors on interpretation of these borderline criteria.[11]
   - Hospital exemption: Target markets for ATMPs are often small and not appealing for larger pharmaceutical organisations to invest in their development. The hospital exemption (HE) was implemented to encourage ATMP production in the hospital setting for non-commercial purposes to facilitate patient access to affordable novel therapies. For example, the price of a CAR-T developed under the HE-ATMPs pathway is one-third of the cost of commercial CAR-Ts available.[12] However, the HE has been interpreted and implemented differently across Member States, which risks undermining patient safety[13]. This is because there is no requirement to collect data on safety of efficacy of HE products. Furthermore, HE products do not fall under the centralised procedure (CP) limiting patient access. However, the HE has enabled the manufacture of a 'modest' number (~12) of ATMPs within EU between 2009 and 2017[14]. There are also concerns the HE is creating a competitive

[10] Iglesias-López, C., Agustí, A., Obach, M., & Vallano, A. (2019). Regulatory framework for advanced therapy medicinal products in Europe and United States. *Frontiers in Pharmacology*, *10*(JULY), 921. https://doi.org/10.3389/FPHAR.2019.00921/BIBTEX

[11] BTC impact assessment

[12] Trias, E., Juan, M., Urbano-Ispizua, A. et al. The hospital exemption pathway for the approval of advanced therapy medicinal products: an underused opportunity? The case of the CAR-T ARI-0001. Bone Marrow Transplant 57, 156–159 (2022). https://doi.org/10.1038/s41409-021-01463-y

[13] EuropaBio (2020) *EU ATMP Hospital Exemption*.

[14] Coppens, D. G. M., Hoekman, J., de Bruin, M. L., Slaper-Cortenbach, I. C. M., Leufkens, H. G. M., Meij, P., & Gardarsdottir, H. (2020). Advanced therapy medicinal product manufacturing under the hospital exemption and other exemption pathways in seven European Union countries. *Cytotherapy*, *22*(10), 592–600. https://doi.org/10.1016/J.JCYT.2020.04.092

disadvantage to commercial ATMP developers that incur higher development costs through the CP.

2. Combinational products: Medicines are increasingly being used in combination with a medical device, usually to enable the delivery of the medicine. Medical products are regulated through the pharmaceutical legislation, whereas devices are regulated through the medical device legislation. However, these combinational products have brought regulatory difficulties for NCAs in terms of uncertainty whether they should be classified as a medical product or medical device and what regulatory framework applies.
3. Industrial process/manufacture: Technological and scientific advances have raised issues regarding the definition of 'industrial process' or 'industrial manufacture'; these terms were to limit the scope of what products fall within pharmaceutical legislation. Differences in the interpretation of the definition has caused challenges for Member States in determining what legislation is appropriate or created legislative gaps where products are not regulated, meaning some products are not regulated under pharmaceutical legislation when they should be, thus potentially compromising the safety of patients. This has been particularly problematic for bedside production, personalised medicines, industrially prepared radionucleotides and medical products derived from blood in the hospital setting.
4. Novel technologies and approaches: There is an increasing number of novel technologies and approaches emerging that are transforming the development and production of medicines[15]. Notable examples include the application of novel manufacturing approaches to a range of areas from developing personalised medicines to addressing medicine shortages. Other areas of notable advancement include the application of artificial intelligence to medicines in a range of areas from improving medicine development, clinical trials, and medicine manufacturing[16]. These rapidly advancing technologies are bringing new regulatory challenges in terms of how best to accommodate them under the current legislation.

Medicinal products that contain or consist of GMOs, such as gene based and cell-based therapies, will increasing become more important as they have great potential to treat a range of diseases, including areas of unmet medical needs. There are specific requirement for products contain or consist of GMOs. During marketing authorisation: the evaluation of the environmental impacts of medicinal products for human use that contain or consist of GMOs is done, in accordance with the principles set out in Directive 2001/18/EC, by EMA or the national competent authority, as applicable, in the context of the assessment of the marketing authorisation application pursuant to the medicinal product legislation. Investigational medicinal products for human use (those in clinical trials) that contain or consist of GMOs are subject to the GMO legislation. Some Member States apply Directive 2001/18/EC, other Member States apply Directive 2009/41/EC and others decide on a case-by-case basis or apply both. This creates complexities for developers as different MSs have different requirements and stakeholders involved, ultimately causing regulatory burdens and delays in

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[15] Anklam, E., Bahl, M. I., Ball, R., Beger, R. D., Cohen, J., Fitzpatrick, S., Girard, P., Halamoda-Kenzaoui, B., Hinton, D., Hirose, A., Hoeveler, A., Honma, M., Hugas, M., Ishida, S., Kass, G. E. N., Kojima, H., Krefting, I., Liachenko, S., Liu, Y., … Slikker, W. (2022). Emerging technologies and their impact on regulatory science. *Experimental Biology and Medicine*, *247*(1), 1–75. https://doi.org/10.1177/15353702211052280

[16] Paul, D., Sanap, G., Shenoy, S., Kalyane, D., Kalia, K., & Tekade, R. K. (2021). Artificial intelligence in drug discovery and development. *Drug Discovery Today*, *26*(1), 80–93. https://doi.org/10.1016/J.DRUDIS.2020.10.010

market authorisations. To overcome these challenges, NCAs and the EC have updated and published good practice documents and common application forms concerning the conduct of clinical trials with GMOs to harmonise approaches across Member States. Specific ERA for GMO-containing medicinal products has been introduced for certain categories of investigational medicinal products containing GMOs that are highly unlikely to pose a risk to the environment or to public health to simplify requirements for developers.

According to our stakeholder consultation the current approach is still not ideal, and these main challenges were highlighted:

- Delayed authorisations of GMO-containing therapies and ultimately slower access to medicines[17]: GMO assessments are complex and vary across the EU leading to delays in clinical trials and authorisation of GMO-containing medicinal products[18]. Further harmonisation is needed for Contained Use versus Deliberate Release classification, risk classifications for the same GMOs (within Contained Use), and data requirements (content and format). GMO assessments are not always necessary as exemplified by the temporary derogation from some provisions of the GMO requirements for potential COVID-19 treatments and vaccines.
- Increased cost and burden of clinical trials in EU leading to reduced attractiveness to conduct trials in EU[19]: The EU is considered less attractive than other regions for conducting clinical trials. The number of new gene therapy clinical trials is proportionally lower in EU (55% of all new clinical trials) than in North America (71% of all new clinical trials)[20].
- Reduced investment and consequently development of GMO containing therapies[21]: In the US, a "categorical exclusion" exists for gene therapies, vectored vaccines, and related recombinant viral or microbial products[22]. However, in the EU, these types of GMO-containing products require a GMO assessment. This is seen to be delaying and restricting access to GMO-containing medicinal products in the EU[23]. Furthermore,

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[17] Technopolis. (2022). *Stakeholder Consultation Narrative Data: KIIs, OPC, Targeted Survey*.

[18] Beattie, S. (2021). Call for More Effective Regulation of Clinical Trials with Advanced Therapy Medicinal Products Consisting of or Containing Genetically Modified Organisms in the European Union. *Human Gene Therapy*, *32*(19–20), 997–1003. https://doi.org/10.1089/hum.2021.058;

Lambot, N., Awigena-Cook, J., Reimer, T., Persson, A., Romanetto, J., Friedeberg, B., Acha, V., Dandapat, S., Ruppert, T., Correas, C., Wonnacott, K., Fleischmann, T., Holzhauser, C., Galaup, A., Montes, F., Garcia, S., Tellner, P., & Beattie, S. G. (2021). Clinical trials with investigational medicinal products consisting of or containing genetically modified organisms: implementation of Clinical Trials Regulation EU 536/2014. *Cell and Gene Therapy Insights*, *7*(9), 1093–1106. https://doi.org/10.18609/CGTI.2021.143

[19] Technopolis. (2022). *Stakeholder Consultation Narrative Data: KIIs, OPC, Targeted Survey*.

[20] Alliance for Regenerative Medicine. (2019). *CLINICAL TRIALS IN EUROPE: RECENT TRENDS IN ATMP DEVELOPMENT*. www.alliancerm.org

[21] Technopolis. (2022). *Stakeholder Consultation Narrative Data: KIIs, OPC, Targeted Survey*.

[22] U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research. (2015). *Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products; Guidance for Industry*. https://www.fda.gov/media/91425/download

[23] Iglesias-Lopez, C., Obach, M., Vallano, A., & Agustí, A. (2021). Comparison of regulatory pathways for the approval of advanced therapies in the European Union and the United States. *Cytotherapy*, *23*(3), 261–274. https://doi.org/10.1016/J.JCYT.2020.11.008

globally companies invested €20.1B in cell- and gene- based therapies in 2021; EU only raised €2.9B funding which was down 8% compared to 2020[24].

- EU patients are at risk of not having access to novel life-saving therapies[25]: Developers plan to submit ten market authorisation applications (MAAs) for gene therapies in the United States (USA) next year (2022), whereas they only plan to submit two of these MAAs in the EU[26]. However, a retrospective analysis until 2020 reported the EU authorised fifteen ATMPs, compared to nine in the USA[27].

This suggests EU regulatory framework is not well aligned with other regions, and a proportion of new medicines are being developed and launched in other markets (US) rather than the EU. Thus, further streamlining and harmonisation of the GMO assessment process would be desirable to avoid unnecessary delays in authorisation of GMO-containing medicines and for EU to be competitive concerning innovation of GMO medicines. Otherwise, EU patients may be at risk of not having timely access to novel life-saving therapies.

Table 4 presents an assessment of the likely future scenario if the existing scope, definitions GMO requirements for market authorisation and clinical trials continue without amendment. For most impact types, we have concluded that the effect of the baseline policy option would be largely negative. This reflects the continuing and rapid pace of technological change which will increasingly challenge the legislation in this baseline situation leading to decreasing efficiency, predictability and gaps in the regulatory framework.

*Table 4 Baseline Policy Option: summary assessment of future proofing*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Scope and definitions | - | - | +/- | - | - | - | +/- | - | +/- |
| GMOs | +/- | +/- | +/- | - | - | - | +/- | +/- | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### *A.2.4. Policy Block D (Baseline): Access*

To promote timely access to innovative medicines, particularly those that meet a previously unmet medical need or would be used in a public health emergency, the EMA may fast-track approval by granting a conditional marketing authorisation (CMA). This allows for medicines to enter the market on less comprehensive clinical data than normally required. It does,

[24] Alliance for Regenerative Medicine. (2022). *Cell & Gene State of the Industry Briefing*. https://alliancerm.org/arm-event/sotibriefing/;

Lambot, N., Awigena-Cook, J., Reimer, T., Persson, A., Romanetto, J., Friedeberg, B., Acha, V., Dandapat, S., Ruppert, T., Correas, C., Wonnacott, K., Fleischmann, T., Holzhauser, C., Galaup, A., Montes, F., Garcia, S., Tellner, P., & Beattie, S. G. (2021). Clinical trials with investigational medicinal products consisting of or containing genetically modified organisms: implementation of Clinical Trials Regulation EU 536/2014. *Cell and Gene Therapy Insights*, *7*(9), 1093–1106. https://doi.org/10.18609/CGTI.2021.143

[25] Technopolis. (2022). *Stakeholder Consultation Narrative Data: KIIs, OPC, Targeted Survey*.

[26] Alliance for Regenerative Medicine. (2022). *Cell & Gene State of the Industry Briefing*. https://alliancerm.org/arm-event/sotibriefing/

[27] Iglesias-Lopez, C., Obach, M., Vallano, A., & Agustí, A. (2021). Comparison of regulatory pathways for the approval of advanced therapies in the European Union and the United States. *Cytotherapy*, *23*(3), 261–274. https://doi.org/10.1016/J.JCYT.2020.11.008

however, require the MAH to fulfil specific obligations including the generation of additional post-authorisation evidence.

At present, there is no obligation on MAHs of centrally authorised medicines to enter a specific number or a particular set of EU markets. The only legal provision, known as the 'sunset clause', that applies is that the MA will cease to be valid if a medicine is not placed on any EU market within three years of the authorisation being granted or if the medicine is removed from the market for three consecutive years. This provision, however, is satisfied by placement on a single EU market. The EU pharmaceutical legislation currently also does not provide any incentives for MAHs to place their products on markets that, on their own, do not offer a sufficient business case for doing so.

*Table 5 Baseline situation: Access*

| **Continuation of baseline situation: effect on access** |
|---|
| *1. Accelerated assessment* |
| Accelerated procedures, conditional marketing authorisations (CMA) exist. |
| *2. Obligations and incentives for placement on the market* |
| For centrally authorised medicines companies market the product as they see fit in one or more Member States. Placing on the market in a single Member State satisfies the obligation to place on the EU market. There is a sunset clause - a marketing authorisation can be withdrawn if the product is not placed on the market within 3 years. |

Technopolis Group, based on information provided by client

A 2019 longitudinal analysis of the CMA instrument has suggested it has primarily been used as a path for regulators and companies to take when available evidence was not (yet) strong enough to support a regular authorisation[28]. This study furthermore suggested the pathway is plagued by substantial ambiguity about the need to balance patient's need for swift access to potentially life-saving medicines on the one hand with generation of sufficient evidence on effectiveness and risk on the other. These concerns have been echoed by interviewed representatives of NCAs and public health organisations who fear that increased use of accelerate access pathways places a heavy burden on health systems charged with deciding whether to allow these fast-tracked medicines into packages of reimbursed care based on limited evidence. It stands to reason that without changes to the procedure or to the ability of regulators to enforce post-authorisation evidence generation obligations, this trend will continue to put pressure on health systems.

In the market access and pricing environment the current trend is towards increasing use of 'gatekeeping' measures and price controls[29]. Such measures may have the effect of further limiting the number of markets in which products are launched or causing longer delays between authorisation and availability. Although a 2018 study by Ferrario found that, for medicines launched between 2010 and 2014, the time between authorisation and first use of

[28] Hoekman, J., & Boon, W. (2019). Changing standards for drug approval: A longitudinal analysis of conditional marketing authorisation in the European Union. *Social Science & Medicine (1982)*, *222*, 76–83. https://doi.org/10.1016/J.SOCSCIMED.2018.12.025

[29] Deloitte Centre for Health Solutions. (2019). *Patient access to innovative medicines in Europe A collaborative and value based approach*.

cancer medicines had shortened[30], analysis by IQVIA has suggested that between 2014 and 2018 in several countries the average delay had increased.

Thus, there is an assumption that, without EU intervention, the problems of selective market entry and delayed patient access to innovative medicines could remain or even worsen.

*Table 6 Baseline – Summary assessment of incentives for innovation*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Accelerated assessment | +/- | +/- | +/- | +/- | +/- | ++ | - | - | +/- |
| Obligations and incentives for placement on the market | +/- | +/- | +/- | +/- | +/- | +/- | - | - | +/- |
| OVERALL | +/- | +/- | +/- | +/- | +/- | ++ | -- | -- | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### *A.2.5. Policy Block E (Baseline): Competition*

Table 7 presents an assessment of the likely future scenario if the current arrangements on competition are continued with no changes. The current system has resulted in more generics and biosimilars entering EU markets and led to improved access to medicines and lowered healthcare costs.

Evidence from 2005 to 2015 for 7 chronic conditions shows that patient access to treatment has doubled while overall spending has remained flat.[31] In Germany, the waiting time for patients with rheumatoid arthritis to be treated with a biologic has been reduced from 7.4 years to 0.3 years after the introduction of biosimilars.[32] Currently, generics offer 80%[33] savings on average and biosimilars 20%[34] compared to originator products.

*Table 7 Baseline situation: assessment of competition-related themes*

| **Continuation of baseline situation: effect on competition-related subthemes** |
|---|
| *1. Regulatory measures* |
| There are specific, abridged pathways that are applicable for generics and biosimilars. |

[30] Ferrario, A. (2018). Time to Entry for New Cancer Medicines: From European Union-Wide Marketing Authorization to Patient Access in Belgium, Estonia, Scotland, and Sweden. *Value in Health : The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, *21*(7), 809–821. https://doi.org/10.1016/J.JVAL.2018.01.003

[31] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

[32] https://www.pharmatimes.com/magazine/2021/may_2021/15_years_of_biosimilar_access_in_europe

[33] Mestre-Ferrandiz, J., Towse, A. & Berdud, M. Biosimilars: How Can Payers Get Long-Term Savings?. *PharmacoEconomics* **34**, 609–616 (2016).

[34] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilarsv

| **Continuation of baseline situation: effect on competition-related subthemes** |
|---|
| Development and submission times for generics under Art. 10 (1) i.e. standard generic (abridged) application and Art. 10(3) i.e. hybrid (abridged) application are 2-5 and 3-7 years respectively, and are 5-8 years for biosimilars under Art. 10 (4).[35]<br>Generics account for the majority of DCP/MRP applications.[36] Of these, the assessment usually takes 210 days with the national phase of DCP/MRP taking between 4 weeks and 2 years.[35] |
| *2. Faster market access of generics and biosimilars* |
| The Bolar exemption makes it possible to conduct the testing required to obtain regulatory approval for the generic/biosimilar to take place during the patent/supplementary-protection-certificate (SPC) protection period of the reference medicine. According to NCAs, payers and industry representatives (including generic industry representatives) interviewed for this study, this has been beneficial for entry of generics/biosimilars but the provision is applied differently in different member states.[37]<br>There is currently no additional regulatory protection for new biosimilar products. |
| *3. Duplicates* |
| Ordinarily only one market authorisation is granted to an applicant for a specific medicinal product, however the applicant/holder can obtain a duplicate authorisation at reduced cost for the same medicinal product where "*there are objective verifiable reasons relating to public health regarding the availability of medicinal products to healthcare professionals and/or patients, or co-marketing reasons*". MAHs have been making use of this exception to obtain a duplicate authorisation for the first generic product on the basis that its inaugural launch into the market can improve availability.<br>No changes to the duplicate regime will have implications for the biosimilar market (including anti-competitive effects) and could also undermine the availability of treatment options for patients despite the intention behind the existence of the duplicate MA provision. |

The EMA has recommended approval of 5 biosimilars on average each year (based on 84 biosimilars authorised between 2006 and 2021[38]). It is however foreseen that the number of biosimilars approved will increase over time with regulatory protection running out on many biologics esp. in oncology. About 139 biologics are due to lose regulatory protection between 2021 and 2030.[39] EMA has recommended approval of 19 generics on average each year (296 generics authorised between 2006 and 2021[40]) with around 1015 MA applications submitted via the MRP/DCP procedures per year (based on 8120 applications under Art. 10.1 between 2006 and 2013[41]). If current compound annual growth rates for generics and biosimilars (7.1%[42] and 10.5%[43] respectively) are maintained to 2035, the European markets for these product

[35] Mohammed, Y.M. (2019) Regulatory pathways for development and submission activities. *Medical Writing*, 28(2), 8–19.

[36] Ebbers, H. C., Langedijk, J., Bouvy, J. C., Hoekman, J., Boon, W. P., de Jong, J. P., & De Bruin, M. L. (2015). An analysis of marketing authorisation applications via the mutual recognition and decentralised procedures in Europe. *European journal of clinical pharmacology*, *71*(10), 1237–1244.

[37] https://cms.law/en/content/download/77965/2989749/version/1/file/BolarProvisioninEU.pdf

[38] GaBI Online - Generics and Biosimilars Initiative. Biosimilars approved in Europe. Mol, Belgium: Pro Pharma Communications International. Available from: www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe

[39] https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf?_=1640100592119

[40] EMA website

[41] Ebbers, H. C., Langedijk, J., Bouvy, J. C., Hoekman, J., Boon, W. P., de Jong, J. P., & De Bruin, M. L. (2015). An analysis of marketing authorisation applications via the mutual recognition and decentralised procedures in Europe. *European journal of clinical pharmacology*, *71*(10), 1237–1244.

[42] https://www.marketdataforecast.com/market-reports/europe-generic-drugs-market

[43] https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf?_=1640100592119

types would reach around €175 billion and €36 billion respectively from values of €67 billion and €8.8 billion in 2021.

Table 8 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories. For most impact types, we have concluded that the effect of the baseline policy option would be largely neutral. Considering the current regulatory regime, we expect the positive impacts relating to increased competition, savings for health systems and access to patients to continue.

*Table 8 Baseline Policy Option - Summary assessment of competition*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Regulatory measures | +/- | +/- | +/- | +/- | + | +/- | + | + | +/- |
| Faster market access of generics and biosimilars | +/- | +/- | +/- | +/- | + | + | + | + | +/- |
| Duplicates | +/- | +/- | +/- | +/- | - | +/- | - | - | +/- |
| OVERALL | +/- | +/- | +/- | +/- | + | +/- | + | + | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### A.2.6. *Policy Block F (Baseline): Supply Chain Security*

The EU pharmaceutical legislation currently has two provisions that directly connect to security of supply. The first (Article 23a) places an obligation on MAHs to notify NCAs in the relevant Member States if they expect a temporary or permanent withdrawal of an authorised medicine from an EU market. The second (Article 81) obliged MAHs and wholesalers to ensure appropriate and continued supplies of authorised medicines. Both articles need to be transposed into national legislation by the Member States, who may opt to add more specific requirements.

In December 2016, the EMA and Heads of Medicines Agencies (HMA) set up a 'Task Force on the Availability of Authorised Medicines for Human and Veterinary Use'. To improve the collection and standardisation of information on shortages across the EU, in 2019 this task force published a 'Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)'[44]. The guidance includes a template detailing what information should be included. However, many elements are not mandatory and, thus far, are not required by NCAs.

*Table 9 Baseline situation: Security of supply*

| **Market withdrawal notification system** |
|---|
| • *Obligation to notify a withdrawal two months before the interruption in the placing on the market of the product (Article 23a)*<br>• *Obligation to ensure appropriate and continued supplies by MAHs and distributors (Article 81).* |
| **Detecting and reporting shortages** |

[44] European Medicines Agency. (2019). *Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)*.

| Market withdrawal notification system |
|---|
| *The EMA/HMA guidance on detecting and reporting medicine shortages.* |

Despite several methodological challenges posed by lack of standardised comprehensive data, available evidence suggests that across the EU the frequency of shortages and their impact on patients and healthcare providers is increasing. The expectation thus is that, without further action, supply chain disruptions and shortages will continue to happen. At the same time, MS have already introduced a variety of actions at the national level to help protect their security of supply[45]. The impact of these measures on preventing and mitigating the impact of shortages is not yet sufficiently understood but it is likely that, at least at the MS level, they can be effective in protecting the national availability of medicines.

Many MS have invested in recent years in setting up and/or improving shortage notification systems. This has resulted in increased notification of shortages and better insight into key issues such as the extent of the problem, products affected and causes. Nonetheless, substantial space remains to further improve and standardise the collection of information. Given the increasing emphasis on data collection, it may be expected that the costs associated with notifying shortages (to MAHs and wholesalers) and administratively processing notifications (by NCAs) will continue to rise. Introduction of more automated systems for detection of supply problems and sharing of information between parties, however, could reduce these costs.

*Table 10 Baseline Policy Option - Summary assessment of competition*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Market withdrawal notification | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| Detecting and reporting shortages | +/- | - | +/- | +/- | +/- | +/- | - | +/- | +/- |
| OVERALL | +/- | - | +/- | +/- | +/- | +/- | - | +/- | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### *A.2.7. Policy Block G (Baseline): Quality and Manufacturing*

Table 11 presents an assessment of the likely future scenario if the current arrangements on quality and manufacturing are continued with no changes.

*Table 11 Baseline situation: assessment of quality and manufacturing-related themes*

| Continuation of baseline situation: effect on quality and manufacturing |
|---|
| *1. Inspections and sanctions* |

[45] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages* (Issue December).

| **Continuation of baseline situation: effect on quality and manufacturing** |
|---|
| GMP inspections are carried out by national competent authorities (NCAs). The HMA (Joint Human and Veterinary) established an audit programme among the GMP inspectorates of all EEA GMP human and veterinary medicines agencies known as the Joint Audit Programme (JAP) in 2002.[46] Mutual recognition agreements are in place between 44 inspectorates to optimise the use of inspection resources; grant mutual recognition of reports, certificates, authorisations issued by national authorities; reduce technical barriers to trade and avoid duplication of audit work.<br>Under Article 84(1) of Regulation (EC) No 726/2004 and Article 111(8) of Directive 2001/83/EC, Member States are asked to penalise marketing authorisation holders (MAHs) who fail their obligations. The penalties must be dissuasive, proportionate and effective. Such penalties however vary from country to country. Moreover, Regulation 2019/5 has changed the scope of financial penalties by including Article 84a on Regulation 726/2004. This article ensures that financial penalties imposed by the Commission are applicable to the correct legal entities, for example legal entities that are part of the same economic entity as the MAH, legal entities that have decisive influence over the MAH or that could address a non-compliance issue. |
| *2. Sustainability performance of supply chain actors* |
| Sustainability performance of supply chain actors is currently not included. Environmental risk of the API is covered under the ERA (as discussed in the next section). |
| *3. New manufacturing methods* |
| Non-industrial manufacturing methods such as decentralised, continuous manufacturing, etc are not accommodated adequately by the current legislation. |

Table 12 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories. For most impact types, our assessment is that the effect would be largely neutral. We expect that inspections and sanctions will continue to involve administrative burden on the part of MAHs and NCAs.

*Table 12 Baseline Policy Option - Summary assessment of quality and manufacturing-related measures*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Inspections and sanctions | +/- | - | +/- | +/- | +/- | +/- | - | +/- | +/- |
| Sustainability performance | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| New manufacturing methods | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### *A.2.8. Policy Block H (Baseline): Addressing environmental challenges*

Table 13 presents an assessment of the likely future scenario if the current arrangements for addressing environmental challenges are retained.

The ERA is the main mechanism within the current legislation for ensuring environmental sustainability of pharmaceuticals. It is required for all new MA applications whether through a centralised, mutual recognition, decentralised or national procedure and ensures the

[46] https://www.hma.eu/about-hma/working-groups/hma/ema-joint-audit-programme-jap/hma/ema-joint-audit-programme-jap.html

potential environmental risks of pharmaceuticals are adequately assessed. While the outcome of the ERA does not affect the decision to award an MA, it serves as the basis for minimising the amount of pharmaceuticals released into the environment (using appropriate measures), identification of specific risk-minimisation activities to be undertaken by the user of the medicine and appropriate labelling to ensure correct disposal.[47]

*Table 13 Baseline situation: assessment of themes addressing environmental challenges*

| **Continuation of baseline situation: effect on addressing environmental challenges** |
|---|
| *1. Environmental risk assessment (ERA)* |
| If no changes are made to current requirements, the ERA would continue to be performed by companies when applying for an MA. A 0.01 µg/L threshold value for predicted environmental concentration in surface water ($PEC_{SW}$)[48] would continue to be used and any active substance with $PEC_{SW}$ greater than this threshold would undergo further assessment as to its fate in the environment and potential effects on representative organisms. Thereafter precautionary measures or recommendations to minimise risk would be provided if necessary. |

Table 14 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories. For most impact types, we have concluded that the effect of the baseline policy option would be largely neutral. Continued review of potential risks to environment from medicinal products and increased awareness of and promotion of prudent use of pharmaceuticals (outside the legislation e.g. based on the European Union Strategic Approach to Pharmaceuticals in the Environment[49]) could help drive down emissions of pharmaceuticals in the environment and improve waste management to some extent, at least for medicines requiring new MAs.

The impact of these measures on patient and public health is however unknown. There is not enough evidence to show the direct effect of pharmaceutical residues found in the environment e.g. drinking water on human health. The potential effect of long-term exposure on vulnerable populations is also as yet unknown. Potential impacts of AMR have already been covered above.

*Table 14 Baseline – Summary assessment of measures to address environmental challenges*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| ERA | +/- | +/- | +/- | +/- | +/- | +/- | +/- | unknown | + |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### *A.2.9. Policy Block I (Baseline): Lessons from COVID-19*

The pandemic has underlined the added value of an EU-level response to a global pandemic and has resulted in Member States agreeing to extend the role of the EMA in respect to future crises, with the publication of the Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices.

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[47] EMA. (n.d.). *Environmental risk-assessment of medicines*.

[48] Whomsley, R., Brendler-Schwaab, S., Griffin, E. *et al.* Commentary on the draft revised guideline on the environmental risk assessment of medicinal products for human use. *Environ Sci Eur* **31,** 17 (2019).

[49] European Commission, 2019. European Union Strategic Approach to Pharmaceuticals in the Environment

The EMA is now responsible for monitoring medicine shortages that might lead to a crisis, as well as reporting shortages of critical medicines during a crisis. It is also updating the role of the EU Single Point of Contact (SPOC) network, to improve the flow / exchange information on shortages among member states and provide recommendations on management of shortages. The EMA is also updating its plan for Emerging Health Threats; and establishing a list of the main therapeutic groups of medicines necessary for emergency care, surgeries and intensive care, to help prepare the lists of critical medicines to respond to public health emergencies or major events. The EMA will also invest in real-world evidence efforts through the establishment of DARWIN EU[50], a pan-European network of real-world data.

The pandemic focused attention on the EU's ability to forecast demand during crises, secure supplies and manage shortages of critical medicines going forwards.[51] There is an assumption that public health crises are highly likely to occur in future and that against the backdrop of a growing problem with medicines shortages more generally, there is a case for more concerted action at the EU level.

Moreover, learning from this exceptional experience, the EU has sought to improve the regulatory framework in two main areas: a) reducing the number of immature marketing authorisation applications, which can waste public authority resources and create uncertainty over decisions; b) providing a rolling review regulatory pathway for medicinal products addressing UMN, which will allow earlier engagement with developers around potentially critical new medicines.

*Table 15 Baseline situation: assessment of lessons learned from the pandemic*

| **Continuation of baseline situation: effect on shortages, resourcing and speed of assessment** |
|---|
| *Monitoring and mitigating shortages of medicines and devices* |
| The EMA's extended mandate and the main actions agreed in respect to improving the management of shortages of critical medicines should produce improvements in the situation more generally, with greater coordination, data transparency and reallocation of medicines (cross-border) being expected to strengthen a Member State's ability to respond to any important shortages. The proposed European Shortages Monitoring Platform (ESMP) is planned to be implemented by early 2025 and should help to overcome some of the residual technical challenges relating to the fragmented and sometimes inconsistent implementation of reporting systems nationally. The question of interoperability will need to be tackled also through agreements on common data records, architectures, process definitions, etc. |
| Reducing numbers of immature marketing authorisation applications |
| Assessment procedures for CMAs usually involve resolving differences of opinions among regulators regarding the evaluability or suitability of a marketing authorisation application for processing through the CMA pathway. This can be time consuming and slow down the approval process. Between 2006 and 2016, the median number of days spent on assessment procedures for CMAs was 421 (329-491), in comparison to 337 (281-400) for standard applications in the same period. There were 30 CMA granted and 22 unsuccessful CMA applications in the same period. From these 52 applications, 24 did not include a proposal for CMA in the initial application, despite not qualifying for standard marketing authorisation. |
| Rolling reviews of innovative medicines addressing an unmet medical need |
| Unmet medical needs (UMN) are usually conditions that are complex and/or affect small patient populations, which creates uncertainty for medicinal product developers and results in a market failure. Creating better regulator/developer interaction and reducing the approval time for medicinal products addressing UMN can bring very important benefits for patients. The median approval time for medicinal products that address UMN (accelerated assessment) between 2016 and 2020 was 251 days, with an average reduction in the approval time |

[50] https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu

[51] https://www.ema.europa.eu/en/documents/other/reflection-paper-forecasting-demand-medicinal-products-eu/eea_en.pdf https://www.ema.europa.eu/en/documents/other/reflection-paper-forecasting-demand-medicinal-products-eu/eea_en.pdf

| Continuation of baseline situation: effect on shortages, resourcing and speed of assessment |
|---|
| of 1.5 days per year. Rolling reviews for medicinal products that address UMN could help to reduce the total approval time. |

Table 16 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories.

*Table 16 Baseline – Summary assessment of lessons learned from the pandemic*

| Policy sub-themes | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Managing shortages | +/- | - | +/- | +/- | + | +/- | + | ++ | +/- |
| Immature marketing authorisation applications | +/- | +/- | +/- | +/- | +/- | +/- | - | +/- | +/- |
| Rolling Reviews for UMN | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

## A.3. Policy Option A

### *A.3.1. Policy Block A (A.A): support for innovation, including unmet medical needs*

#### Assessment of the key impacts for the policy elements

Table 17 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

*Table 17 Option A - Assessment of the proposed Incentives for Innovation*

| Assessment |
|---|
| 1. Expedited regulatory schemes |
| A.1.1. PRIME – remains under the current scheme |
| This is business as usual (BAU) and as such there would be no additional impacts in comparison with the baseline policy option discussed earlier. |
| 2. Repurposing |
| A.1.2. Establish a non-binding system for scientific assessment |
| The ability to include academic and other scientific evidence within applications for extensions might encourage MAHs to seek approvals for repurposing medicines that are being used off-label, albeit these tend to be older medicines where there is less opportunity to secure sufficient additional income to offset the costs of repurposing. |

Research suggests that where new indications are added, this tends to happen earlier in the period of regulatory protection.[52]

Moreover, due to the non-binding nature of this policy element, companies are expected to keep deciding not to go on-label for certain extensions if this could affect their more lucrative on-label indications[53] or for liability reasons.

Given these competing pressures on MA holders, the initiative seems unlikely to have a significant impact on the level of repurposing overall.

Where it is implemented, the initiative would not impose significant additional costs for developers, as the use of this broader evidence base would be voluntary. Moreover, updating the SmPC and printing an indication on the product's label does not involve substantial extra costs. Small administrative costs are expected related to pharmacovigilance (smaller relative to a binding system).

EMA statistics show an upward trend in the annual number of extensions of indications it is recommending (87 in 2021, up from 83 in 2020 and 60 in 2019), with an annual growth rate of 5-10%.

We assume a non-binding system would at best increase that growth rate only marginally, by one or two percentage points, perhaps reaching an annual growth rate of 6-12%. In the longer term, even such a small boost to repurposing, would result in perhaps tens of additional treatment options for patients and expanded geographical access to those now on-label medicines.

3. Incentives: Adaptation of the period of regulatory protection

**A.1.3 A special incentive bonus for products with a demonstrated ability to address an UMN.**

An additional year of regulatory protection would increase the numbers of medicines being developed for UMNs

The baseline of c. 15 UMNs a year might be increased by 2-4 products a year

This would result in additional income for originators of perhaps €320m-€640m, associated with those products (based on €160m average peak sales in the EU)

The bonus would result in a delay in the market entry for generics for these additional products, which might amount to a loss of income of around €77m-€154m a year for the generics industry

A small additional administrative burden for originators, assuming the burden of proof for demonstrating that a product meets the UMN criterion falls on the MAH applicant

There would be some additional costs for health payers, which result from the delay in the market entry of generic competition. This may amount to €163m-€326m a year

A small additional cost for regulators involved in the development of the UMN criteria and the implementation of the UMN 'test'

There would be an improvement in patient benefits from the expansion in the flow of medicines addressing UMNs

**A.1.4. Special incentive bonus: if data package includes comparative trial with standard of care (+6 months)**

We assume a 6-month extension might increase the use of comparative trials for 8-10 products a year.

We assume the additional costs of a comparative trial design might amount to €10m.

With average additional peak income (EU) of €160m, a 6-month extension might secure an additional €80m in income, or €640m-€800m a year in additional protected sales for originators

The bonus would result in a delay in the market entry for generics for these additional products, which might amount to a loss of income of around €154m-€192m a year for the generics industry

There would be some additional costs for health payers, which result from the delay in the market entry of generic competition. This may amount to €326m-€408m a year

This should deliver faster access to markets and costs savings thanks to improved reimbursement decisions

Moore et al (2020) in a review of 101 new FDA medicines (225 individual clinical trials), found the median cost of an individual clinical trial was around $19m (range = $12m-$33m).[54] They found the Phase 3 development costs almost doubled with second trial (albeit the single biggest cost driver is the number of patients).

[52] Sahragardjoonegani, B., Beall, R.F., Kesselheim, A.S. *et al.* Repurposing existing drugs for new uses: a cohort study of the frequency of FDA-granted new indication exclusivities since 1997. *Journal of Pharmaceutical Policy and Practice* **14,** 3 (2021). https://doi.org/10.1186/s40545-020-00282-8

[53] https://www.fiercepharma.com/sales-and-marketing/sanofi-pulls-campath-to-clear-way-for-higher-priced-lemtrada

[54] Moore, T. J., Heyward, J., Anderson, G., & Alexander, G. C. (2020). Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval of new therapeutic agents, 2015–2017: a cross-sectional study. *BMJ open*, *10*(6), e038863.

Moore et al identified 62 (27.5%) of the total set of 225 clinical trials had a comparison group rather than a placebo or uncontrolled trial.

### Assessment of the principal costs and benefits by impact type

Table 18 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block A under Policy Option A and for each impact type.

*Table 18 Option A - Summary assessment Incentives for innovation*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| A.1.1. | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| A.1.2. | +/- | +/- | +/- | +/- | +/- | +/- | - | +/- | +/- |
| A.1.3 | + | - | +/- | + | +/- | + | - | + | +/- |
| A.1.4. | + | - | +/- | +/- | +/- | + | + | + | +/- |
| Overall impact | + | - | +/- | + | +/- | + | - | + | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

In summary, the introduction of:

- A special incentive bonus for UMNs should have a positive impact overall. It would bring additional costs for developers offset by an additional period of premium pricing, which should support an increase in R&D investment and expand the numbers of products in the pipeline. This should flow through to an increase in treatment options and benefit more patients. There may be substantial deadweight costs associated with the additional rewards granted to products that would have been developed without the bonus
- A special incentive bonus for comparative trials should have a positive impact overall. It would bring limited additional costs for developers that should be more than offset by the additional protected income and a more straightforward and robust assessment by regulators, with any positive recommendations being accompanied by a better evidence base for HTAs, which should lead to a greater proportion of authorised medicines being approved for reimbursement and thereby improving treatment options and benefiting more patients
- A non-binding system for the scientific assessment of new evidence would be unlikely to have any significant impact on the underlying situation regarding the numbers of extensions to new indications or the repurposing of older medicines more generally, given the commercial uncertainty around repurposing and potential additional liabilities of third-party evidence

### Assessment of synergies and tensions

Within the Policy Block, the three policy elements proposed under Policy Option A are complementary, comprising additional special bonus incentives for both novel innovations (new medicines relevant to UMNs; and for the use of comparative trials) and incremental innovations (e.g. the inclusion of additional types of scientific evidence to encourage MA holders to consider extending their existing medicines for use with new indications).

## Assessment of the proposed incentives for antimicrobial resistance

Policy Option A proposes measures to stimulate the development of novel antimicrobials and comprises three policy elements. Table 19 presents an overview of these three proposals, noting the key design assumptions and likely strengths and weaknesses.

*Table 19 Option A - Assessment of the proposed incentives for antimicrobial resistance*

| **Assessment** |
|---|
| A.2.1 Harmonisation of summary of product characteristics for nationally authorised antimicrobials to support prescription practices |
| The harmonisation process will affect market authorisation holders, in as much as any referral for reassessment will result in the company being invited to carry out a wide-ranging review of evidence on efficacy, indications, posology, etc. to prepare an up-to-date technical dossier for consideration by the EMA and a resulting new SmPC and Product Leaflet for sharing with member states. The Opsalka et al study suggests the majority of updated SmPCs would result in a narrower set of more specific indications and more stringent dosage guidelines, resulting in a reduction in the numbers of prescriptions and the associated volume / sale of those antimicrobials. In simple terms, updated SmPCs supports more prudent use and would result in lower sales volumes for the 3-5 MA holders subject to a reassessment each year.[55] |
| The reassessment process will bring additional regulatory compliance costs that could amount to many tens of thousands of Euros, and the proposed policy element might be expected to increase the numbers of MAHs affected from 1-2 a year to 3-5. |
| This policy element would not have a significant impact on SMEs. Nationally authorised antimicrobials tend to be the older, broad-spectrum antimicrobials manufactured by larger (generics) companies. |
| The policy element could have a small negative impact on the competitiveness of the EU generics industry, since it would create additional costs for small numbers of generics companies while also reducing their income from the assessed medicines (more prudent use). Given the focus on the most widely used, older antimicrobials, it would disadvantage some MA holders rather than all. Given the relatively narrow geographical markets of these medicines, the policy element may also have a relatively greater (negative) impact on those companies based in or focused on addressing the biggest current users of antimicrobials in the EU (e.g. Greece, Italy, Spain). Indirectly, it should reduce consumption overall, but may increase the diversity of use and in limiting some medicines, it may boost demand for other antimicrobials. |
| The policy element could have a small positive impact on the functioning of the single market, inasmuch as the harmonised SmPCs should result in more consistent prescription practice across the EU and broader / more consistent demand for these generic medicines across EU member states. |
| The reassessment process might entail some limited additional research by the MA holders and could trigger a small increase in the demand for work by technology consultancies or academic researchers. However, the number of harmonisation exercises is likely to be limited. We have estimated 3-5 reviews a year initially, perhaps increasing to 5-10 a year, if the process proves to be useful and the resources can be found to coordinate the reviews and manage the resulting assessments. From this perspective, the total additional investment in research might be €1m-€3m a year. The policy element is unlikely to have a direct impact on innovation, albeit indirectly, it may make a small contribution to increasing demand for newer and more novel antimicrobials. |
| There would be an additional cost for the EMA in overseeing the increase in the number of reviews / assessments from the current baseline. There would be additional costs too for member state regulators in providing at least some of the staff and scientist that will be involved in the assessments. There would also be some limited costs in the implementation of the resulting SmPCs nationally. |
| Patients should benefit from improved prescription with medicines being prescribed only where they are likely to be effective and at more prudent levels. There would be a one-off cost to national health systems when implementing the new SmPCs, and the need to update relevant guidance and otherwise communicate about the required changes in prescription. There should be a reduction in the usage of the affected medicines, which could save money, albeit this may be offset by healthcare practitioners prescribing different antimicrobials (some more expensive, and a greater diversity of consumption may also reduce discounts and increase prices). Indirectly and in the longer term, the reductions in overuse and misuse should have a positive impact on the number of instances of AMR in the EU and the negative health impacts associated with that. This is the most critical social benefit, however, an increase in harmonisation may have only modest impacts here. |
| The more prudent prescription of antimicrobials should result in fewer and smaller prescriptions. Indirectly and over the longer term, this should reduce usage overall in the EU. |

[55] Opalska, A., Kwa, M., Leufkens, H., & Gardarsdottir, H. (2020). Enabling appropriate use of antibiotics: review of European Union procedures of harmonising product information, 2007 to 2020. *Eurosurveillance*, *25*(45), 2000035.

| Assessment |
| --- |
| These improvements should result in fewer antibiotics entering the environment (whether through lower levels of manufacturing activity, better stewardship, or improved disposal practices). If the harmonised SmPCs do affect prescribing behaviour (and there are some major cultural factors that could frustrate ambitions here), then the policy element's targeting of the oldest and most widely used antimicrobials could result in quite significant reductions in usage (especially in those countries with the highest per capita usage), so the volume of releases to the environment may be equally positive affected. |
| **A.2.2. Transferable voucher (TV) independent to data/market protection for antimicrobial products** |
| The right to be transferred relates to the transfer of the right to extend the data protection by a length to be determined. The assumption/calculation is based on an extension of data protection by 1 year.<br>The antimicrobials that would be applicable to generate this right are all antimicrobials or a subgroup e.g. antibiotics only or their alternatives which either (i) represent a new class and/or new mode of action, addressing new target or absence of known cross-resistance (WHO innovation criteria) or candidates targeting priority pathogens (WHO list for antibiotics) or innovative platform technologies able to confer break-through clinical benefit, (ii) ground-breaking innovation within an existing class.<br>The average number of TVs we expect per year is 1. EU JAMRAI predicts fewer.<br>Companies may use a TV on existing successful medicines that are still covered by data protection, and which are still at least 2 years (EFPIA proposal) away from the expiry of their data protection period.[56,57]<br>The TV would be most relevant to products where the last defence before generic entry is the regulatory protection. For those where there is a 10+ years patent or SPC protection, the extended data protection does not give any benefit. Hence, only a part of all products could benefit from a TV.<br>In principle the extension would need to be sufficient to provide a substantial incentive to compensate for the development of a new antibiotic, which is estimated to be on the order of €1.2bn. However, the EU market is some 20% of the total pharmaceutical market globally, and so a proportionate contribution to the development cost with the EU voucher may be a sufficient incentive. It would be possible for companies to receive the right to a TV for antimicrobial products that were already in the pipeline ahead of the implementation of the new regulation, to generate additional income / profits within 2-3 years of implementation, and thereby underpin an early expansion in investments in novel antimicrobials.<br>Based on the application of a voucher to an average top-10 product, we estimate an originator would secure an additional €543m in non-contested sales because of the 1-year extension.<br>There would be a cost to the generics industry of a year's delay on the order of €164m.<br>There would a cost to the health system too, which we estimate at €283m. We further estimate the patient + payer monetised loss would be on the order of €441m<br>Some vouchers may be sold rather than used directly by the developer of the antimicrobial and we have estimated the average sale value of a voucher at €360m.<br>Each year, about 33,000 Europeans die as a consequence of antibiotic-resistant bacteria.[58] On average, a hospitalised patient with antibiotic-resistant infections costs an additional 10,000 to 40,000 USD.[59] The expansion in the development and authorisation of novel anti-microbials should help to manage and even reduce AMR, with fewer hospitalisations and deaths, although it has so far not been possible to estimate the scale of these potential benefits, in order to compare with the social costs of the incentives for taxpayers and health payers. |
| A.2.3. Adapted system for authorisation of phages therapies and other alternative products |
| This policy element would support the development of phage therapies potentially increasing the number of companies willing to invest and develop these therapies which will in turn increase competition, reducing prices of these therapies. The use of phage therapies may also reduce healthcare costs/budgets since phages are an inexpensive natural resource present in the environment, and offer immense potential as an alternative when |

[56] There is also the TEE: https://www.ifpma.org/wp-content/uploads/2018/09/IFPMA_AMR_Position_Incentives_Pull_2018.pdf

[57] Recent paper: https://healthpolicy.duke.edu/sites/default/files/2022-01/Transferable%20Exclusivity%20Voucher%20Program.pdf

[58] Cassini, A., Högberg, L. D., Plachouras, D., Quattrocchi, A., Hoxha, A., Simonsen, G. S., Colomb-Cotinat, M., Kretzschmar, M. E., Devleesschauwer, B., Cecchini, M., Ouakrim, D. A., Oliveira, T. C., Struelens, M. J., Suetens, C., Monnet, D. L., Strauss, R., Mertens, K., Struyf, T., Catry, B., … Hopkins, S. (2019). Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *The Lancet Infectious Diseases*, *19*(1), 56–66. https://doi.org/10.1016/S1473-3099(18)30605-4

[59] https://www.oecd.org/els/health-systems/Antimicrobial-Resistance-in-G7-Countries-and-Beyond.pdf

| Assessment |
|---|
| antibiotics are rendered ineffective due to bacterial resistance[60]. Finally, by reducing the use of antibiotics it would help reduce the presence of antibiotics in the environment. |

### Summary assessment by impact type

*Table 20 Option A - Summary assessment of prudent use of antimicrobials*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| A.2.1 | - | -- | -/+ | -/+ | + | -/+ | -/+ | ++ | + |
| A.2.2. | +++ | -/+ | +++ | ++ | -/+ | +++ | --- | + | +/- |
| A.2.3. | + | -/+ | -/+ | + | + | + | - | + | + |
| Overall impact | +++ | -- | +++ | ++ | + | +++ | --- | ++ | + |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

### Assessment of any synergies and tensions within the Policy Block

Within the AMR Policy Block, the policy elements proposed under Policy Option A are largely complementary to each other, whereby the proposal to accelerate the rate at which SmPCs are harmonised and updated would address one of the key sources of differences in prescribing practices across the EU in respect to older, lower cost, broad spectrum antibiotics and should restrict and support more prudent use in general. The Transferrable Voucher addresses one of the other key challenges around AMR, which is the inadequacy of the global pipeline for antimicrobials and the substantial gap that exists between the cost to develop innovative antimicrobials and their likely market performance. Lastly, the proposal to adapt the legislation to allow authorisation of phage therapy is an important step to allow this promising alternative to conventional antibiotics to be further developed for safe use in humans. These proposals also fit well with the EC's AMR Action Plan and its objectives to increase innovation and reinforce prudent use.

Assuming novel antimicrobials might be considered to address an unmet medical need (UMN), there would be an additional synergy between the Transferrable Voucher proposed here and the proposal to extend the period of regulatory protection for medicinal products addressing an UMN, under the Innovation Policy Block. An additional period of regulatory protection for the novel antimicrobial would generate a period of additional revenue at premium prices (before generic entry) and thereby deliver an additional profit stream to support investment in antimicrobial R&D.

#### *A.3.3. Policy Block C (A.C): Future Proofing*

Policy Option A is a refinement of the current arrangements, with three principal interventions around scope and definitions and GMOs. Table 21 presents our schematic overview of these three proposals, noting the key design assumptions and likely strengths and weaknesses.

[60] https://www.nesta.org.uk/blog/when-the-drugs-dont-work-could-bacteriophages/?gclid=Cj0KCQjw_4-SBhCgARIsAAlegrUn5LXTOVza5VKzwfA4XcfpeUXcHW8jiSFfDhOBM2_MUMNcQ0GrXVQaAtQVEALw_wcB

*Table 21 Option A - Assessment of the proposed incentives for Future Proofing*

| **Assessment** |
|---|
| 1. Scope and Definitions |
| A.3.1 Maintain **current** exemptions from the **scope** of the legislation –add some **clarifications**/conditions |
| Technological advances are providing innovative medicines that test the limits of the pharmaceutical legislative framework in terms of scope and definitions. Products can end up in a legislative gap (such as novel manufacturing processes) or there is risk of duplication or misalignment between frameworks (BTC, clinical trials, hospital exemption).<br>A.3.1 has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. It would also address the issues of accommodating technological advancements in the legislation. For instance, by promoting coordination with concerned authorities in particular in the framework of medical devices and substances of human origin. However, these impacts may be short term and not sustained as technological change is ongoing and increasing in pace the changes could soon be outdated and may lack flexibility to keep pace. |
| 2. GMO |
| A.3.2 Clinical trials: a **risk-based** approach is applied to determine when a specific GMO assessment is required. Where required, the assessment of the GMO aspects of investigational medicinal products is performed by **EMA**, within the maximum timelines defined in the Clinical Trial Regulation (centralised assessment). |
| Clinical trials for investigational medicinal products (IMPs) for human use that contain or consist of GMOs are subject to both clinical trials and GMO legislations under national competences. This causes delays in clinical trials as the directives are not uniformly interpreted or applied between MSs and is especially problematic for clinical trials that are conducted over multiple MSs. These differences in interpretations also impact on the authorisation of GMO-containing medicinal products that fall under the mandatory scope of the centralised procedure creating complexities for developers as different MSs have different requirements and stakeholders involved, ultimately causing regulatory burdens and delays in market authorisations.<br>A3.2 has potential to improve the efficiency of GMO assessment and thus accelerate authorisation of GMO-containing medicinal products by focussing regulatory efforts on GMO containing medicines that pose the greatest threat to the environment. A centralised approach to GMO assessment has already been adopted by the United States where the review of medicinal products containing GMOs has been centralised within the FDA to improve efficiency and regulatory agility[61]. |
| A.3.3. An environmental risk assessment continues to be performed (by EMA) in the context of the marketing authorisation procedure |
| This is the same as business as usual for this element. |

Table 22 contains a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under Option A.

*Table 22 Option A - Summary assessment of future proofing*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| A.3.1 | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| A.3.2 | + | + | + | + | + | + | - | + | +/- |
| A.3.3. | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |

[61] U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research. (2015). *Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products; Guidance for Industry*. https://www.fda.gov/media/91425/download

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Overall impact | +/- | +/- | +/- | +/- | +/- | +/- | - | + | +/- |

### Assessment of any synergies and tensions within the Policy Block

Policy option A is most like the baseline policy option and least impactful in terms of future proofing as it risks not keeping pace with new products and technologies. It is the least 'friendly' towards innovation due to relying on 'hard law' changes that would suffer the same issues in a short time and are not flexible enough to consistently adapt moving forwards. Ultimately this creates a tension with the overarching policy option goal to: "use additional incentives to address unmet medical needs and to support public health objectives."

Future proofing elements in this policy option related to risk-based approach for GMO assessments (A3.2) have synergies with innovation in UMN (Block A) in creating incentives and removing barriers for innovation. The element related to reduction of regulatory burden - definitions and scope (A3.1) has synergies with horizontal streamlining measures. There are also complementary measures in Block E (Creating new simpler regulatory pathway for generics (A.5.1), Block F (Encourage use of HMA/EMA guidance definitions A.6.1.) and Block G (Adaptation of legislation to cover new manufacturing methods (A.7.3.))

## *A.3.4. Policy Block D (A.D): Access*

### Assessment of the key impacts for the policy elements

Table 23 presents our broad assessment of the likely costs and benefits of each of the proposed legislative actions. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

*Table 23 Option A - Assessment of the proposed elements to improve access*

| **Assessment** |
|---|
| *A.4.1 Facilitate 'multi-country packs' with labelling to allow their placing on the market in several Member States with the same packaging and pack sizes* |
| Currently, information on the pack (outside and inside) must be in the official language(s) of the MS where a product will be placed on the market, bar a few exceptions for certain products that are not intended to go directly to a patient. This language requirement, along with other potentially country-specific requirements, means that MAHs must produce packs specifically designed for each market. This increases production costs and may make smaller markets, where these costs cannot sufficiently be offset by revenues, commercially unattractive. Additionally, country-specific requirements can hinder the movement of medicines between different EU markets when products need to be repacked and relabelled, to meet all requirements of the importing country.<br>Facilitating 'multi-country packs' may result in more products being placed on a greater number of markets, in particular smaller or less economically attractive markets. In addition, medicines can be moved between EU countries more easily to mitigate or resolve shortages. This would improve security of supply and mitigate some of the risks resulting from product unavailability (e.g. treatment interruption, suboptimal treatment with alternatives). It will, however, be important to ensure that use of multi-country packs does not limit the ability of patients and healthcare providers to access information regarding, for instance, the correct use and safety profile of medicines. No studies were identified that detail experiences with multi-country packs as a way to overcome access challenges and that thus could inform an estimation of impact.<br>In economic terms, it is expected that multi-country packs would result in a cost saving to MAHs by reducing the number of different presentations they need to produce and streamlining production lines. The magnitude of these savings will depend primarily on the number of countries and languages included, whilst the size of the markets reached by multi-country packs will further influence the profit potential for the MAH. |

In theory, multi-country packs may have the added benefit of facilitating joint procurement between countries. Several initiatives already exist whereby smaller countries engage in joint procurement to increase their purchasing power. Such initiatives have the potential to negotiate lower prices. A 2020 study for WHO shows that whilst these initiatives hold promise, they often take months or years of cooperation before tangible results are achieved[62]. The study did not specifically look at the role of multi-country packs in facilitating joint procurement.

*A.4.2 Additional period of data protection [6 months] if proven that the product has been placed on the market in all Member States within 6 years of authorisation.*

If the incentive succeeds in encouraging MAHs to place their products in a greater number of EU markets, this can have substantial positive impacts on access to medicines and consequently on the health and wellbeing of people in previously unserved markets. These impacts scale with the size of the target populations that would be reached but are also dependent on the ability of health systems in those markets to adequately diagnose conditions and provide appropriate treatment. As such, not all countries stand to equally benefit from such incentives. The impacts will also depend on product characteristics, whereby expanded access to medicines that address high unmet medical needs will have greater impact than other medicines.

The incentives, however, may carry a significant cost to national health systems and payers by potentially delaying generic entry. The cost of this to authorities, and conversely the value of the reward to MAHs, depends on by how much the additional period of regulatory data protection would extend the overall protection on the product that delays generic competition and on the likelihood of such competition emerging more generally (e.g. competition for biological and orphan medicines is often slow or non-existent even after expiry of any protections).

Although data protection can have significant (economic) value for innovators, in various consultations, industry stakeholders have suggested that additional regulatory protection of six months will not be an adequate incentive for wider market launch. Whether this will be the case will most likely depend on the balance between the expected ratio between the costs of doing business in less commercially attractive markets and the value of the incentive.

*A.4.3 Promote a voluntary reporting of market launches and a commitment to initiate pricing negotiations in all MSs within 2 years of centralised authorisation. (non-regulatory option)*

It is assumed that the EMA would serve as the central point of contact for reporting but that the information may then be shared also with authorities in each of the Member States. The policy element additionally intends to obtain a commitment from MAHs to initiate price negotiations in all MS. However, it is assumed that neither the EMA nor any other regulatory authority will be granted powers to monitor or enforce these (voluntary) commitments and that there will be no sanctions on MAHs when these commitments are not fulfilled. As such, it is difficult to see how this measure intends to achieve the desired impact of launch in a greater number of countries or earlier launch and, consequently, increased access.

Nonetheless, if the measure succeeds in obtaining commitments from MAHs to initiate price negotiations in all MSs within two years of granting of the MA, this may lead to earlier and wider access. It is expected that other factors (e.g. market characteristics and price policies) that currently influence where and when MAHs enter a market will continue to shape decision-making. As such, the impact of such a non-regulatory and voluntary measure on access may be rather limited.

*A.4.4 Allow generic competition entry in the EU market, in case a centrally authorised medicine is <u>not</u> placed on the market in the majority of Member States (small markets included) within 5 years of granting the MA*

Any measure that promotes market entry into a greater number of EU countries or accelerates access, will be beneficial to patients who are otherwise unable to access these medicines. The impacts of this measure will scale with the number of countries and patients reached and with the importance of the medicine. Earlier access to generic medicines will also improve patient access to (generic versions of) these medicines when generic competition comes in, provided that those generic versions will be placed on these markets.

Pressure to enter a set number of markets, at the threat of generic competition, may force companies to market these products in countries where it does not make commercial sense to do so. The question is whether the threat of loss of protection and earlier generic competition will be sufficient to overcome the lack of financial incentive for MAHs to enter such markets voluntarily. SPCs, orphan market exclusivity and regulatory data protection each carry a significant financial value and industry has often cited these instruments as essential to stimulate innovation. Limiting access to these protections, by making them conditional, could thus risk slowing down innovation.

[62] Cross-country collaborations to improve access to medicines and vaccines in the WHO European Region, (2020).

Changes to the entire system of intellectual property and regulatory protections for medicines to make them contingent on market placement should be expected to make the system considerably more complex. It will require regular reporting by MAHs on market launches and potentially verification of this information by regulatory authorities to determine whether the MAH has fulfilled all the conditions to be, or remain, eligible for such protections. Questions also remain as to how eligibility for protections would be affected if countries decide not to admit the medicine into the package of reimbursed care (and consequently there is no possibility for the MAH to place the product on that market) or if the duration of the decision-making on reimbursement is such that the 5-year period after granting of the MA is exceeded. In these cases, the MAH may lose its protection from generic competition because of factors outside of its immediate control. This may introduce unpredictability into the system that could discourage companies from entering the EU market, although the risk of this may still be limited as the EU represents a major pharmaceutical market which MAHs are unlikely to forego.

### Summary assessment of the principal costs and benefits by impact type

Table 24 presents a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under Option A, for each impact type.

*Table 24 Option A - Summary assessment of access elements*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| A.4.1 | ++ | + | +/- | + | ++ | +/- | + | + | +/- |
| A.4.2 | ++ | - | +/- | - | + | +/- | +/- | + | +/- |
| A.4.3 | +/- | - | +/- | +/- | +/- | +/- | - | + | +/- |
| A.4.4 | --- | -- | +/- | -- | +/- | - | ++ | ++ | +/- |
| Overall impact | +/- | --- | +/- | -- | ++ | - | ++ | +++ | +/- |

- Facilitating the use of multi-country packs is expected to result in cost savings for MAHs by reducing the need for country-specific packaging and presentations and streamlining production lines. It may also facilitate the movement of medicines within the EU internal market, thereby promoting competition.
- Access to additional incentives for market entry in all EU countries grants MAHs a longer period of exclusive prices, representing increased revenue.
- An expectation to place centrally authorised medicines on the market in a majority of EU MS and a concomitant disincentive for not doing so in the form of loss of protection, may result in loss of revenue for innovator companies. This may make the EU market overall less attractive to these companies. Generic manufacturers on the other hand may benefit from this measure, as they may be granted earlier market access in the whole of the EU.
- MAHs will have to provide additional information to regulators to demonstrate their eligibility for incentives. This implies increased administrative costs. Increasing the number of MS in which the MAH places a product on the market may also increase the administrative cost of filing for (MRP/DCP) authorisation and the subsequent costs for interacting with regulatory agencies and health technology assessment bodies in these countries.
- The existence of intellectual property rights and regulatory protections is generally considered a driver for research and development of new medicines. By making access to these market protection mechanisms conditional and forcing MAH to operate in markets where they have no commercial interest, developers could be discouraged from investing in R&D.

- To determine eligibility with new incentives and qualification for existing protections, regulators (presumably the EMA) would incur greater costs due to an increased workload. Regulatory authorities in the MS where products are placed in the market will see an increase in cost due to a greater number of medicines for which they provide regulatory oversight. Similarly, HTA bodies will have to conduct a greater number of assessments.
- The intended and expected impact of increased access to medicine is that patients will be provided with earlier and wider access to more effective and safer treatments. This will have a positive impact on their health status and wellbeing. Whilst increased access to medicines is an intended positive outcome, it may result in increased health care expenditure. At the same time, new medicines may displace less (cost-)effective treatments, resulting in net savings. Further indirect savings from increased access to medicines may result from improved health and productivity.
- Granting of additional incentives (extension of regulatory data protection) that delay access to cheaper generic versions of medicines will lead to higher costs to payers / health systems. Conversely, allowing earlier generic entry when launch expectations are not sufficiently met, represents a cost saving.

### Assessment of any synergies and tensions within the Policy Block

Facilitating the wider use of multi-country packs not only may be a way to address problems with selective market launches that ignore the needs of smaller markets but could also facilitate the movement of product between countries in case of supply disruptions and shortages. It therefore is synergistic with other measures to improve supply chain security discussed in Block F.

Extending the regulatory data protection period as an incentive for wider market launch needs to be considered alongside other proposed revisions to the system to incentivise innovation, in particular in areas of unmet medical need (e.g. Policy element B.1.4).

Introducing a market placement expectation and allowing earlier generic entry in case the expectation is not fulfilled will require simultaneous revision of several other parts of the EU pharmaceutical legislation for medicines, in particular the EU Orphan and Paediatric Regulations.

#### *A.3.5. Policy Block E (A.E): Competition*

Policy Option A is a refinement of the current legislative arrangements for encouraging competition, with only one change overall: A new simpler regulatory pathway for generics.

No other changes to the current situation are envisaged, including to the current conditions for duplicate MAs.

### Assessment of the key impacts for the policy elements

Table 25 presents our assessment of the key impacts of each of the proposed measures, drawing on our consultations, desk research and targeted literature review.

*Table 25 Option A - Assessment of the proposed measures for competition*

| **Assessment** |
|---|
| A.5.1 New simpler regulatory pathway for generics |
| The key impact from a simpler regulatory pathway with shorter approval times will be faster availability of generics to patients. It should create more clarity and potentially less administrative burden for marketing authorisation applicants, encouraging more applications and increased development activity for generics. |

| |
|---|
| We assume that generics will be on the market soon after approval and access to generics will be similar in all member states. The latter assumption has been adopted for ease of analysis as generics market penetration varies considerably across member states[63] and would add uncertainties to our assessment. |
| A.5.2 No change to current situation and no restriction on duplicate marketing authorisations |
| This is business as usual (BAU) and as such there would be no additional impact, as compared with the baseline policy option. As such we assume that the types of products being developed will not change (as no change in Bolar provision) and behaviour around duplicate marketing authorisations will also remain the same. |

### Summary assessment of the principal costs and benefits by impact type

Table 26 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block A under Policy Option A and for each impact type.

*Table 26 Option A - Summary assessment of the proposed measures for competition*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| A.5.1 | + | + | + | + | + | + | + | + | -/+ |
| A.5.2 | -/+ | -/+ | -/+ | -/+ | + | -/+ | + | + | -/+ |
| Overall impact | + | + | + | + | + | + | + | + | -/+ |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

The following key impacts are envisaged based on interviews (industry representatives and payers) and literature:

- Greater certainty for businesses in terms of their development cycles and application requirements for generics with reduced complexity of the submission because of the simplified pathway. This would improve the situation compared to the lack of clarity that has been reported regarding which current abridged application procedures (generic or hybrid) should be followed[64]
- A high likelihood of positive impact through making medicines more readily available to those that need them and reducing costs for health systems (generics represent around 80% cost reduction compared to originators, and entry of a generic also reduces price of the off-patent medicine by 61%[65]; biosimilars are 20% cheaper[66] compared to originator products)
- Benefit to patients (and public health) through the greater likelihood that getting MA for generics will be easier and quicker, and thus access to medicines will be improved

[63] Wouters OJ, Kanavos PG, McKEE M. Comparing Generic Drug Markets in Europe and the United States: Prices, Volumes, and Spending. Milbank Q. 2017 Sep;95(3):554-601.

[64] *Klein, K., Stolk, P., De Bruin, M.L., Leufkens, H.G., Crommelin, D.J., & de Vlieger, J.S. (2019). The EU regulatory landscape of non-biological complex drugs (NBCDs) follow-on products: Observations and recommendations. European Journal of Pharmaceutical Sciences, 133, 228–235.*

[65] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

[66] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilarsv

### Assessment of any synergies and tensions within the Policy Block

This option does not present major changes compared to the current legislation, hence the opportunity for added impact in combination with other blocks is limited. Fundamentally, increasing competition via market entry of generics and biosimilars increases access and affordability and thus has added value in terms of improved patient health and lower costs for health systems. However, this added value will be in line with current benefits.

There is synergy with the horizontal measure of streamlining and harmonisation with making the regulatory pathway for generics simpler. No change to the duplicates regime creates some tensions with regard to timely availability of biosimilars on the market and thus access.

#### *A.3.6. Policy Block F (A.F): Supply Chain Security*

Option A includes a variety of measures aimed at improving the availability, quality, timeliness, and exchange of information about (potential) shortages (A.6.1, A.6.2, A.6.4, A.6.5). The underlying idea is that such information will allow authorities and other parties to better mitigate the impact of supply disruptions and thereby reduce negative health impacts and costs. It would furthermore also improve the understanding of the causes of shortages and of what products are at increased risk.

The option additionally seeks to preserve the availability of medicines that the MAH intends to withdraw from the market by mandating that the MA is first offered to another party (A.6.3).

### Assessment of the key impacts for the policy elements

Table 27 presents our assessment of the key impacts of each of the proposed measures, drawing on our consultations, desk research and targeted literature review.

*Table 27 Option A - Assessment of the proposed measures for Supply Chain Security*

| **Assessment** |
|---|
| A.6.1 Encourage the use of HMA/EMA guidance definitions |
| Overall, encouragement of the use of standardised guidance definitions can help create a more harmonised system of shortage monitoring across the EU. It should be noted though that adoption of such a definition itself cannot directly reduce the incidence of shortages, but rather is a stepping-stone in the introduction of further harmonisation measures. If wider adoption of a single harmonised definition contributes to improved information sharing between MS about shortage situations, this may in turn support earlier identification of potential supply disruptions and more effective mitigation strategies. The impact of this will still depend to a large extent on how national authorities further operationalise these guidance definitions within their own notification systems. |
| A.6.2. Notifications two months in advance, encouraging the use of the HMA/EMA reporting template. |
| The current notification timeframe under Article 23a of two months stipulates the minimum in all EU countries. As such, A.6.2. does not constitute a change to the current timing of notification. It also emphasises the use of the HMA/EMA reporting template. The main foreseeable impact thus relates to the type and amount of information MAHs may be expected to provide. Whilst possible that, compared to the current situation, the information requirements would increase in some MS, standardisation of requested information is more likely to facilitate central coordination of shortage reporting, thereby reducing transactional costs.<br>Potential impacts on the security of the supply of medicines are primarily indirect. Greater standardisation of information collected as part of shortage notifications likely will improve information sharing between countries and allow for a better understanding of the causes of shortages. This may allow for the development of more tailored policy approaches to address the issue of shortages at both EU and national levels and ultimately improve security of supply. |
| A.6.3 Marketing authorisation offered for transfer to another MAH before a permanent withdrawal |
| Requiring a MAH to offer the MA to another party before allowing it to withdraw the product from a specific market could delay the original MAH's withdrawal decision, as it seeks to avoid enabling its own competitors.<br>Hypothetically, requiring MAHs to offer the MA to another manufacturer could benefit such manufacturers who are enabled to market a product that already has an established patient base. However, as indicated previously, |

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| a large proportion of product withdrawals can be traced to low product-level profitability[67]. It is not clear to what extent a MA transfer could effectively address these underlying profitability issues. Such transfers would only be feasible/interesting in case a product remains commercially interesting for the new MAH or if commercial viability is not required for another party to take over the MA (e.g. in case of transfer to a not-for-profit entity).<br>The study team has identified no experiences with similar measures that could inform a (quantitative) estimation of potential impact. Moreover, the EU trade association for the generics industry (Medicines for Europe) has indicated that it considers this proposal unconstitutional and not compliant with the proportionality requirements of EU treaties. It indicates that permanent withdrawals for commercial reasons are often necessitated by national market conditions, such as pricing and reimbursement policies (e.g. price cuts, reference pricing, claw backs and rebates), that are imposed by Member States and over which the MAH has no control. Mandating that the MAH offers the authorisation to another party before allowing it to withdraw is therefore considered a form of regulatory expropriation in violation of Art. 16 of the European Charter of Fundamental Rights. |
| A.6.4. Use of the Falsified Medicines Directive (FMD) system to monitor shortages |
| EU-wide monitoring of shortages could reduce the need for decentralised notification and improve the quality of information available to stakeholders. Similar to B.6.1, better quality information could contribute to more effective prevention and mitigation strategies.<br>Given the fact that the European Medicines Verification System (EMVS) is currently not yet deemed fit for purpose, this measure is likely to require a significant investment to develop the system in this direction.<br>Some industry stakeholders have also called attention to the need for accelerating the implementation of IDMP/SPOR (IDentification of Medicinal Products[68]/Substances Products Organisations and Referentials) standards, which could improve data standardisation and linkage across systems and offer regulators more insight into supply chain structures, supply levels and demand. |
| A.6.5. EU coordination to exchange information on supply and supply chains to identify areas of consolidation |

### Summary assessment of the principal costs and benefits by impact type

Table 28 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block F under Policy Option A and for each impact type.

*Table 28 Option A - Summary assessment of the proposed measures for supply chain security*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| A.6.1. | +/- | +/- | +/- | +/- | +/- | +/- | +/- | + | +/- |
| A.6.2. | +/- | + | +/- | +/- | +/- | +/- | +/- | + | +/- |
| A.6.3. | - | - | +/- | - | +/- | +/- | +/- | ++ | +/- |
| A.6.4. | - | + | +/- | +/- | +/- | +/- | - | ++ | +/- |
| Overall impact | - | +/- | +/- | - | +/- | +/- | +/- | ++ | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

The following key impacts are envisaged:

- Collectively, the proposed measures are expected to allow for improved decision-making to prevent and mitigate the impact of shortages (A.6.1, A.6.2) and offer public authorities additional tools for protecting the domestic supply of medicines (A.6.3). If successful, this

[67] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages* (Issue December).

[68] IDMP is a suite of five standards developed within the International Organization for Standardization (ISO)

will in turn result in greater continuity of supply for medicines that are needed to offer appropriate healthcare to patients. Health care costs resulting from shortages would also be reduced.

- The costs associated with industry players are lower than in other policy options given that most measures are formulated in a non-binding language. The impact on industry players is therefore expected to be limited.

### Assessment of any synergies and tensions within the Policy Block

The policy elements proposed for Security of Supply under the Option A are overall synergistic. The are no major areas where tensions are expected to arise if all these elements are implemented together.

#### *A.3.7. Policy Block G (A.G): Quality and manufacturing*

### Assessment of the key impacts for the policy elements

Table 29 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing mainly on desk research and targeted literature review.

*Table 29 Option A - Assessment of the proposed measures for quality and manufacturing*

| **Assessment** |
|---|
| A.7.1. Strengthen enforcement of responsibilities of MAH as regards the quality of the products by introducing harmonised system of sanctions |
| There is potential for more robust internal assessment before sanctions and less heterogeneity of sanctions across Member States. This would have a positive effect on quality standards in the long-term, with MAHs making sure to fulfil their obligations to avoid penalties. The harmonisation of sanctions may also positively impact the workload of the relevant competent authorities by streamlining the process.<br><br>There may also be short and long-term negative effects on the EU pharma industry due to the financial costs of penalties incurred and reduction in international competitiveness of the sector if the sanctions regime is considered too severe. The burden of sanctions or threat thereof could present barriers for smaller actors such as SMEs, which could lead to companies leaving the sector or the EU. |
| A.7.2. Inclusion of the information on the sustainability performance of supply chains actors by using international standards in the application dossiers |
| The proposed measure would improve the sustainability of production of medicines, which would be favourable for the environment. However, companies (MA applicants) would be negatively affected due to the additional burden of collating and submitting this information and complexity of submission to comply with the environmental requirements. It may encourage more supplies to be sourced from the EU and will also have an impact on manufacturers in third countries.[69] |
| A.7.3. Adaption of legislation/inclusion of specific provision covering new manufacturing methods (decentralised, continuous manufacturing, etc) to ensure levels of quality and safety equivalent to current methods. |
| The proposed measure has the potential to bring several product categories that are currently excluded from the legislation into the fold and provide regulatory certainty to manufacturers. These include magistral formulae (pharmacy-based preparation for an individual patient), radionuclides in sealed sources, hospital-manufactured medicines, and single-batch medicines. In addition, manufacturing methods such as decentralised manufacturing (where manufacturing occurs at different locations) and 3D printing-based methods could be accommodated.<br><br>Covering new manufacturing methods in the general pharmaceutical legislation has the main advantage of helping to standardise the methods themselves, quality control of the methods and resultant products and associated regulatory pathways at the EU level. Thus, there is a harmonisation benefit. Moreover, accommodating new technologies sends a positive signal to innovators as well as companies and will encourage more innovation |

[69] Eeb. (2018). Policy options for regulating pharmaceuticals in the environment.

| Assessment |
|---|
| and research activity and adoption of the new methods. There will be further knock-on effects on competition, competitiveness, and access to medicine. If greener manufacturing methods are used there will be an impact on environmental sustainability, but the likelihood and extent of that is unclear.<br><br>With more certainty over the manufacturing methods and the resultant products as well as more medicine developers adopting these methods, we could imagine a very high increase in the number of new therapies in comparison to the baseline. |

### Summary assessment of the principal costs and benefits by impact type

Table 30 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block G under Policy Option A and for each impact type.

*Table 30 Option A - Summary assessment of the proposed measures for quality and manufacturing*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| A.7.1 | - | - | - | - | - | -/+ | + | +/- | +/- |
| A.7.2 | - | - | - | - | + | +/- | +/- | +/- | + |
| A.7.3 | -/+ | -/+ | -/+ | + | + | + | -/+ | + | -/+ |
| Overall impact | - | - | - | - | + | + | + | + | + |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

Some of the key costs and benefits are

- Additional transaction, compliance and administrative costs for businesses to adapt to the new regulatory and data requirements. These costs along with the threat of sanctions may have effects on international competitiveness and internal markets (e.g. security of supply)
- Future proofing for new manufacturing methods within the legislation could increase the competitiveness of the EU pharmaceutical sector, promote innovation and help improve sustainability (if new methods are greener)
- There is potential for public health impacts through improved sustainability (lower CO2 emissions) and new products coming on board (those manufactured using novel methods)

### Assessment of any synergies and tensions within the Policy Block

There could be tensions between policy elements A.7.1 (harmonised system of sanctions) and A.7.3 (adaption of legislation for new manufacturing methods). While A.7.3 should ensure quality and safety standards of new manufacturing methods, which should result in more therapies being developed, A.7.1 may reduce this positive effect if the sanctions are not appropriately designed.

#### *A.3.8. Policy Block H (A.H): Addressing environmental challenges*

Policy Option A involves no changes to the ERA compared to the baseline. As such, there should be no change in impact compared with the baseline.

*Table 31 Option B – Assessment of the proposed measures for addressing environmental challenges*

| Assessment |
|---|
| A.8.1. No legislative change; Continue the implementation of the actions under the EU Strategic approach to pharmaceuticals in the environment. |
| There should be no major change in impacts and costs compared to the baseline scenario except for positive environmental sustainability impacts to some extent owing to implementation of actions under the EU Strategic approach to pharmaceuticals in the environment outside the legislation. |

### Summary assessment of the principal costs and benefits by impact type

The table presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block H under Policy Option B for each impact type.

*Table 32 Option A – Summary assessment of the proposed measures for environmental challenges*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| A.8.1. | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | + |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

#### *A.3.9. Policy Block I (A.I): Lessons from COVID-19*

Policy Option A refers to the EMA's extended mandate, which is the same as the baseline, and as such, the assessment of likely future benefits under the baseline / Option A is already presented above.

## A.4. Policy Option B

#### *A.4.1. Policy Block A (B.A): support for innovation, including unmet medical needs*

### Assessment of the key impacts for the policy elements

Policy Option B includes 3 sub-fields and 8 policy elements relating to Policy Block A and the legislation's support for innovation including unmet medical needs (UMNs).

*Table 33 Option B - Assessment of the proposed Incentives for Innovation*

| Assessment |
|---|
| Expedited regulatory schemes |
| B.1.1. Codification of PRIME in the legislation |
| The inclusion of the PRIME scheme within the legislation would give a strong signal to developers that the EU is committed to increasing support for UMNs.<br>It will also reassure developers that the scheme is permanent and that they continue to benefit from the active support that comes with PRIME designation (which is focused on medicines that promise a major therapeutic advantage in an area of unmet medical need). The scheme is well regarded by stakeholders (industry, regulators, health systems) and the EMA analysis of its first five years of operation found that PRIME designation is |

| Assessment |
| --- |
| associated with faster assessment times and an improved likelihood of a positive recommendation for authorisation.[70]<br>There should be no significant additional administrative or compliance costs for businesses, when compared with the current situation.<br>Codification may increase the popularity of the scheme still further, and that may increase the number of companies that have to bear the administrative costs associated with making an unsuccessful PRIME-eligibility request. The popularity of the scheme has increased in the recent past (+15% between 2019 and 2020), and we would expect to see further growth in future. This would be even more likely should the EU implement an additional period of regulatory protection for UMNs. These additional costs (linked with unsuccessful requests) are being limited by an equivalent expansion in the number of medicines accepted onto the scheme, which has also increased (from 23% in 2018 to 33% in 2020).<br>The impact on regulators should be broadly neutral, as while the scheme does involve additional effort to businesses with advice on the development of their PRIME-designated medicines, the resulting applications tend to be better framed and evidenced, making assessment more efficient and improving success rates for submissions (improving EMA productivity in this important area of UMNs).<br>Small biopharma firms have a particular interest in advanced therapies relevant to UMNs, and the codification and expansion of PRIME ought to have positive impact of SMEs. They benefit disproportionately from EMA advice, where larger developers have considerably more experience in preparing an application for assessment. Moreover, for some startups (e.g. cell and gene therapy companies), PRIME may have the effect of a 'seal-of-approval,' which could improve their investability and market value.<br>In the longer term, codification should reinforce the regulator's wider efforts to reduce UMNs, improving treatments, reducing hospitalisations and improving patients' quality of life.<br>As with the other regulatory proposals designed to focus developers' attention on UMNs, there is a small risk this will displace investment in other areas of medical research, possibly even slowing down the rate of progress in other disease areas that have good treatment options currently, but which still constitute a major health burden. |
| Repurposing |
| B.1.2. Establish a binding system for scientific assessment of evidence |
| A binding system would increase the numbers of older off-patent and off-label medicines where available scientific evidence is brought together for assessment by the EMA, such that the wider EU healthcare system is informed about the safety and efficacy of medicines being used in for new indications.<br>While the costs of obtaining the new evidence would have been incurred already by clinical researchers or academics, there may be some additional costs for MA holders where they look to review, replicate or challenge the new evidence.<br>This element would work in conjunction with B.1.3, obliging MA holders to include a new indication when supported by new evidence.<br>EMA statistics show an upward trend in the annual number of extensions of indications it is recommending (87 in 2021, up from 83 in 2020 and 60 in 2019), with an annual growth rate of 5-10%.<br>We assume a binding system for new evidence may nudge that growth rate up by 1-2 percentage points annually, and more if applied in conjunction with B.1.3., perhaps reaching 8-15% CAGR within 3-5 years.<br>This policy element will help broaden access to what are otherwise rather selective and uneven use of safe and effective medicines off-label. It will be a much stronger intervention than the non-binding system. In the longer term, we may see more treatment options for patients and improved geographical access. |
| B.1.3. Obligation for marketing authorisation holders to include a new indication when supported by scientific evidence and assessment. |
| The *obligation* for MAHs to include new indications when supported by scientific evidence will help reducing the problem of companies deciding selectively on which indications to include on-label.71 As such, it should help broaden patient access across the EU to safe and effective medicines that are used successfully off-label currently, but only in some but not all healthcare settings.<br>This policy element would impose additional costs on MA holders, as they will be required to make an application for an extension that they would not have done otherwise. For originators, this might trigger a process that could take several years and costs tens of millions of Euros to conclude. The academic evidence may reduce the costs for developers, in some degree, however there will be additional information demands relating to the application – and possibly a need to replicate trials in order to manage the liability issues. There would also be post |

[70] https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience_en.pdf

[71] https://www.fiercepharma.com/sales-and-marketing/sanofi-pulls-campath-to-clear-way-for-higher-priced-lemtrada

| Assessment |
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| authorisation processes and additional administrative costs are expected related to pharmacovigilance. While the additional costs may be similar on average for any MA holder, they may prove more problematic for generics companies, or developers that have withdrawn fully from a market, where the sales volumes / prices of the existing uses may not underwrite the costs for its extension to a new indication.<br>EMA statistics show an upward trend in the annual number of extensions of indications it is recommending (87 in 2021, up from 83 in 2020 and 60 in 2019), with an annual growth rate of 5-10%.<br>We assume a non-binding system may nudge that growth rate up only marginally, perhaps to 12-22%<br>In the longer term, we may see more treatment options for patients and improved geographical access. |
| Incentives: Adaptation of the period of regulatory protection |
| B.1.4. Reduce the duration of incentives for originators from 8+2 years to a new combination (6+2 years) taking into account the interaction between data protection and intellectual property rights. |
| For originators, a reduction in the period of regulatory protection will reduce overall income and profitability for new medicines since generics companies will be able to enter markets and begin to erode monopoly prices a year earlier. The new period of protection may prompt developers to increase prices in general to protect their current business model or otherwise rebalance their portfolios towards those market segments with greater commercial potential.<br>SMEs originators may find it more difficult to invest in riskier novel medicines given the reduction in future returns on investment and their relatively weaker market position when it comes to negotiating prices.<br>It could weaken the global competitiveness of EU based originators overall, compared with the current situation, unless prices are adjusted upwards to reflect the new protection period, and ensure global ROI norms can continue to be achieved.<br>The threat to EU-based originators will be offset to some degree by giving a boost to Europe's generic industries, broadening their portfolios and potentially creating a prime-mover advantage in global markets.<br>Considering that this policy element affect SMEs more than larger firms and the latter are based in bigger economies, while the former may be based in smaller economies this may affect the functioning of the internal market and limit access to medicines across Europe. This will also be the case if some companies adjust prices upwards in response.<br>Health payers may benefit from lower average lifetime costs for medicines due to earlier generic entry and patients may benefit if those savings are used in the health care sector. The extent of these benefits will depend on originators response to the reduced incentives, and it is highly likely that average prices will be adjusted upwards in some degree to offset the shortened period of protection. |
| B.1.5. Authorised medicines with demonstrated ability to address UMN get +2 years data protection. Other medicines will be entitled to additional protection only if they can demonstrate no return on investment in view of investment costs (including for research and development). |
| A +2 year period of premium pricing will offset the higher development costs and / or lower market volumes associated with a proportion of UMNs, whereby a larger number of all UMNs would pass the private sector's ROI thresholds. While companies cannot determine in advance which products will be successful and make a smaller or larger positive contribution to their overall income and profitability, the additional period of regulatory protection will have a positive impact on estimates of potential income and profitability used in stage-gate assessments.<br>The additional period of protection would improve the competitiveness and investment flows towards EU based originators producing UMN medicines.<br>Increasing developers focus on UMNs may increase their development and regulatory costs, in some limited degree, as applicants would need to meet the UMN criteria<br>For other developers, with products that do not address a UMN, the focus would be on demonstrating the absence of a return on investment from their R&D should they not be able to secure a period of additional regulatory protection. This would increase administrative cost associated with the data-hungry and exacting ROI methodology businesses would need to follow). This would also imply higher administrative costs for the EMA and NCA partners involved in checking compliance with the ROI test.<br>This incentive is expected to increase investments in R&D resulting in a higher number of novel medicines addressing UMNs as compared with the baseline and an increase in treatment options, treatments and improved patient health. |
| B.1.6. Breaking market protection in case of urgency and insufficient coverage by authorised medicines (compulsory licensing) |

| Assessment |
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| There has only been one instance of an EU member state using a Compulsory Licence,[72] as such this is an ultra-low probability event, and the link with the EU general pharmaceutical regulation is about ensuring external coherence.<br>There should be no or minimal direct impact on EU pharma in general, given it would be implemented indirectly and by exception and for a localised and time limited period.<br>It may increase burden on regulators and expand the numbers of government bodies that have to become involved in explaining their use of this regulatory exception<br>The time and costs involved in developing safe and effective copies of protected medicines may mean that the policy lacks the speed or certainty to respond with confidence to public health crises |
| **B.1.7. Require public transparency on any relevant public contribution or funding, including of research and development costs** |
| Commercial sensitivity around companies' willingness to disclose information about their use of public funding and tax reliefs to underpin their development costs makes it difficult for governments and healthcare organisations to judge the distance between manufacturers' costs and the prices they seek to realise.<br>Greater transparency around public support for medicines development may strengthen reimbursement agencies' position when negotiating with MA holders, helping to place a downward pressure on prices and thereby helping to maintain or improve access to medicines with concomitant benefits to patient health.<br>Indirectly and in the longer term, greater transparency may help public authorities justify higher healthcare budgets and thereby drive support for publicly funded medicines development. This in turn may increase the number of developers in the market and raise competition.<br>The private sector may resist such measures where they require disclosure of commercially sensitive information that could be used by their competitors within the EU and globally. Moreover, the link between R&D grants / tax reliefs and individual medicines is complex and would demand the development of new costing models and assessment frameworks. The proposal to make this information available to the public may be in tension with EU competition and IP law and could result in legal challenges.<br>Moreover, the proposal implies the EU pharmaceutical industry would need to tolerate a switch to cost+ pricing strategies in its dealings with EU payers as compared with value-based pricing that is in use currently and applies across all open markets globally.<br>There may be substantial additional administrative costs for firms needing to prepare the required information using the templates and rules of thumb on the attribution of wide-ranging public supports to specific medicines.<br>There would be substantial additional costs for the EMA compliance teams that need to develop the new procedures and tools (one off costs) and implement / assure the implementation of those protocols, including possibly upgrading the EMA's existing portals to provide better public access to individual dossiers. |
| B.1.8. Give regulators the possibility to impose a post authorisation obligation for additional studies on the effectiveness compared to the standard of care |
| Imposing a post-authorisation obligation for MAHs to include new information about the effectiveness of the medicines (i.e comparative clinical trials) may impose additional costs on MA holders, albeit this may be a matter of timing and degree, as many businesses carry out additional research on the cost-effectiveness of their medicines with a conditional approval. The EMA annual reports show that around one third of all medicines that have been granted a CMA since 2006 have gone on to be granted a full marketing authorisation (i.e. sufficient additional evidence has been gathered to confirm effectiveness). As such, it may increase and bring forward costs associated with such studies for tens of businesses. Those costs might amount to €20-€50m for each product.<br>MA holders will have to bear some additional costs and there may be a small increase in the number of medicines that are found to be less cost-effective than had been anticipated. This last point could impact on the ability of individual companies to raise finance or otherwise weaken their competitive position, but there would be no substantive impact – positive or negative – on overall competitiveness, or the functioning of the internal market.<br>This obligation would help to confirm the relative effectiveness of the products in question several years earlier than is the case currently. The EMA annual report (2020) shows that the 30% of CMAs that have been granted full marketing authorisation took an average of 3.5 years post-authorisation to get their products fully authorised. This would allow more timely action in respect to individual medicinal products – e.g. withdrawal or more widespread use – and would indirectly give HTAs and payers greater confidence in the CMA pathway.<br>There would be some additional administrative costs for the EMA and NCA staff working with them following from the increasing numbers of assessments of these additional studies and consideration of the case for granting full authorisation. |

[72] https://www.keionline.org/35558

| Assessment |
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| The improved clarity as regards the relative cost-effectiveness of medicines should increase confidence across health systems in making full use of those products, and thereby benefiting patient health. |

### Summary assessment of the Incentives for innovation

Policy Option B foresees several important changes to the current arrangements. With regard to the incentives for innovation, this option reviews the current protection periods with reduced standard regulatory protection periods and modulation subject to certain conditions. Authorised medicines with demonstrated ability to address UMN are entitled to longer protection than the standard protection.

Other medicines will be entitled to additional protection only if they can demonstrate no return on investment in view of investment costs, including for research and development.

MAH are given increased obligations regarding the repurposing of off-patent medicines. It gives regulators the possibility to impose a post-authorisation obligation for comparative studies on the effectiveness compared to the standard of care. This will facilitate decision-making throughout the lifecycle of medicines.

*Table 34 Option B - Summary assessment of the Incentives for innovation*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.1.1. | + | +/- | + | +/- | +/- | + | - | - | +/- |
| B.1.2. | +/- | - | - | +/- | + | + | +/- | + | +/- |
| B.1.3. | - | -- | -- | +/- | ++ | +/- | +/- | + | +/- |
| B.1.4. | -- | +/- | -- | -- | - | --- | + | - | +/- |
| B.1.5. | ++ | -- | -- | + | +/- | + | - | + | +/- |
| B.1.6. | - | - | - | - | - | - | - | +/- | +/- |
| B.1.7. | - | -- | - | - | +/- | - | - | +/- | +/- |
| B.1.8. | +/- | - | - | +/- | +/- | + | - | + | +/- |
| Overall impact | -- | --- | -- | -- | + | - | - | + | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

### Assessment of any synergies and tensions

Within the Innovation Policy Block, the policy elements proposed under Policy Option B are largely complementary to each other, whereby the proposal to reduce the period of regulatory protection for the standard innovative medicines pathway (by 2 year) is mirrored by a policy element to provide a +2 year special bonus for new medicines relevant to UMNs.

The ability to impose a requirement for additional studies would complement existing provisions relating to the EMA's various expedited regulatory pathways building support among member states (HTAs, health payers) for CMAs in particular.

## Assessment of the incentives for innovation and prudent use of antimicrobials

Policy Option B encourages the development of antimicrobials through novel incentives. It introduces a 'pay or play' model. Either a company holds an antimicrobial in its portfolio, or it pays to a fund that is destined to finance the development of novel antimicrobials. It includes measures for prudent use of antimicrobials as well as monitoring consumption and use of human antimicrobials.

*Table 35 Option B - Assessment of the proposed incentives for Innovation and prudent use of antimicrobials*

| **Assessment** |
|---|
| B.2.1 Make the central procedure mandatory for new antimicrobials. |
| As this policy element largely formalises what happens in practice already, there would be little or no additional impact on the development of novel antimicrobials or their more prudent use. |
| B.2.2. PRIME like support scheme, including rolling review |
| If the system in place for rolling reviews is easy for SMEs and large companies to navigate and flexible, there is potential for a large positive effect on EU pharma businesses by increasing company-regulator interactions in areas that may not be currently attractive for business to invest in R&D. This could result in a positive impact on innovation rates and overall EU pharma industry output.<br>The targeted survey revealed that industry respondents were broadly in favour of codifying rolling reviews, in particular for new technologies or major innovations in medicinal products. However, the demands on Rapporteurs are high, with significant increase in workload; one NCA interviewed stated that the COVID-19 pandemic rolling review required approximately 50% increase in resources/workload. The demands on companies are also relevant, as the process requires more communication and clarifications (data packages may not be structured, may contain errors, etc). Furthermore, rolling reviews bring uncertainty on the added therapeutic value of medicines and inequity of access is larger for orphan medicines73. Considering these reasons, some civil society and public authority respondents were against codifying rolling reviews in a way that would expand the scope of use of this procedure outside exceptional medical conditions and public health emergencies. |
| B.2.3. Optimise package size |
| This policy element would encourage the use of smaller package sizes, thereby increasing manufacturers' costs relating to product packaging and distribution.<br>It may also increase the cost of antimicrobials for health payers (smaller package sizes are more costly), including an increase in average prices for a course of treatment for an individual patient, albeit these price increases should be offset in some small degree by lower levels of consumption.<br>It may have implications for storage costs (more space required) but may ease dispensing and take pressure off pharmacists' local storage requirements.<br>We don't foresee additional extra administrative costs on the side of businesses and authorities.<br>By helping to reduce overall levels of consumption, this policy element may contribute in some small degree to reducing AMR and avoiding AM releases to the environment. The smaller pack sizes will increase packaging waste, which would increase costs associated with waste management and recycling. |
| B.2.4. Stricter rules on disposal |
| The legislation and accompanying guidelines would have no direct impact on EU pharmaceutical manufacturers, wholesalers or pharmacies, indirectly it may lead to an expansion in overall sales volumes and income, as pharmacies buy smaller volumes more frequently, prescribers push for smaller pack sizes, and patients a less likely to self-medicate. In the longer term, and indirectly, the initiative should encourage industrial actors across the value chain and across member states to give more weight to these issues and adhere more closely to applicable legislation and professional guidance.<br>Stricter disposal rules would bring additional costs for public authorities, with a substantial one-off cost for EU / MS authorities in developing and championing the roll-out / adoption of the guidelines and additional ongoing costs |

[73] https://www.efpia.eu/media/602652/efpia-patient-wait-indicator-final-250521.pdf

| Assessment |
| --- |
| for national authorities in maintaining / monitoring adherence and for the EMA and its advisory groups in tracking developments and giving ad hoc advice.<br>Stricter disposal rules / smaller pack sizes may increase the unit costs of antimicrobials and stricter management of stocks may also add costs and even increase susceptibility to shortages. Patients should see a benefit from a reduction in self-medication using unused and out of date medicines.<br>Given the high proportion of citizens that hold onto medicines indefinitely or otherwise dispose of them inappropriately[74], improved advice and collection should reduce poor disposal and indirectly benefit the environment and help to curtail an important vector for AMR |
| **B.2.5. Tighten prescription requirements for antimicrobials** |
| While prescribing policies are a matter for national authorities in the first instance, the legislation can invite member states to do more to bring practice in line with international standards.<br>These obligations and guidelines do not affect industry directly. Indirectly, and if successful, better prescribing would accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for the pharmaceutical industry overall and particularly those generics companies that supply older, lower-cost, broad-spectrum antimicrobials.<br>Indirectly, there may be a differential impact on the generics industry and particularly that sub-set of pharma businesses that include older, broad-spectrum antimicrobials in their portfolio. There may be a small benefit for MA holders with more specific antimicrobials, if prescribers both reduce overall prescription numbers and switch from cheap, broad-spectrum medicines to more specific (more expensive) antimicrobials.<br>Indirectly, tighter prescription is likely to reduce usage and that may weaken the return on investment for antimicrobials in general, worsening the investment case in an area of medicines research that is already regarded as being uneconomic.<br>Indirectly, health systems may see savings because of better prescription practices and reduced consumption, albeit this may be offset by increased costs associated with diagnostic tests and a switch to more costly antimicrobials. If successful, this policy element should reduce consumption and that in turn should reduce the potential for negative environmental impacts. |
| **B.2.6. Mandatory use of diagnostics prior to prescription of antimicrobials** |
| Similar impacts as with B.2.5 but since this policy element is seeking to encourage EU member states to make the use of diagnostics a mandatory requirement, there may be a greater impact on prescribing behaviour and consumption (albeit, as with prescribing practice in general, the use of diagnostics is a matter for member states in the first instance, with many wider factors determining the use of such screening techniques[75]).<br>There may be territorial issues around access and affordability with respect to diagnostic tests, whereby some of the proportionately largest consumers of antimicrobials are central and southern European member states, that rely heavily on low-cost broad-spectrum antibiotics supplied by generics manufacturers, and where there is less good access to more specific and costly branded antimicrobials and a similarly less good access to point-of-care tests, microbiologists, and test labs. These countries also have a stronger tradition in prescribing antibiotics as a first line of defence.<br>Greater use of diagnostic tests should improve prescribing practice in some degree, which should have a positive impact on patients, avoiding unnecessary medication or poor therapeutic outcomes that result from using the wrong anti-microbials. Depending upon the success of the proposed legislation and guidelines, these changed practices could reduce consumption considerably and make a significant contribution to efforts to contain AMR. |
| **B.2.7. Pay or play model: either a company holds an antimicrobial in its portfolio, or it pays into a fund that is destined to finance the development of novel antimicrobials.** |
| A pay or play model would impose additional costs on EU pharma businesses, and while a minority may look to avoid a levy by beginning to develop antimicrobials, or by acquiring businesses with an antimicrobial in the portfolio, the majority would be likely to view the surcharge as an unavoidable additional cost to be factored into their wider pricing policies.<br>Additional administrative costs related to the pay or play model are expected to be relatively small, with the sub-set of firms that are developing or supplying antimicrobials needing to certify that fact in order to avoid the surcharge. |

[74] Mitkidis, K., Obolevich, V., Chrysochou, P. and Mitkidis, P., 2021. Harmonisation of Pharmaceutical Take-Back Systems in the EU. *European Journal of Health Law*, pp.1-27.

[75] https://www.imi.europa.eu/projects-results/project-factsheets/value-dx

| **Assessment** |
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| SMEs would not be impacted directly by this policy since it is expected that EMA continues to put in place preferential policies for these firms. Indirectly, and over time, the system could lead to a series of acquisitions and an expansion in demand among larger developers for the results of early-stage R&D involving SMEs.<br>The proposed pay or play model would raise the cost of doing business in Europe, this could affect the competitiveness of pharma companies in Europe relative to US companies.<br>It may encourage developers willing to avoid the fees to broaden their product portfolios through commercial activities (e.g. mergers, acquisitions, licences, etc. with smaller biopharma companies that develop antimicrobials). It will incentivise competition between large pharmaceuticals to win the research and development grants financed by the fund.<br>The EMA would need to establish a new unit to decide on the allocation of the research grants to the best suited developers.<br>This pay or play model would not increase substantially the number of novel antimicrobials in the market and may risk increasing prices in other markets, creating substantial social costs. |
| B.2.8. Establish a monitoring system for data collection on human antimicrobial consumption and use and potentially on the emission of APIs to the environment |
| Expanded surveillance would have no direct impact on EU pharmaceutical companies conduct of business. Indirectly, and in the longer term, improved surveillance data may help to accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for industry overall.<br>Expanded surveillance would have no direct impact on EU pharmaceutical companies' administrative costs. Indirectly, and in the longer term, improved surveillance may facilitate the more robust scrutiny of MAH environmental risk assessments (ERA) and this would be expected to require all businesses to develop more comprehensive - possibly more costly - ERA presentations as part of their submissions to the EMA.<br>This policy element would not have a direct impact on SMEs, however, indirectly, any implications for enhanced environmental risk assessments could be more challenging for SMEs to carry out / afford.<br>Expanded surveillance would have no direct impact on EU pharmaceutical companies conduct of business. Indirectly, and in the longer term, the improved surveillance data would be expected to facilitate more robust scrutiny of MAH environmental risk assessments. More and better data may also accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for industry overall, but possibly with a relatively bigger negative impact on generic companies.<br>This policy element would have no direct impact on the functioning of the single market; however, it is conceivable that an expanded surveillance system would reveal environmental hot spots across the EU that could trigger referrals to the EC / EMA and possibly change national procurement behaviour, with more interest in sourcing medicines from producers with the best environmental record no matter where they are based.<br>Expanded surveillance would have no direct impact on EU pharmaceutical research and innovation. Indirectly, it is likely to reduce overall demand and thereby worsen the market failure associated with the development of new antimicrobials<br>An expanded surveillance system could have a significant impact on the costs borne by public authorities, both one off and in the longer term. The additional costs would fall most heavily on national agencies. Environmental impacts go far beyond the mandate and competence of the network members and given the many routes by which such active ingredients may come into the environment (e.g., agriculture), there would need to be a considerable amount of work done to agree definitions and set up data collection systems. There would also be questions around the interpretation of the results and any causal relationship between the pharma legislation, human use and the environmental signature.<br>An expanded surveillance system would not have a direct benefit to public health, however, indirectly it may provide a small additional impetus to encourage more prudent use of antibiotics. In this way, and in the longer term, it may help to combat AMR to some limited extent. On the negative side, and indirectly, it could weaken incentives slightly for industry to invest in the kinds of novel antibiotics that are needed to combat AMR more robustly.<br>An expanded surveillance system could provide a good platform from which to improve the management of antimicrobial production and consumption, with more prudent use and more informed production and disposal helping to reduce the level of human-related active ingredients getting into the environment. |
| B.2.9 same as A.2.3. Consider adapted system for authorisation of phage therapies and other alternative products |
| This policy element would create the regulatory space to encourage an increase in ongoing efforts to develop phage therapies for routine use in human medicine, potentially increasing the number of companies willing to invest and develop these emerging alternatives to conventional antibiotics.<br>In the longer term, the adaptation should ensure novel therapies can be authorised and this will in turn increase investment, develop a new market segment where the EU industry enjoys a competitive advantage, while also reducing prices of these therapies such that they will become affordable. |

| Assessment |
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| In the longer term, the emergence and growing use of phage therapies may also reduce healthcare costs/budgets since phages are an inexpensive natural resource present in the environment and offer potential as an alternative when antibiotics are rendered ineffective due to bacterial resistance (AMR).[76]<br>Finally, by reducing the use of antibiotics it would help reduce the presence of antibiotics in the environment. |

### Summary assessment of the incentives for innovation and use of antimicrobials

Policy Option B is largely concerned with enhanced prescribing practices and stewardship, which will have limited direct impact on industry or markets – beyond reinforcing the downward pressure on demand for antimicrobials in general – but should have benefits for patients and the environment. There is no substantive direct support for innovation, but rather Policy Option B proposes introducing a Pay or Play model to create a fund for reinvesting in AM R&D, which would add costs and administrative burden for industry in general without generating the volume of funds necessary to impact the AM pipeline. The adaptation of the system for the authorisation of phage therapies may catalyse increased investment in this emerging and innovative technology.

*Table 36 Option B - Summary assessment of measures for innovation and use of antimicrobials*

| Policy elements | COB | Admin | SMEs | CTI | Internal Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.2.1 | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| B.2.2. | + | - | + | +/- | +/- | + | - | + | +/- |
| B.2.3. | - | +/- | +/- | +/- | +/- | +/- | - | + | + |
| B.2.4. | +/- | +/- | +/- | +/- | +/- | +/- | - | + | + |
| B.2.5. | +/- | +/- | +/- | +/- | +/- | +/- | - | + | + |
| B.2.6. | +/- | +/- | +/- | +/- | +/- | +/- | - | + | + |
| B.2.7. | - | -- | -- | - | +/- | + | - | +/- | +/- |
| B.2.8. | +/- | +/- | +/- | +/- | +/- | +/- | - | +/- | + |
| B.2.9 | + | +/- | +/- | + | + | + | - | + | + |
| Overall impact | +/- | -- | - | +/- | +/- | + | - | + | + |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element. Policy Option C – Summary assessment of the Incentives for innovation

### Assessment of any synergies and tensions

Within the AMR Policy Block, the policy elements proposed under Policy Option B are largely complementary to each other, with the mandating of the use of the Central Procedure dovetailing with the proposal for the EMA to create a PRIME-like scheme for AM products, while also introducing the Pay or Play model to create a fund for reinvesting in AM R&D. The adaptation of the system for the authorisation of phage therapies is a further complementary

[76] https://www.nesta.org.uk/blog/when-the-drugs-dont-work-could-bacteriophages/?gclid=Cj0KCQjw_4-SBhCgARIsAAlegrUn5LXTOVza5VKzwfA4XcfpeUXcHW8jiSFfDhOBM2_MUMNcQ0GrXVQaAtQVEALw_wcB

initiative that recognises the potential for this emerging and innovative technology to make a substantial contribution to combatting AMR through support for the development of a non-traditional technology trajectory. Moreover, the proposals on prescribing practices, package size, and disposal all work well together in supporting more prudent use. The expansion in the scope of the existing surveillance system would also provide an important means by which to track progress in optimising consumption across the EU.

Under Policy Option B, there is no specific policy element that will reward innovators with an additional period of regulatory protection, however, the proposals under the Innovation Policy Block do include a policy element to provide a +2 year special bonus for new medicines relevant to UMNs. This would be an important synergy across these blocks, assuming most innovative antimicrobials would be considered as being relevant to an UMN (e.g. targeting a WHO priority pathogen where there are no or too few effective treatment options) and therefore eligible for the additional protection.

### *A.4.3. Policy Block C (B.C): Future Proofing*

Policy Option B is a refinement of the current arrangements, with four principal interventions.

Table 37 presents our schematic overview of these proposals, noting the key design assumptions and strengths/weaknesses of each one.

*Table 37 Option B - Assessment of the proposed measures for Future Proofing*

| **Assessment** |
|---|
| 1. Scope and Definitions |
| B.3.1. Adapted regulatory framework for certain categories of novel products/technologies or low volume products (hospital preparations) on the basis of well-defined conditions and respecting the principles of quality/safety/efficacy. Such frameworks could be adapted or expanded through delegated acts to set the technical framework that can be adapted to emerging scientific and technical advances (adaptive framework).<br>Where applicable, such delegated acts should be developed in close coordination with other relevant competent authorities such as e.g. medical devices, IVDs or substances of human origin) |
| As changes to legislation can be lengthy with a high administrative burden especially in the case where legislation needs to change regularly (for example to adapt to emerging technologies) adaptive legislation can be an option. In an adaptive framework change can be more iterative and responsive, 'soft-law' tools such as best-practice guidance can be employed and can be developed more collaboratively with stakeholders (who bring in depth technical knowledge) and later certified or adopted by regulators.<br>For novel products or technologies this is to respond to the emergence of new technologies that do not fit the legislation scope or definitions to ensure the legislation remains relevant. For low volume products this is assumed to respond to challenges with hospital preparations (via the hospital exemption, pharmacy exemption or as bedside manufacturing of a centrally authorised product) where regulatory gaps currently exist due to manufacturing process being out of scope or unsuitability of some aspects of GMP for hospital context.<br>B.3.1. has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. It would also address the issues of current technological advancements that are not adequately legislated for and provide the legislation with a mechanism of keeping pace with technology through both facilitating adaptation and drawing on the expertise of deeply engaged stakeholders with in-depth technical knowledge of emergent areas. However, there would be an associated increase in administrative burden due to a likely expansion of the number of specific non-legislative (soft law) tools that would require development, maintenance, review etc. and ongoing need for feedback loops, iteration and adopting delegated acts. EMA and the regulators need to stay in control and ensure that the soft law tools are meeting the overall objectives of the legislation since the incentives and alignment of all stakeholders (some of whom have valuable technical expertise that this framework is designed to harness) is not implicit. With respect to low volume products specifically this will represent an increase in regulation and associated regulatory burden but will reduce gaps in the legislation and improve patient safety while providing the legislation with the tools to consistently adapt to this rapidly paced area of technological |

| **Assessment** |
| --- |
| change (e.g. pharmacoprinting, bedside manufacture, personalised medicines etc.) contributing to hospital preparations as a legitimate and robust production mechanism. |
| 2. GMO |
| B 3.2. Same as A.3.2 but for clinical trials: Where required, the assessment of the GMO aspects of investigational medicinal products is performed at Member State level, within the maximum timelines defined in the Clinical Trial Regulation (decentralised assessment). |
| This is as A3.2 however with the understanding that the assessment would take place at the Member State Level rather than EMA level.<br>This element would likely have less potential to improve efficiency of assessment and thus speed of authorisation of GMO-containing medicinal products. This is because complications with assessments may arise if NCA apply risk-based approach differently. However, if implemented well regulatory efforts would be focused on assessing GMO containing medicines that pose greatest threat to the environment. |
| B.3.3. Adapt certain definitions, including that of medicinal product and *delink scope from industrial process* to address technological developments, gaps/borderline questions, taking into consideration the views of regulatory authorities for other relevant legal frameworks (e.g. medical devices and blood, tissue and cells) - linked to scope of the legislation. |
| The 2004 Directive 2001/83/EC covers all 'medicinal products' that are "either prepared industrially or that are manufactured by a method involving an industrial process". By "delinking" we assume removing the manufacturing process specification from the legislation scope such that it will automatically bring into scope products that could be considered as being exempted purely through not meeting that definition. By adapting 'certain' definitions we assume this is firstly 'medicinal product' to be less specific and more similar to that found fit for purpose in other markets, secondly 'batch' which is a cornerstone of GMP but ill-fitting for continuous manufacturing processes in addition to other more specific ones around different categories of medical product.<br>This element has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. Delinking scope from industrial process would immediately bring under regulation a number of excluded or potentially excluded products and processes – most notably novel manufacturing such as bedside such as pharmacoprinting. It would be important that upon their being brought in scope the GMP was able to accommodate them or that sufficient alternative tailored guidance was available: the adaptive framework for low volume products in element B3.2 could be a facilitator to this. Addressing gaps in the legislation would impact positively on patient safety though could cause a (likely short term) reduction or delay in access while adaptations for compliance to greater regulation were made. There would be additional regulatory burden to implement the extended scope of the legislation. However, long term the efficiencies and predictability are anticipated to increase investment and innovation, reduce the time to access and improve patient safety. |
| B.3.4. Create a central *classification mechanism* for advice on whether products are medicines or not, building on the current EMA Committee for Advanced Therapies (CAT) mechanism for ATMPs to all medicinal products (borderline products) in close coordination with other concerned authorities in particular in the frameworks of medical devices and substances of human origin. |
| Medicines are increasingly being used in combination with a medical device, usually to enable the delivery of the medicine. However, these combinational products have brought regulatory difficulties for NCAs in terms of uncertainty whether they should be classified as a medical product or medical device and what regulatory framework applies.<br>B.3.4 would improve consistency of the classification of borderline products and the resulting choice of the most appropriate pathway through the EMA committee structure. This should harmonise coordination between concerned authorities in particular in the framework of medical devices and substances of human origin, and thereby deliver some small efficiency gains and avoid assessment committees being distracted from their assessment work by definitional questions. It may also improve the overall timeliness of assessments. The creation of a central screening mechanism may be timely as more definition questions arise: for example, 1 in 4 centrally approved medicines typically include a |

| Assessment |
| --- |
| medical device component[77]. Success would depend on EMA finding the capacity to deliver relevant advice at speed. |

## Assessment of the key impacts for the policy elements

Table 38 provides a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under option B.

*Table 38 Option B - Summary assessment of future proofing*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| B3.1 | ++ | + | + | ++ | + | ++ | -- | ++ | +/- |
| B3.2 | +/- | +/- | + | +/- | + | ++ | - | + | +/- |
| B3.3 | + | + | +/- | + | ++ | + | - | ++ | +/- |
| B3.4 | + | + | + | + | + | + | +/- | + | +/- |
| Overall impact | + | + | + | + | + | + | - | + | +/- |

## Assessment of any synergies and tensions

Within this block there is tension around significant ongoing administrative burden for legislators (and other stakeholders in complex novel technologies) associated with regular and continuous amendments via delegated acts. While this undoubtedly has positive impacts regarding efficiency of applications, reduction of legislative gap and therefore products reaching the market more quickly and better regulated it should be recognised that it does represent a transfer or trade-off of administrative burden (from scientific committees and applicants in navigating an ill-fitting framework) that it represents any overall reduction. This also creates a tension with some of the horizontal streaming measures looking to reduce administrative burden where otherwise there are synergies with B3.3 and B3.4 very much related to streamlining and reduction of burden.

The relationship of all medicinal products with industrial process is not the same. While generally a delinking from industrial process was regarded positively in stakeholder consultation and according to our research would have positive impacts overall particularly for resolving scope issues and preventing legislative gaps around novel manufacturing processes, certain sectors (plasma in particular) suggest this would for them create regulatory uncertainty.

Future proofing elements in this policy element related to improved mechanisms/approaches for innovation to promote access to novel medicines (B3.2, B3.3) complementing measures in Block A – innovation for UMN, Block D-access as well as competition (Block E). There are also definition synergies with Block F (Introduce EU definition of a shortage and a definition of a critical medicine (B6.1)) and G (Adaption of legislation/inclusion of specific provisions covering new manufacturing methods (B7.4)).

[77] European Medicines Agency. (2020). *ANNUAL REPORT 2020*.

### *A.4.4. Policy Block D (B.D): Access*

Under Option B, four elements are included. The first (B.4.1) is aimed at regulating access to products that have been conditionally authorised by giving regulators greater powers to act when the generation of new evidence post-approval is not satisfactory or in case benefit is not confirmed. The other three measures (B.4.2, B.4.3 and B.4.4) have similar objectives to the elements previously discussed in Option B in that they are aimed at expanding the number of EU markets where products are launched. Unlike Option A, however, the measures under Option B exclusively focus on imposing greater requirements on MAHs and do not include incentives or voluntary options. Furthermore, whilst obligations under Option A were linked exclusively to products authorised through the centralised procedure, Option B also targets those that are authorised through the MRP/DCP route (B.4.4).

#### Assessment of the key impacts for the policy elements

Table 39 presents our high-level assessment of the likely costs and benefits of each of the proposed legislative actions. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

*Table 39 Option B - Assessment of the proposed elements to improve access*

| **Assessment** |
|---|
| *B.4.1* Conditional Marketing Authorisation: introduce more powers to regulators to take measures in case of non-compliance with obligations for post-market evidence generation or in case benefit is not confirmed |
| Whilst available evidence primarily points in the direction of issues with the *standards* of evidence imposed on post-market evidence generation, policy element B.4.1. aims at increasing the ability of regulators to *enforce compliance* with the SOB. For the measure proposed under B.4.1 to have meaningful impact on access to medicines, whilst maintaining rigorous standards of effectiveness, quality and safety it must thus be assumed that:<br>• The standards for evidence generation imposed through the SOB are sufficient or will be further raised to a level whereby post-market evidence can better inform assessment of the risks and benefits<br>• Delays in submitting data in compliance with the SOB are due to insufficient commitment on the part of the MAH to meet specified timelines and there is scope to accelerate fulfilment of the requirements.<br>If regulators exercise their expanded powers to impose stricter obligations on the generation of post-marketing evidence (e.g. better quality study designs) and/or better enforce compliance with the SOB, this may raise the quality of evidence generated with regards to a medicine's effectiveness and safety. Earlier access to such information could mean that ineffective or unsafe medicines are removed from the market more quickly. This will have a positive impact on public health, as well as reduce the costs from use of ineffective or unsafe treatments. Conversely, when the generated evidence supports the conversion of the authorisation from conditional to full, this too will be beneficial for patients and health providers who can be better guaranteed of the medicine's continued availability. It also provides more certainty to payers and health systems about future health expenditures on such medicines. |
| *B.4.2* Require the MAH to notify regulators, during the authorisation process, of their market launch intentions through a roll out plan for all centrally authorised medicines |
| The requirement to report on launch intentions is similar to the (voluntary) reporting proposed under A.4.3 except that voluntary reporting has here been converted into a requirement. It further differs in that it does not ask for a commitment to initiate pricing negotiations. In this regard it is both a stricter and a narrower proposal.<br>Earlier notification of launch intentions allows regulators, health systems and payers to better prepare for (potential) entry of new medicines into the package of reimbursed care. It also facilitates timelier discussion between the MAH and authorities about pricing and reimbursement.<br>It has been assumed that this requirement does not come with powers to regulators to enforce MAHs to follow up on their expressed launch intentions, nor imposes sanctions on MAH for not doing so. It is therefore highly uncertain whether, on its own, this measure could increase the number of markets in which MAH launch or encourage earlier launch. Additional obligations such as those proposed under B.4.3 would be needed to support this measure. |
| ***B.4.3* Obligation to place a centrally authorised medicine on the market in the majority of Member States (small markets included) within 5 years of authorisation** |
| The proposed obligation is similar to that specified under A.4.4. but is less explicit in that it does not indicate what the sanction is for non-compliance. In the absence of this information, it is assumed the sanction will be withdrawal of regulatory protection that would allow generic competition from year 6. |

| |
|---|
| Any measure that promotes market entry into a greater number of EU countries, will be beneficial to patients who are otherwise unable to access these medicines. The impacts of an obligation to place centrally approved products on the market will scale with the number of countries and patients reached and with the importance of the medicine.<br>A potential risk is that MAHs of products that are within the optional, but not compulsory, scope of the CP will avoid the CP authorisation route to not fall under the obligations. This could result in a reduction in the number of countries where the product is authorised and decrease rather than promote equitable access. |
| *B.4.3.1* Requirement to offer products to a majority of national health systems (including small markets)] within 5 years from authorisation |
| This element is offered as an alternative to B.4.3. The main difference is that it requires MAH only to *offer* the product to national health systems but does not make fulfilment of this obligation contingent on whether this results in actual market placement. Whilst not explicitly stated, it is assumed that – as an alternative to B.4.3 – this requirement would apply only to centrally authorised medicines.<br>This element imposes somewhat less stringent obligations on MAHs by making its fulfilment dependent only on whether an MAH has entered into discussions with national authorities about pricing and reimbursement but not on a successful outcome of those discussions. Since this still allows MAHs to refrain from market entry if no mutually acceptable agreement can be reached, the direct impact of this element on improved access will likely be smaller than under option B.4.3. It may, however, be less of a deterrent for MAHs of products in the *optional* scope of the CP than B.4.3. |
| B.4.4 Requirement on MAH applying for MRP/DCP to include small markets (in particular address the post-BREXIT challenges) or possibility for MS to opt-in a pending MRP/DCP procedure |
| Most generic medicines are currently approved through the MRP/DCP route[78]. Because of this, these products would not fall within the scope of the requirements imposed by B.4.2 and B.4.3. By also extending greater obligations for inclusion of smaller markets in the application for approval via the MRP/DCP, the Commission aims to increase access to a wider group of products, in particular generic medicines, than would be achieved via marketing obligations on centrally approved medicines alone. It is assumed that the proposed element intends only to require the applicant to include specific countries into the MRP/DCP application, such that there is a valid MA in these markets, but does not require the applicant to directly place products on these markets.<br>Requiring MAHs applying for an authorisation via the MRP/DCP route to include specific markets – or allowing countries to opt-in – will enable these countries to obtain medicines more easily from other EU MS (through parallel distribution), even when the MAH does not place the product directly on the market. This may have the effect of increasing access to medicines that are not within the scope of the CP, especially generic medicines. This, in turn, may be expected to positively affect both health outcomes for patients and the affordability of treatment by increasing access to low-cost generic versions. It will also improve security of supply for included countries by facilitating redistribution in case of shortages. |

## Summary assessment of the principal costs and benefits by impact type

Table 40 presents a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under Option B.

*Table 40 Option B - Summary assessment of Policy Block D (Access)*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.4.1 | -- | - | - | -- | +/- | ++ | ++ | ++ | +/- |
| B.4.2 | +/- | - | +/- | +/- | +/- | +/- | + | + | +/- |
| B.4.3 | --- | -- | -- | -- | + | - | ++ | +++ | +/- |
| B.4.3.1 | -- | -- | -- | - | + | - | ++ | ++ | +/- |
| B.4.4 | --- | -- | - | -- | + | - | ++ | +++ | +/- |

[78] European Medicines Agency. (n.d.). *Authorisation of medicines*. Retrieved April 4, 2022, from https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Overall impact | --- | --- | -- | -- | ++ | - | +++ | +++ | +/- |

- Greater obligations on the quality of evidence generated may require additional activities by the MAH (e.g. larger and additional trials), that would increase the cost for conduct of business to the MAH. Estimation of the magnitude of any potential impact would require insight into the size and type of additional activities that would be requested to raise the post-market evidence generation to a more widely accepted level.
- Obligations on MAHs to place centrally authorised medicines on the market in a majority of MS, presumably at risk of penalty in case of non-compliance, may carry substantial costs to the MAH. They may either be required to operate in markets where they cannot generate a sufficient ROI or incur fines if they refuse to do so. The MAH will also have to provide additional information to regulators to demonstrate their compliance with obligations. This implies increased administrative costs.
- Increasing the number of MS in which the MAH places a centrally approved product on the market will increase the costs to MAHs for interacting with regulatory agencies and HTA bodies in these countries. Obligations for market placement in a minimum number of MS, including smaller markets, may be more challenging to meet for SMEs that do not yet have market presence or distribution channels in such markets.
- For products approved via the MRP/DCP, a separate fee for each country in which the application is recognised will also be required. Further fees are required to annually renew the authorisation and to submit variations. However, to promote inclusion of smaller MS, special procedures with shortened time schedules and reduced fees exist (20).
- The policy elements included under Option B impose a number of additional obligations on MAHs and do not offer any incentives in return. As such, they are likely to present a significant cost for any company operating in the EU. This will reduce the competitiveness of EU-based companies compared to those in, for instance, the United States.
- Inclusion of additional countries, in particular smaller MS, in the MRP/DCP application will facilitate the movement of medicines between markets where the product has been authorised. As such, this measure may be expected to promote the functioning of the EU internal market.
- Regulatory authorities in the MS where products are placed in the market will see an increase in costs due to a greater number of medicines for which they provide regulatory oversight (B.4.3 and B.4.4). Similarly, HTA bodies will have to conduct a greater number of assessments. Expansion of the number of countries included in MRP/DCP applications will result in more work for authorities in those countries to process applications. The resulting costs may be offset, at least in part, by application fees.
- The intended and expected impact of increased access to medicine is that patients will be provided with earlier, more effective and safer treatments. This will have a positive impact on their health status and wellbeing. Whilst increased access to medicines is generally positive, it may result in increased health care expenditure. At the same time, new medicines may displace less (cost-)effective treatments, resulting in net savings. Further indirect savings from increased access to medicine may result from improved health and productivity.

### Assessment of any synergies and tensions within the Policy Block

Requiring additional, and in particular smaller, countries to be included in the MRP/DCP application procedure (or allowing countries to opt-in) may be considered synergistic with the

objectives of the policy elements in Block F to improve supply chain security, by facilitating the import of medicines from other EU countries in case of shortages.

### *A.4.5. Policy Block E (B.E): Competition*

Policy Option B involves several changes to the current legislative arrangements for encouraging competition with a view to improving time to market entry for generics and biosimilars.

#### Assessment of the key impacts for the policy elements

Table 41 presents our assessment of the likely impacts (costs and benefits) of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected.

*Table 41 Option B - Assessment of the proposed measures for competition*

| **Assessment** |
|---|
| B.5.1 New simpler regulatory pathway for generics (adapted EMA/CHMP working methods, shorter approval timelines, potentially distinguishing between complex generics/biosimilars – reducing requirements for known biologics) |
| As described for A.5.1.<br>The key impact from a simpler regulatory pathway with shorter approval times will be faster availability of generics to patients. It should create more clarity and potentially less administrative burden for marketing authorisation applicants, encouraging more applications and increased development activity for generics.<br>We assume that generics will be on the market soon after approval and access to generics will be similar in all member states. The latter assumption has been adopted for ease of analysis as generics market penetration varies considerably across member states and would add uncertainties to our assessment. |
| B.5.2 Interchangeability of biosimilars with their reference product will be generally recognised in guidance or e.g. through a recital in the legislation and will be scientifically assessed as part of the product assessment and indicated in the summary of product characteristics (SmPC, product information) to inform healthcare professionals and their patients as well as downstream decisions makers |
| Interchangeability, switching (by prescriber) and substitution (by pharmacy) of a reference medicine by its biosimilar currently fall within the remit of EU Member States. Guidance on interchangeability from one originator (reference) or biosimilar product to another at the EU level would enable all member states to make decisions on whether to allow switching and/or substitution for certain products, especially those countries where the relevant technical capacity is not available. There is potential to pool the best expertise from across the EU if product assessment is done as part of the centralised procedure, reducing burden on individual member state authorities. Inclusion of the guidance in a recital in the legislation and product information (SmPC) would inform prescribers, patients, and decision makers about interchangeability of specific products, potentially increasing uptake of biosimilars. This could improve access to biologics for patients and reduce health system costs if cheaper biologics were switched or substituted for more expensive ones.<br>It is not clear if additional data will be requested for the scientific assessment of interchangeability e.g. switch studies.[79] Our assumption is that no additional data will be required – a study by Kurki et al. (2021) which analysed post-marketing surveillance data suggests that biosimilars approved in the EU are highly similar to and interchangeable with their reference products.[80] A recent qualitative study also shows that European and UK regulatory, legal and policy experts do not see any added value in additional data or switching studies.[81] |
| B.5.3 Broader Bolar exemption – allow additional beneficiaries (companies, producers of active pharmaceutical ingredients (APIs) and non-industry actors) to conduct studies/trials |

[79] Alvarez, D.F., Wolbink, G., Cronenberger, C. *et al.* Interchangeability of Biosimilars: What Level of Clinical Evidence is Needed to Support the Interchangeability Designation in the United States?. *BioDrugs* **34,** 723–732 (2020)

[80] Kurki, P., Barry, S., Bourges, I. *et al.* Safety, Immunogenicity and Interchangeability of Biosimilar Monoclonal Antibodies and Fusion Proteins: A Regulatory Perspective. *Drugs* **81,** 1881–1896 (2021).

[81] Druedahl LC, Ka¨lvemark Sporrong S, Minssen T, Hoogland H, De Bruin ML, van de Weert M, et al. (2022) Interchangeability of biosimilars: A study of expert views and visions regarding the science and substitution. PLoS ONE 17(1): e0262537.

| Assessment |
|---|
| Overall, the broader Bolar exemption is likely to increase legal certainty, access to medicines, cost savings and research activity in the EEA compared with a narrower exemption.[82] |
| B.5.4 Extend Bolar exemption beyond generics – Allow repurposing studies/comparative trials without infringing patent rights |
| Overall, the extended Bolar exemption is likely to increase legal certainty, access to medicines, cost savings and research and innovation activity in the EEA compared to a narrower exemption.[82] |
| B.5.5 Specific (regulatory) incentive for a limited number of first biosimilars [market exclusivity for 6 months] |
| The key expected impact would be new biosimilars on the market as a result of additional research and innovation related to biosimilars undertaken to capture the benefits of the incentive. However, any such impact is likely to be extremely limited according to feedback from industry in the impact assessment workshop. According to industry, the incentive proposed is unlikely to significantly alter R&D activity or availability of biosimilars. This point is supported by literature – for example, a one-year extension of market protection for approval of a new indication has rather marginal effects.[83]<br>At this stage it is unclear, how the market exclusivity would work and whether it will be simultaneous or sequential as not all biosimilars within the group will enter the market at the same time. |
| B.5.6a Reforming the duplicates regime: No auto-biologicals<br>OR<br>B.5.6b Duplicates restricted to cases of intellectual property protection or co-marketing |
| The main effect of B.5.6.a will be increased competition in the biosimilars market with no monopoly conditions for the first entrant. This will mean greater choice for patients and health systems.<br>In case of B.5.6.b, there will be a reduction in barriers to competition and monopolisation of the market by the first generic/biosimilar of an originator product to receive an MA. Consequently, there will be no delay in the second generic/biosimilar coming onto the market once it receives approval. This will mean greater consumer choice and price competition. |

## Summary assessment of the principal costs and benefits by impact type

Table 42 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block E under Policy Option B and for each impact type.

*Table 42 Option B – Summary assessment of the proposed measures for competition*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.5.1 | + | + | + | + | + | + | + | + | -/+ |
| B.5.2 | -/+ | -/+ | -/+ | + | + | -/+ | ++ | ++ | -/+ |
| B.5.3 | + | + | -/+ | + | + | + | ++ | ++ | -/+ |
| B.5.4 | + | + | -/+ | + | + | + | ++ | ++ | -/+ |
| B.5.5 | -/+ | -/+ | -/+ | -/+ | -/+ | -/+ | -/+ | -/+ | -/+ |
| B.5.6 | -/+ | -/+ | + | + | ++ | + | ++ | + | -/+ |
| Overall impact | + | + | + | + | ++ | + | +++ | +++ | -/+ |

[82] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

[83] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, *Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe : final report*, Publications Office, 2018, https://data.europa.eu/doi/10.2873/886648

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Some of the key expected impacts are as follows:

- Increased international competitiveness through creation of a more favourable regulatory environment for generics/biosimilars (simplified generics pathway, specific incentive for first biosimilars), which might encourage more MAHs to apply for first filing in EU. The broader scope of the Bolar exemption will increase the share of EU-based API producers and API manufacturing jobs and lower costs of supply for European generics.[84] The cost savings would be more pronounced for European generics manufacturers of specialised products e.g. for oncology or central nervous system. Increased competitiveness may possibly encourage new entrants
- Improved consumer choice and competition through availability of both generics/biosimilars and originators on the market, resulting in lower prices and improved access for patients across member states. Modification of the duplicate regime will mean originator companies will not be able to severely undercut the price of potential biosimilar competitors through a duplicate authorisation for an autobiological while allowing the reference originator product to maintain a high price.[85]
- Market exclusivity for first biosimilars may allow higher prices to be charged[83]. It may also limit competition by preventing new biosimilars from entering the market during the exclusivity period. On the other hand, with protection being awarded to a set of biosimilars for the same originator product, price competition may also occur. The level of discounting is typically around 20% of the price of the originator product for a single new biosimilar entering the market, or 30–50 percent for multiple biosimilars entering the market simultaneously.[86]
- Increase in R&D for generics/biosimilars with regulatory pathway becoming quicker and clearer, Bolar exemption broadened to include additional beneficiaries, modification of the duplicate marketing authorisation regime and specific (regulatory) incentive for first biosimilars. The latter may encourage more investment in biosimilar development (there is a positive relationship between market protection and R&D investments by companies[87]), but this effect will be limited considering development costs[88] and only six months' market exclusivity as incentive.
- The extended scope of the Bolar exemption will increase returns to innovation and therefore increase incentives to innovate for European R&D based pharmaceutical companies in countries that currently have a narrow Bolar scope, such as Belgium, the Netherlands and Sweden. This might increase the number of regulatory tests/medicine trials

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[84] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

[85] https://www.biosliceblog.com/2019/11/update-on-eu-duplicate-marketing-authorisations/

[86] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilars

[87] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, *Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe : final report*, Publications Office, 2018, https://data.europa.eu/doi/10.2873/886648

[88] Mestre-Ferrandiz, J., Towse, A. & Berdud, M. Biosimilars: How Can Payers Get Long-Term Savings?. *PharmacoEconomics* **34**, 609–616 (2016).

conducted in these countries and can be expected to lead to an increase in the number of skilled jobs[84]

- A very high likelihood of positive impact on patients through making medicines more readily available and reducing costs for health systems (generics represent around 80% cost reduction compared to originators, and entry of a generic also reduces price of the off-patent medicine by 61%[89]; biosimilars are 20% cheaper[90] compared to originator products)
- An extended Bolar exemption will result in more timely access to medicines for patients.[91] If the measure leads to more clinical trials in a country, this will benefit the country patient population, as it has been shown that new medicine adoption is wider in countries where the clinical trial was run.[91]
- Increased access to medicines and security of supply through alternatives being defined (interchangeability)

### Assessment of any synergies and tensions

There is synergy with the horizontal measure of streamlining and harmonisation with making the regulatory pathway for generics simpler. There is a high likelihood of synergistic effects on biosimilar adoption from the combination of interchangeability guidance and the other incentives and measures.

Changes to the duplicates regime should alleviate some tensions with regard to timely availability of biosimilars on the market and thus could improve access. On the other hand, the measures to promote earlier generic/biosimilar entry to the market e.g. extending/broadening the Bolar exemption and specific regulatory protection for first biosimilars may create tensions with the measures supporting innovation.

#### *A.4.6. Policy Block F (B.F): Supply Chain Security*

Compared to Option A, Option B introduces a considerably more extensive set of measures that introduce or increase various obligations and requirements on MAHs and wholesalers.

### Assessment of the key impacts for the policy elements

Table 43 presents our assessment of the key impacts of each of the proposed measures, drawing on our consultations, desk research and targeted literature review.

*Table 43 Option B - Assessment of the proposed measures for Supply Chain Security*

| **Assessment** |
|---|
| B.6.1. Introduce EU definition of a shortage, including a critical shortage and critical medicine |
| The measure has the potential to harmonise numerous definitions of shortages that exist across the EU. The clarification of criticality criteria can further help in making changes in shortage notification to cover shortages for most critical medicines. Overall, many stakeholders, and particularly industry representatives have advocated for the adoption of the concept of 'product criticality' into definitions of shortages and regulatory measures aimed at notification and prevention of shortages. The study of medicines shortages also called for the introduction of criticality criteria and further measures associated with it.[92] |

[89] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

[90] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilarsv

[91] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

[92] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages*

| |
|---|
| The clarification of shortage criticality criteria can further help in making changes in shortage notification to cover the most impactful shortages. |
| B.6.2. Increase notification period to 6 months in advance using a common template for reporting withdrawals and shortages including details of root causes, alternatives medicines and impact. |
| This option differentiates between planned (permanent) market withdrawals and temporary supply disruptions, setting different notification timeframes for each. There is more explicit recognition of the fact that not all shortages can be foreseen 6 months in advance. It is uncertain whether this element will result in earlier notification than presently the case, given that most shortage notification are currently made with less than 2 months' notice, citing 'exceptional circumstances'. There is no clear reason why extending the notification period would remedy this situation. Where potential shortages are notified more in advance, these situations often are resolved before they result in an actual shortage. Extending the notification period may thus increase the number of 'false alarms'. There is also a risk that a longer notification period will increase the administrative burden on both MAHs and public authorities without clear benefits.<br>In some countries, parallel distributors also fall under a notification obligation. In consultation, this industry has indicated that a 6-month notification requirement would not be possible to meet since they typically do not hold stocks for more than 2-3 months.<br>Earlier notification of planned withdrawals may be more feasible and provide authorities more time to identify and source alternatives.<br>The obligation to utilise a common reporting template is received positively by the stakeholders. Common data collection approaches, particularly if linked to a standardised reporting portal and automatic sharing of information between MS could, in the longer term, result in cost savings for authorities. Greater standardisation of information may also enable a better understanding of the causes of shortages and allow for the development of better-tailored policy approaches to address the issue of shortages. |
| B.6.3. Shortage prevention and mitigation **plans added to GMP** for **all medicines** |
| Early identification of risks to the security of supply and of possible mitigation steps could reduce the occurrence and impact of supply disruptions. Fewer medicine shortages, as well as faster and more effective mitigation of the impact of shortages when these occur, improves patient access to (critical) medicines and leads to better health outcomes. The health system experiences fewer costs associated with dealing with medicine shortages.<br>Depending on the level of detail required and the degree to which risk mitigation steps (e.g. contractual agreements with backup suppliers) are expected, MAHs may make additional costs not only in drawing up the plans but also in implementing the actions therein specified.<br>Industry representatives have indicated that an important condition for the submission of shortage prevention plans would be that the company retains ownership of the plan, and that information remains confidential, as this could be commercially sensitive. |
| B.6.4. Stockpiling requirements for MAHs and wholesalers for unfinished critical medicines, as appropriate |
| Some further elaboration is needed to determine criteria to establish what constitutes 'as appropriate'. More detailing is also needed about the expected quantity of such stock, what state the product needs to be in (e.g. intermediates or finished but unlabelled/unpacked products), at what level the stock will be held (e.g. EU, national, regional), who has ownership and responsibility for the stock (e.g. MAHs, wholesalers or authorities) and whether stock may be redistributed according to need. All such factors may strongly influence the operational feasibility of this measure and its acceptability to involved stakeholders.<br>Among wholesalers there is a sense that a limited level of additional reserve stockholding (~2-3 weeks) – with reserves dynamically rolled into normal stock – for critical measures may be a cost-effective measure against supply disruptions, holding larger volumes of stock is both unfeasible and unnecessary.<br>It is expected that the costs of increased stock holding will either need to be shared between MAHs and public authorities, or if not, that MAHs will seek to recoup the increased costs by raising prices. For generic manufacturers, whose products are typically under strict price regulations and caps, this may not always be possible. Among generic manufacturers, there is therefore a fear that in the absence of a balanced cost/risk sharing arrangement, companies may be unable to continue operating in markets where these stock obligations apply. |
| B.6.5. Introduce an **EU shortage monitoring system** |
| Improved monitoring of supply and demand of shortages may enable earlier identification of potential supply problems and allow for mitigating actions to be taken before these can impact patients unduly.<br>EU-wide monitoring of shortages would reduce the need for decentralised notification and national (mirror) reporting systems, which should improve the overall consistency / timeliness / quality of information available to stakeholders. This can be expected to result in cost savings for parties under a notification obligation if it is assumed that notification into an EU shortage system negates the need to report to one or more individual national authorities and for those national agencies to maintain their own reporting systems. |

| |
|---|
| Most shortages are limited in geographic scope and are not the result of global supply disruptions but rather inequitable distribution. Improved monitoring at the EU level could allow to improve the balance between supply and demand across the EU and can support the functioning of the internal market by matching excess supply in one location to unmet demand in another.<br><br>Standardisation of the information collected on shortages across the EU would overcome current reporting issues and would significantly aid research into understanding the characteristics of products most at risk and the causes of shortages. This, in turn, will inform better evidence-informed policy making. |
| B.6.6. Require specific **penalties** for breaking supply obligations. |
| If (the threat of) penalties are effective in improving the continuity of supply, this reduces the negative health and economic impacts to patients resulting from medicine shortages.<br><br>If levied, financial penalties for failure to meet supply obligations represent an additional cost to suppliers (MAHs and wholesalers). The height of penalties and the conditions under which these are imposed in practice will determine the economic impact of this. In past, penalties have been imposed only rarely and often are not financially significant for companies. (DG SANTE, 2021)<br><br>To enable more stringent monitoring of suppliers' obligations by authorities, suppliers will be expected to adequately document and communicate the steps they have taken to fulfil their responsibilities. This is likely to increase administrative costs associated with dealing with public authorities. |
| B.6.7 Expanded requirements for key suppliers and back-ups to diversify supply chain for critical medicines |
| B.6.7. aims to force MAHs to diversify their supply chains to prevent shortages and thus improve the availability of medicines and overall patient outcomes.<br><br>Requiring more diverse supply chains most likely will result in increased production costs as MAHs may need to procure goods and services from less economically advantageous suppliers. These costs could be substantial, although no data was collected that would allow this impact to be quantified. There may be additional payments to backup suppliers, to reserve goods and space on production lines, even if not needed.<br><br>These additional costs occurred by the pharmaceutical industry may result in higher medicine prices and greater costs to health systems and patients. If requirements are introduced by individual MS rather than at the EU level, this could discourage MAHs from operating in markets with such requirements and contribute to inequitable access to medicine.<br><br>Importantly, the measure may not be feasible to implement for many medicines, for which globally a limited number of API and raw materials manufacturers exist, meaning that it may not be feasible for MAHs to sufficiently diversify their supply chains. Separate measures would be needed to enable this, e.g. economic incentives for industry to increase the manufacturing of APIs and raw materials. |
| B.6.8. Increase transparency of the supply chain, including:<br>1. active supply sites for all medicines,<br>2. volumes supplied, incl. supply quotas and remaining stocks for critical medicines upon request of NCA's/ EMA,<br>3. parallel traders and wholesalers' transactions for critical medicines upon request of NCAs/ EMA. |
| Improved transparency of the supply chain, at least for public authorities, has the potential of improving the security of supply by better matching supply and demand.<br><br>MAHs and parallel distributors each have a clear commercial interest in keeping (aspects of) information about their transactions confidential and are not generally welcoming of disclosing this to the other. For instance, parallel traders fear that full public disclosure of information about their transactions will render their trade practically impossible by allowing MAHs to throttle their supply to the level where no surplus is created.<br><br>For these parties to agree to share information with public authorities, it will be essential that strong agreements are made about what information is disclosed, for what purposes, how this will be used and who has access to it. Without this, it is unlikely that industry will cooperate. Mandatory disclosure of commercially sensitive information could furthermore distort competition between MAHs.<br><br>It may be assumed that regular sharing of information between supply chain actors and authorities – particularly when not done though an automated system – entails substantial administrative costs on all sides. |

### Summary assessment of the principal costs and benefits by impact type

Table 44 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block F under Policy Option B.

*Table 44 Option B – Summary assessment of Security of Supply elements*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.6.1 | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| B.6.2. | - | - | +/- | - | +/- | +/- | +/- | ++ | +/- |
| B.6.3 | - | + | +/- | +/- | +/- | +/- | - | ++ | +/- |
| B.6.4 | +/- | +/- | +/- | - | +/- | +/- | + | ++ | +/- |
| B.6.5 | +/- | + | +/- | +/- | +/- | + | + | ++ | +/- |
| B.6.6 | --- | -- | - | +/- | -- | +/- | +/- | ++ | +/- |
| B.6.7 | --- | --- | -- | -- | - | +/- | +/- | ++ | -- |
| B.6.8 | +/- | -- | +/- | -- | - | +/- | + | ++ | +/- |
| Overall impact | - | +/- | +/- | - | +/- | +/- | +/- | ++ | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

The following key impacts are envisaged:

- Collectively, the proposed measures are expected to allow for improved decision-making to prevent and mitigate the impact of shortages (B.6.1, B.6.3, B.6.4) and offer public authorities additional tools for protecting the domestic supply of medicines (B.6.2). If successful, this will in turn result in greater continuity of supply for medicines that are needed to offer appropriate healthcare to patients. Health care costs resulting from shortages would also be reduced. With added coordination at EU level and use of an EU-wide monitoring system, the public health benefits will be greater compared to Option A.

### Assessment of any synergies and tensions within the Policy Block

Overall, the elements are synergistic and do not contradict each other.

### *A.4.7. Policy Block G (B.G): Quality and manufacturing*

### Assessment of the key impacts for the policy elements

Table 45 presents our high-level assessment of the likely costs and benefits of each of the proposed policy elements.

*Table 45 Option B – Assessment of the proposed measures for quality and manufacturing*

| Assessment |
|---|
| B.7.1. Improve the oversight of the sites within a supply chain (including distributors and active pharmaceutical ingredients (APIs) manufacturing sites) by modifying provisions on inspections (frequency, content, triggering points) |
| This measure will strengthen end-to-end oversight of the supply chain and could improve GMP/GDP compliance. However, it could impose significant additional burden on businesses and competent authorities if the frequency of inspections is increased and the triggering points are changed such that in effect more inspections take place. This would substantially increase the workload of inspectors, which would need to be met with more resources. |
| B.7.2. Reinforcing Member States GMP and good distribution practices (GDP) inspections capacity by setting up a mandatory joint audit scheme |

| Assessment |
|---|
| This policy element has the potential to increase inspection efficiency through more cooperation and knowledge transfer. This may have a positive effect on manufacturing and distribution practices within the EU and globally, which would ultimately positively impact public health in the long-term. |
| B.7.3. Stronger overall responsibilities of MAH vis a vis suppliers of raw materials and clarification of responsibilities of business operators over the entire supply chain. This would include transfer of information between each actor for each to fulfil their legal obligations with respect to quality, safety, efficacy. |
| Greater burden on MAHs and other business operators with additional responsibilities, complexity of submissions and costs could lead to reduction in international competitiveness and a decrease in companies within the sector, in particular SMEs. This may threaten security of supply of medicines.<br>Depending on the information required to be provided by the manufacturers/suppliers and the mechanism for receiving, analysing and sharing this information with the stakeholders, sufficient safeguards should be introduced to ensure that information sharing does not run counter EU antitrust rules. |
| B.7.4. Adaption of legislation/inclusion of specific provision covering new manufacturing methods (decentralised, continuous manufacturing, etc). to ensure levels of quality and safety equivalent to current methods. |
| Same as A.7.3<br>The proposed measure has the potential to bring several product categories that are currently excluded from the legislation into the fold and provide regulatory certainty to manufacturers. These include magistral formulae (pharmacy-based preparation for an individual patient), radionuclides in sealed sources, hospital-manufactured medicines, and single-batch medicines. In addition, manufacturing methods such as decentralised manufacturing (where manufacturing occurs at different locations) and 3D printing-based methods could be accommodated.<br>Covering new manufacturing methods in the general pharmaceutical legislation has the main advantage of helping to standardise the methods themselves, quality control of the methods and resultant products and associated regulatory pathways at the EU level. Thus, there is a harmonisation benefit. Moreover, accommodating new technologies sends a positive signal to innovators as well as companies and will encourage more innovation and research activity and adoption of the new methods. There will be further knock-on effects on competition, competitiveness, and access to medicine. If greener manufacturing methods are used there will be an impact on environmental sustainability, but the likelihood and extent of that is unclear.<br>With more certainty over the manufacturing methods and the resultant products as well as more medicine developers adopting these methods, we could imagine a very high increase in the number of new therapies in comparison to the baseline. |

## Summary assessment of the principal costs and benefits by impact type

Table 46 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block G under Policy Option B and for each impact type.

*Table 46 Option B – Summary assessment of the proposed measures for quality and manufacturing*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.7.1 | - | - | - | - | - | -/+ | - | +/- | +/- |
| B.7.2 | +/- | +/- | +/- | + | +/- | +/- | + | +/- | +/- |
| B.7.3 | - | - | - | - | +/- | +/- | +/- | +/- | +/- |
| B.7.4 | -/+ | -/+ | -/+ | + | + | + | -/+ | + | -/+ |
| Overall impact | - | - | - | +/- | +/- | + | -/+ | + | -/+ |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Overall, modifying provisions on inspections and expanding oversight to all sites within a supply chain (including distributors and API manufacturers) will create additional transaction,

compliance and administrative costs which might result in smaller players leaving the market and thus loss of choice and competition. Moreover, NCAs will need additional inspection capacity and training to accommodate the changes in the provisions and actors. On the other hand, a mandatory joint audit scheme for member states will allow greater efficiency, cooperation, and knowledge transfer across NCAs.

Adaptation of the legislation or inclusion of specific provisions to accommodate new manufacturing methods will improve international competitiveness, encourage greater research and innovation, and increase choice and competition in the sector. It would also have a direct impact on patients by making more treatments available. The other measures improve oversight of manufacturing but the quality standards are already high so there is unlikely to be greater added benefit to public health.

### Assessment of any synergies and tensions within the Policy Block

Policy elements B.7.1, B.7.2 and B.7.3 have synergies as they aim to improve quality and safety of medicinal products through improved oversight. Stronger supply chain oversight through increased inspections should work well with setting up a mandatory joint audit scheme and should also help to enforce the stronger overall responsibilities of MAHs.

#### *A.4.8. Policy Block H (B.H): Addressing environmental challenges*

### Assessment of the key impacts for the policy elements

Table 47 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

*Table 47 Option B – Assessment of the proposed measures for addressing environmental challenges*

| **Assessment** |
|---|
| C.8.1 Include assessment of the environmental risk of manufacturing into ERA, including main supply chain actors (API, raw materials) |
| This measure represents considerable additional burden for medicine developers and supply chain actors, and public authorities in terms of compliance and administration costs and review costs respectively. On the other hand, it will allow tracking of the environmental risks of manufacturing across the supply chain providing a more comprehensive assessment of the potential environmental impact of a new medicine. For example, if risk associated with active pharmaceutical ingredient discharges from manufacturing sites is included in the ERA, it would increase the relevance of the assessments by including a part of the life cycle of the product responsible for the highest environmental concentrations detected.[93] |
| B.8.2 Strengthen the ERA requirements and conditions of use for medicines, while taking stock of research under the innovative medicines initiative |
| The proposed measure should enable robust assessment of the environmental risks of pharmaceuticals as well as promote prudent use, supporting sustainable consumption and helping to minimise the environmental footprint of medicines. However, this may place slight additional burden on public authorities for reviewing ERA submissions (in case of additional data requirements) and monitoring medicine use (if required) as well as on businesses and other stakeholders responsible for complying with said requirements and conditions. |
| B.8.3 Include the AMR aspects into GMP to address the environmental challenges |
| This measure would help minimise amounts of antibiotics entering the environment via manufacturing and thus prevent emergence of AMR from pharmaceutical manufacturing. Recent evidence indicates the presence of a |

[93] Eeb. (2018). Policy options for regulating pharmaceuticals in the environment.

selection pressure for AMR within environments receiving wastewater from antimicrobial manufacturing, as opposed to environments receiving wastewater from municipal sewage treatment plants (containing antibiotics from human use) that do not receive waste from antimicrobial manufacturing.[94]

There would be the additional costs for businesses to comply with the AMR requirements in GMP and data requirements and for public authorities for enforcement of the requirements. This could present barriers for smaller actors.

The KPI would be amount of an antibiotic in waste and wastewater in µg/l. Suggested annual mean value for an erythromycin environmental quality standard (EQS) is 0.2 µg/l.95

For the current impact assessment, we would assume that compliance with the measure will result in levels below the EQS and thus there is a high likelihood of impact on sustainable production (environmental impact).

### Summary assessment of the principal costs and benefits by impact type

Table 48 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block H under Policy Option B for each impact type.

*Table 48 Option B – Summary assessment of the proposed measures for addressing environmental challenges*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.8.1. | - | - | - | - | - | +/- | - | + | ++ |
| B.8.2. | +/- | +/- | - | - | - | +/- | +/- | + | ++ |
| B.8.3. | - | - | - | - | +/- | +/- | - | + | + |
| Overall impact | - | - | - | - | - | +/- | - | + | ++ |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Policy Option B is unlikely to impact on areas other than sustainability and waste management since it does not mark a major departure from current requirements. The impact on patients and health systems will be neutral owing to the uncertain health impacts of pharmaceutical residues in the environment as well as lack of direct impact of the proposed measures on quality and safety of medicines.

### Assessment of any synergies and tensions within the Policy Block

No synergies or tensions.

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[94] WHO Expert Committee. (2020). *Annex 6 Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance*.

[95] UBA – Umweltbundesamt (Hrsg.) (2018) Empfehlungen zur Reduzierung von Mikroverunreinigungen in den Gewssern, Hintergrund, February 2018, Dessau-Ro lau, https://www.umweltbundesamt.de/sites/default/files/medien/1410/publikationen/uba_pos_mikroverunreinigung_final_bf.pdf

### *A.4.9. Policy Block I (B.I): COVID-19 lessons learnt*

#### Assessment of the key impacts for the policy elements

Table 49 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

*Table 49 Option B – Assessment of the proposed policy elements for COVID-19 lessons learnt*

| **Assessment** |
|---|
| B.9.1. Refusal of immature marketing authorisation applications. |
| The most significant efficiency gains would be for public authorities, which could save time currently spent on assessing immature applications and resolving internal differences of opinion as regards their evaluability or suitability for processing through the CMA pathway. As per baseline, we assume that there could be **2 to 3** marketing authorisation applications every year that do not initially request a CMA despite not containing enough data for standard marketing authorisation. This would likely lead to 2 to 3 immature marketing authorisation applications refused every year in the first one or two years, possibly increasing to 5 to 10 refused applications every year in the next 3-5 years as the evidentiary threshold is established. Industry would begin to recalibrate the acceptable levels of evidence in parallel and the numbers of weak applications should fall back to some minimum within 5 years, perhaps never quite falling below 2-3 a year over the remaining years through to 2035.<br>Overall, assuming an average annual reduction of 3-5% in the total number of applications for assessment and 100-120 applications annually, which are increasing at 5-10% a year (as per EMA annual report 2020), cutting assessments by 3-5% might result in a reduction of EMA / NCA costs of 2-3% (the work of the EMA committees is a major cost driver).<br>There could be a negative impact on cost for developers that are currently submitting immature marketing authorisation applications for valid reasons. For example, addressing an UMN may be difficult in terms of conducting large clinical trials. This may discourage developers of medicinal products for UMN if it is not combined with other policy elements. On the other hand, less immature data means HTA bodies and P&R authorities would be more able to assess therapeutic value, which could have a positive impact on access and affordability. Thus, the impact on healthcare systems could be negative (less developers working on UMN) and positive (more streamlined and coherent procedure leading to faster market launch). |
| B.9.2 Codification of rolling review for UMN |
| The most significant benefit would be to developers of medicinal products for UMN. The increased interactions with regulators could reduce uncertainty, the timeline for EMA scientific opinion (baseline = 150 days) and the total approval time (baseline = 251 days).<br>The impact will depend on the implementation of the system and the specific timeframes proposed by the EMA to respond to each rolling review cycle. As per baseline (COVID-19 pandemic), the average number of rolling review cycles was 2 cycles[96], and the number of days spent by the EMA on each rolling review cycle was 30 days[97].<br>Other factors will also be important, such as the details of the definition of UMN that will be applicable to the rolling review system and the specific requirements for each data package. As such, there would be significant cost to public authorities, even with our assumption that resources would be made available, new ways of working would have to be implemented and adapted over the years.<br>It is expected that such system would streamline the process of evaluating evidence for medicinal products for UMN and therefore increase the number of medicinal products approved by speeding up the process and by attracting new investments areas of UMN. This could also result in a positive impact on innovation rates and overall EU pharma industry output.<br>While patients and healthcare systems would benefit from more medicinal products available, there could be a negative impact on access due to more post-marketing authorisation requirements to allow P&R authorities to assess therapeutic value. Therefore, there is a risk that this policy element would increase the gap/time between availability (centrally approved) and accessibility (Member State market launch), which could affect poorer/smaller Member States disproportionately. |

[96] https://doi.org/10.1016/j.clinthera.2022.01.001

[97] https://doi.org/10.1016/j.clinthera.2022.01.001

### Summary assessment of the principal costs and benefits by impact type

Table 50 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block I under Policy Option B for each impact type.

*Table 50 Option B – Summary assessment of the proposed policy elements for COVID-19 lessons learnt*

| Policy elements | COB | Admin | SMEs | CTI | Internal Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| B.9.1. | - | +/- | - | - | +/- | +/- | + | +/- | +/- |
| B.9.2 | + | + | + | ++ | +/- | + | - | +/- | +/- |
| Overall impact | +/- | + | +/- | + | +/- | + | +/- | +/- | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element. Policy Option C – Summary assessment of the Incentives for innovation

### Assessment of any synergies and tensions within the Policy Block

Within the COVID-19 lessons learned Policy Block, the policy elements proposed under Policy Option B are largely complementary to each other. Refusing immature marketing authorisation applications while codifying rolling reviews for UMN provides a clear pathway for developers to submit their immature data sets. In comparison to the current system, where immature data create challenges for regulators (often leading to ambiguous decisions and/or nudging developers towards CMA), this policy block B should decrease uncertainty, and facilitate developer/regulator interaction.

## A.5. Policy Option C

### *A.5.1. Policy Block A (C.A): support for innovation, including unmet medical needs*

### Assessment of the proposed Incentives for Innovation

*Table 51 Option C – Assessment of the proposed Incentives for Innovation*

| Assessment |
|---|
| Expedited regulatory pathways |
| C.1.1. Codification of PRIME in the legislation |
| same as B.1.1<br>The inclusion of the PRIME scheme within the legislation would give a strong signal to developers that the EU is committed to increasing support for UMNs.<br>It will also reassure developers that the scheme is permanent and that they continue to benefit from the active support that comes with PRIME designation (which is focused on medicines that promise a major therapeutic advantage in an area of unmet medical need). The scheme is well regarded by stakeholders (industry, regulators, health systems) and the EMA analysis of its first five years of operation found that PRIME designation is associated with faster assessment times and an improved likelihood of a positive recommendation for authorisation.<br>There should be no significant additional administrative or compliance costs for businesses, when compared with the current situation.<br>Codification may increase the popularity of the scheme still further, and that may increase the number of companies that have to bear the administrative costs associated with making an unsuccessful PRIME-eligibility request. The popularity of the scheme has increased in the recent past (+15% between 2019 and 2020), and we would expect to see further growth in future. This would be even more likely should the EU implement an additional period of regulatory protection for UMNs. These additional costs (linked with unsuccessful requests) are |

| Assessment |
| --- |
| being limited by an equivalent expansion in the number of medicines accepted onto the scheme, which has also increased (from 23% in 2018 to 33% in 2020).<br>The impact on regulators should be broadly neutral, as while the scheme does involve additional effort to businesses with advice on the development of their PRIME-designated medicines, the resulting applications tend to be better framed and evidenced, making assessment more efficient and improving success rates for submissions (improving EMA productivity in this important area of UMNs).<br>Small biopharma firms have a particular interest in advanced therapies relevant to UMNs, and the codification and expansion of PRIME ought to have positive impact of SMEs. They benefit disproportionately from EMA advice, where larger developers have considerably more experience in preparing an application for assessment. Moreover, for some start-ups (e.g. cell and gene therapy companies), PRIME may have the effect of a 'seal-of-approval,' which could improve their investability and market value.<br>In the longer term, codification should reinforce the regulator's wider efforts to reduce UMNs, improving treatments, reducing hospitalisations and improving patients' quality of life.<br>As with the other regulatory proposals designed to focus developers' attention on UMNs, there is a small risk this will displace investment in other areas of medical research, possibly even slowing down the rate of progress in other disease areas that have good treatment options currently, but which still constitute a major health burden. |
| *Repurposing* |
| C.1.2. Establish a binding system for scientific assessment of evidence for repurposing off-patent medicines (scientific opinions or monographs) that are used by marketing authorisation holders to include a new indication for their products. Plus simplify the obligations regarding certain activities associated with holding a market authorisation in order to facilitate non-commercial entities (e.g. academic) to become marketing authorisation holders. This could be combined with possibility for private, public partnerships for manufacturing and safety monitoring (e.g. for **repurposing** of authorised medicines or hospital preparations). |
| Same as B.1.2.<br>The policy might lead to developers investing more heavily in new indications of their recently approved medicines, with the additional costs of seeking better, earlier scientific advice being offset by a greater likelihood of seeing a new use authorised<br>There may be a reduction in administrative and compliance costs associated with repurposing, as compared with the authorisation of new medicines<br>May provide opportunities for developers to cost-effectively expand their portfolio of medicines / indications (improving R&D productivity); may provide a platform for clinical researcher and academics to play a fuller role in development work and trials<br>MAHs can be reluctant to apply for new indications of existing older medicines close to the end of their period of regulatory protection or where going on-label for new indications could affect the commercial value of any existing medicines used for the same indications[98] or otherwise for liability reasons.<br>This policy element will help broaden access to what are otherwise rather selective and uneven use of safe and effective medicines off-label. It will be a much stronger intervention than the non-binding system. In the longer term, we may see more treatment options for patients and improved geographical access. Its impact would be strengthened by C.1.3 (a period of additional data protection for major public health interest) and C.1.4 |
| C.1.3. Additional data protection period for the new evidence generated to support repurposing of existing products if considered as major public interest for public health or innovation (i.e. criteria for accelerated assessment). |
| Industry may benefit from the (lower cost) of repurposing an existing medicine for use with an UMN, where that insight has arisen based in part on evidence gathered by healthcare providers or academics.<br>While repurposing costs are substantially lower than the costs for wholly new development programmes, the costs can run into the many tens of millions and take several years, and the ROI is often too weak for many older medicines. An additional period of data protection (+1 year becomes +2 years) could help offset that ROI challenge, at least for that subset of extensions where there is a major public health interest associated with an extension of an existing medicine.<br>May increase the workload for regulators (more assessments, more enforcements).<br>May increase the size of the medicines bill for health systems; may reduce the high costs associated with hospitalisations of people with complex conditions and no effective treatment. |
| *Adaptation of the regulatory protection* |

[98] https://www.fiercepharma.com/sales-and-marketing/sanofi-pulls-campath-to-clear-way-for-higher-priced-lemtrada

**Assessment**

**C.1.4. Reduce duration of incentives for originators from 8+2 to a new combination (e.g. 6+2) taking into account the interaction between data protection and intellectual property rights**

same as B.1.4

For originators, a reduction in the period of regulatory protection will reduce overall income and profitability for new medicines since generics companies will be able to enter markets and begin to erode monopoly prices a year earlier. The new period of protection may prompt developers to increase prices in general to protect their current business model or otherwise rebalance their portfolios towards those market segments with greater commercial potential.

SMEs originators may find it more difficult to invest in riskier novel medicines given the reduction in future returns on investment and their relatively weaker market position when it comes to negotiating prices.

It could weaken the global competitiveness of EU based originators overall, compared with the current situation, unless prices are adjusted upwards to reflect the new protection period, and ensure global ROI norms can continue to be achieved.

The threat to EU-based originators will be offset to some degree by giving a boost to Europe's generic industries, broadening their portfolios, and potentially creating a prime-mover advantage in global markets.

Considering that this policy element affect SMEs more than larger firms and the latter are based in bigger economies, while the former may be based in smaller economies this may affect the functioning of the internal market and limit access to medicines across Europe. This will also be the case if some companies adjust prices upwards in response.

Health payers may benefit from lower average lifetime costs for medicines due to earlier generic entry and patients may benefit if those savings are used in the health care sector. The extent of these benefits will depend on originators response to the reduced incentives, and it is highly likely that average prices will be adjusted upwards in some degree to offset the shortened period of protection.

**C.1.5. Authorised medicines with demonstrated ability to address UMN get +1 year data protection**

A +1 year period of premium pricing (during the extra year of data protection) will offset the higher development costs and / or lower market volumes associated with a proportion of UMNs, whereby a larger number of all UMNs would pass the private sector's ROI thresholds.

While companies cannot determine in advance which products will be successful and make a smaller or larger positive contribution to their overall income and profitability, the additional period of regulatory protection will have a positive impact on estimates of potential income and profitability used in stage-gate assessments. It will also mean payers will have larger costs for the medicine for an additional year.

The additional period of protection would improve the competitiveness and investment flows towards EU based originators producing UMN medicines.

Increasing developers focus on UMNs may increase their development and regulatory costs, in some limited degree, as applicants would need to meet the UMN criteria.

This incentive is expected to focus and possibly increase investments in R&D resulting in a higher number of novel medicines addressing UMNs as compared with the baseline and an increase in treatment options, treatments and improved patient health.

The increased flow of medicines for UMNs would have a strongly positive benefit for patients that currently have to live with debilitating conditions with no effective treatment options. The health systems should also benefit from the availability of more effective medicines for these patient groups, making care more cost-effective and reducing costs associated with avoidable hospitalisations.

We assume this extension would increase by around 10% the numbers of UMN products being developed, which would amount to 2-4 new authorisations annually. Our modelling work suggests this would generate #320m-€640m in additional protected sales annually, based on the €160m annual EU revenue for the average product. The increasing number of UMNs – with a longer period of RDP – would lead to additional costs for health payers on the order of €163m-€326m, based on the difference between the premium priced product (in the final year of RDP) and the price of the first generics to enter the market (c. 50%). We estimate that the generics industry would see a loss of income on the order of €77m-€154m as a result of the +12-month delay in market entry.

**C.1.6. Special incentive bonus: if data package includes comparative trial with standard of care (+6 months)**

Same as A.1.4

We assume a 6-month extension might lead to the use of comparative trials for an additional 8-10 products a year. We assume the additional costs of a comparative trial design might amount to €10m.

With average additional peak income (EU) of €160m, a 6-month extension might secure an additional €80m in income, or €640m-€800m a year in additional protected sales for originators.

The bonus would result in a delay in the market entry for generics for these additional products, which might amount to a loss of income of around €154m-€192m a year for the generics industry

**Assessment**

There would be some additional costs for health payers, which result from the delay in the market entry of generic competition. This may amount to €326m-€408m a year.

This should deliver faster access to markets and costs savings thanks to improved reimbursement decisions

Moore et al (2020) in a review of 101 new FDA medicines (225 individual clinical trials), found the median cost of an individual clinical trial was around $19m (range = $12m-$33m). They found the Phase 3 development costs almost doubled with second trial (albeit the single biggest cost driver is the number of patients).

Moore et al identified 62 (27.5%) of the total set of 225 clinical trials had a comparison group rather than a placebo or uncontrolled trial.

C.1.7 Require transparency on public contribution to research and development costs in relation to clinical trials included in the marketing authorisation application (this information would be published)

This proposal for increased transparency around public support for R&D in clinical trials, is narrower than the proposal under Policy Option B, where the issue of transparency covers any aspects of public support for medicines development, including various tax reliefs.

This option would be simpler to implement as it relates to the direct support of specific clinical trials through publicly funded R&D grants. This information is more likely to be in the public domain already (through online, public grants databases) and does not require a complex financial exercise to link / attribute the public support to a specific trial and resultant application for a new medicine. It is therefore likely to meet with slightly less resistance from industry on the grounds of commercial confidentiality.

Greater transparency around public support for R&D may strengthen pricing and reimbursement agencies' position when negotiating with MA holders, helping to place a downward pressure on prices and thereby helping to maintain or improve access to medicines with concomitant benefits to patient health.

Administrative costs may increase for firms needing to prepare the required information.

Understanding the scale of public contributions to clinical trials research would need to be established over time, from the evidence submitted by applicants. We found no good data on this in the wider literature.

The analysis of public support would be reported by applicants in a section of the Common Technical Dossier. This would affect 4,000 clinical trials authorised each year in the EEA. This equals approximately 8,000 clinical-trial applications, with each trial involving two Member States on average.

The statistics show that around 60% of clinical trials are coordinated (sponsored) by industry and around 40% by non-commercial organisations, mainly academia. However, these trials do not necessarily relate to new medicinal products that will be submitted to the EMA and where an academic trial does feed into an industry application it is possible that trial would have been partly funded by industry or a research charity with little or no support from public R&D funders.

C.1.8 Give regulators the possibility, in the context of a marketing authorisation, including a conditional marketing authorisation, to impose a **post authorisation obligation** for **additional studies** on the effectiveness compared to the standard of care

same as B.1.8

Imposing a post-authorisation obligation for MAHs to include new information about the effectiveness of the medicines (i.e comparative clinical trials) may impose additional costs on MA holders, albeit this may be a matter of timing and degree, as many businesses carry out additional research on the cost-effectiveness of their medicines with a conditional approval. The EMA annual reports show that around one third of all medicines that have been granted a CMA since 2006 have gone on to be granted a full marketing authorisation (i.e. sufficient additional evidence has been gathered to confirm effectiveness). As such, it may increase and bring forward costs associated with such studies for tens of businesses. Those costs might amount to €20-€50m for each product.

MA holders will have to bear some additional costs and there may be a small increase in the number of medicines that are found to be less cost-effective than had been anticipated. This last point could impact on the ability of individual companies to raise finance or otherwise weaken their competitive position, but there would be no substantive impact – positive or negative – on overall competitiveness, or the functioning of the internal market.

This obligation would help to confirm the relative effectiveness of the products in question several years earlier than is the case currently. The EMA annual report (2020) shows that the 30% of CMAs that have been granted full marketing authorisation took an average of 3.5 years post-authorisation to get their products fully authorised. This would allow more timely action in respect to individual medicinal products – e.g. withdrawal or more widespread use – and would indirectly give HTAs and payers greater confidence in the CMA pathway.

There would be some additional administrative costs for the EMA and NCA staff working with them following from the increasing numbers of assessments of these additional studies and consideration of the case for granting full authorisation.

The improved clarity as regards the relative cost-effectiveness of medicines should increase confidence across health systems in making full use of those products, and thereby benefiting patient health.

C.1.9. **Breaking market protection** in case of urgency and insufficient coverage by authorised medicines (compulsory licensing)

| Assessment |
|---|
| same as B.1.6<br>There has only been one instance of an EU member state using a Compulsory Licence, as such this is an ultra-low probability event, and the link with the EU general pharmaceutical regulation is about ensuring external coherence.<br>There should be no or minimal direct impact on EU pharma in general, given it would be implemented indirectly and by exception and for a localised and time limited period.<br>It may increase burden on regulators and expand the numbers of government bodies that must become involved in explaining their use of this regulatory exception<br>The time and costs involved in developing safe and effective copies of protected medicines may mean that the policy lacks the speed or certainty to respond with confidence to public health crises |

### Summary assessment of the Incentives for innovation

Policy Option C reduces the current standard period of regulatory protection for new medicines and requires originators to disclose information in their applications regarding the level of public funding of their clinical trials. There is a special bonus available where the data package includes a clinical trial.

Policy Option C does not include any special incentives relating to UMNs, beyond the codification of PRIME in the legislation, which has some relevance to originators working on new medicines targeting UMNs and hoping to benefit from the additional advice that follows from PRIME designation.

MAHs are given increased obligations regarding the conduct of additional studies relating to for example, CMAs.

Policy Option C gives relatively more weight to repurposing, and the overarching objectives of improved access and affordability. It seeks to deliver a significant expansion in the number of extensions of existing medicines to new indications by targeting the under-exploited off-patent and off-label use of older medicines, through a combination of a more inclusive definition of scientific evidence for repurposing, with the simplified obligations for non-commercial entities to become MA holders (possibly through public private partnership) and the obligation on MA holders to include a new indication when supported by that scientific evidence and assessment.

There is an additional period of data protection available for these repurposed medicines, where the extension is judged to be a major public interest for reasons of public health or innovation.

*Table 52 Option C – Summary assessment of the Incentives for innovation*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.1.1 | + | +/- | + | +/- | +/- | + | - | - | +/- |
| C.1.2 | + | + | +/- | - | ++ | ++ | +/- | + | +/- |
| C.1.3 | + | - | + | + | ++ | +/- | +/- | + | +/- |
| C.1.4 | -- | +/- | -- | -- | - | --- | + | - | +/- |
| C.1.5 | ++ | +/- | - | + | +/- | + | - | + | +/- |
| C.1.6 | + | - | + | +/- | +/- | + | + | + | +/- |
| C.1.7 | - | - | - | +/- | +/- | +/- | + | +/- | +/- |
| C.1.8 | +/- | - | - | +/- | +/- | + | - | + | +/- |
| C.1.9 | - | - | - | - | - | - | - | +/- | +/- |

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| Overall impact | ++ | -- | - | - | ++ | ++ | +/- | ++ | +/- |

### Assessment of any synergies and tensions

Within the Innovation Policy Block, the policy elements proposed under Policy Option C are largely complementary to each other, whereby the proposal to reduce the period of regulatory protection for the standard innovative medicines pathway (by 1 year) is mirrored by a policy element to provide a +6 month special bonus for data packs that include comparative trials. The proposed new obligations around the transparency of public funding of clinical trials research may serve to reduce industry's interests in public R&D grants.

Relatively greater weight is given to repurposing under Policy Option C, with a general reduction in the level of support for innovation, at least through the standard EMA regulatory pathways. The ability to impose a requirement on MA holders to carry out additional studies post-authorisation would not reduce the attractiveness of the EMA's various expedited regulatory pathways, but should rebuild support among member states (HTAs, health payers) for conditional marketing authorisations in particular.

## *A.5.2. Policy Block B (C.B): Antimicrobial resistance*

### Assessment of the proposed incentives for innovation and prudent use

Policy Option C is similar to Policy Option B, regarding the proposed measures to encourage more prudent use of antimicrobials. It would reinforce these stewardship measures with the addition of a new requirement for MA holders, whereby developers must prepare an AMR lifecycle plan as part of their marketing authorisation application.

Policy Option C omits the play or pay model in favour of a stronger incentive, a transferrable voucher, similar to that in Policy Option A.

The proposed interventions are assessed in the table below:

*Table 53 Option C – Assessment of the proposed incentives for Innovation and prudent use of antimicrobials*

| Assessment |
|---|
| C.2.1 Novel antimicrobials (new active substance, new mechanism of action, first in class) fall in the central procedure's mandatory scope |
| As this policy element formalises what happens in practice already, there would be no additional impact on the development of novel antimicrobials or their more prudent use. |
| C.2.2. PRIME like support scheme, including rolling review |
| Same as B.2.2<br>If the system in place for rolling reviews is easy for SMEs and large companies to navigate and flexible, there is potential for a large positive effect on EU pharma businesses by increasing company-regulator interactions in areas that may not be currently attractive for business to invest in R&D. This could result in a positive impact on innovation rates and overall EU pharma industry output.<br>The targeted survey revealed that industry respondents were broadly in favour of codifying rolling reviews, in particular for new technologies or major innovations in medicinal products. However, the demands on Rapporteurs are high, with significant increase in workload; one NCA interviewed stated that the COVID-19 pandemic rolling review required approximately 50% increase in resources/workload. The demands on companies are also relevant, as the process requires more communication and clarifications (data packages may not be structured, may contain errors, etc). Furthermore, rolling reviews bring uncertainty on the added therapeutic value of medicines and inequity of access is larger for orphan medicines. Considering these reasons, some civil society and public authority respondents were against codifying rolling reviews in a way that would |

| Assessment |
| --- |
| expand the scope of use of this procedure outside exceptional medical conditions and public health emergencies. |
| C.2.3 Require companies to develop AMR lifecycle management plan as part of marketing authorisation to set out coherent strategy for prudent use, stewardship monitoring and reporting (including consideration of optimised package size and rules on disposal) to address the environmental challenges as well). |
| The AMR Product life-cycle management (or PLCM) document would provide an opportunity for continuous development and improvement, a framework for change management to facilitate assimilation of novel control strategies, analytical procedures, and process tools as they become available to the industry.[99] It may involve reassigning some resources from other areas within companies to develop the AMR PLCM document required for antimicrobials.<br>Expanded surveillance would have no direct impact on EU pharmaceutical companies conduct of business. Indirectly, and in the longer term, improved surveillance data may help to accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for industry overall. The legislation and accompanying guidelines would have no direct impact on EU pharmaceutical manufacturers, wholesalers or pharmacies, indirectly it may lead to an expansion in overall sales volumes and income, as pharmacies buy smaller volumes more frequently, prescribers push for smaller pack sizes, and patients a less likely to self-medicate.<br>Even though preparing the AMR PLCM document may take some time, establishing appropriate mechanisms to share information with regulators and possessing records from inspection or assessment activities can mitigate increased burden on the MAH later on. Any implications for enhanced environmental risk assessments could be more challenging for SMEs to carry out / afford.<br>The AMR PLCM document as any PLCM document could provide an opportunity for continuous development and improvement and assimilation of novel control strategies, analytical procedures, and process tools as they become available to the industry.[99]<br>An expanded surveillance system could impact the costs borne by public authorities, both one-off costs associated with system development, capital investment and training and recurrent costs associated with additional data collection and additional data curation and storage costs.<br>Stricter disposal rules would bring additional costs for public authorities, with a substantial one-off cost for EU / MS authorities in developing and championing the roll-out / adoption of the guidelines and additional ongoing costs for national authorities in maintaining / monitoring adherence and for the EMA and its advisory groups in tracking developments and giving ad hoc advice.<br>Stricter disposal rules / smaller pack sizes may increase the unit costs of antimicrobials and stricter management of stocks may also add costs.<br>Patients should see a benefit from a reduction in self-medication using unused and out of date medicines.<br>The AMR PLCM document would cover the whole lifecycle of antimicrobials and help address AMR in the human and animal health and plant protection sectors.<br>More prudent use and more informed production and disposal of medicines would help reduce the level of human-related active ingredients getting into the environment. |
| **C.2.4. Optimise package size** |
| Same as B.2.3.<br>This policy element would encourage the use of smaller package sizes, thereby increasing manufacturers' costs relating to product packaging and distribution.<br>It may also increase the cost of antimicrobials for health payers (smaller package sizes are more costly), including an increase in average prices for a course of treatment for an individual patient, albeit these price increases should be offset in some small degree by lower levels of consumption.<br>It may have implications for storage costs (more space required) but may ease dispensing and take pressure off pharmacists' local storage requirements.<br>We don't foresee additional extra administrative costs on the side of businesses and authorities.<br>By helping to reduce overall levels of consumption, this policy element may contribute in some small degree to reducing AMR and avoiding AM releases to the environment. The smaller pack sizes will increase packaging waste, which would increase costs associated with waste management and recycling. |
| **C.2.5. Tighten prescription requirements for antimicrobials** |
| Same as B.2.5 |

[99] Schiel and Turner. The NISTmAb Reference Material 8671 lifecycle management and quality plan. Anal Bioanal Chem. 2018.

**Assessment**

While prescribing policies are a matter for national authorities in the first instance, the legislation can invite member states to do more to bring practice in line with international standards.

These obligations and guidelines do not affect industry directly. Indirectly, and if successful, better prescribing would accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for the pharmaceutical industry overall and particularly those generics companies that supply older, lower-cost, broad-spectrum antimicrobials.

Indirectly, there may be a differential impact on the generics industry and particularly that sub-set of pharma businesses that include older, broad-spectrum antimicrobials in their portfolio. There may be a small benefit for MA holders with more specific antimicrobials, if prescribers both reduce overall prescription numbers and switch from cheap, broad-spectrum medicines to more specific (more expensive) antimicrobials.

Indirectly, tighter prescription is likely to reduce usage and that may weaken the return on investment for antimicrobials in general, worsening the investment case in an area of medicines research that is already regarded as being uneconomic.

Indirectly, health systems may see savings because of better prescription practices and reduced consumption, albeit this may be offset by increased costs associated with diagnostic tests and a switch to more costly antimicrobials. If successful, this policy element should reduce consumption and that in turn should reduce the potential for negative environmental impacts.

**C.2.6. Transferable voucher – independent and in addition to data/market protection for antimicrobial products.**

Similar to A.2.2

The right to be transferred relates to the transfer of the right to extend the data protection by a length to be determined. The assumption/calculation is based on an extension of data protection by 1 year.

The antimicrobials that would be applicable to generate this right are all antimicrobials or a subgroup e.g. antibiotics only or their alternatives which either (i) represent a new class and/or new mode of action, addressing new target or absence of known cross-resistance (WHO innovation criteria) or candidates targeting priority pathogens (WHO list for antibiotics) or innovative platform technologies able to confer break-through clinical benefit, (ii) ground-breaking innovation within an existing class.

Given the current pipeline, and the scale of the incentives foreseen, we assume the average number of TVs will be one a year (albeit U JAMRAI predicts fewer).

Companies may use a TV on existing successful medicines that are still covered by data protection, and which are still at least 2 years (EFPIA proposal) away from the expiry of their data protection period. ,

The TV would be most relevant to products where the last defence before generic entry is the regulatory protection. For those where there is a 10+ years patent or SPC protection, the extended data protection does not give any benefit. Hence, only a part of all products could benefit from a TV.

In principle the extension would need to be sufficient to provide a substantial incentive to compensate for the development of a new antibiotic, which is estimated to be on the order of €1.2bn. However, the EU market is some 20% of the total pharmaceutical market globally, and so a proportionate contribution to the development cost with the EU voucher may be a sufficient incentive. It would be possible for companies to receive the right to a TV for antimicrobial products that were already in the pipeline ahead of the implementation of the new regulation, to generate additional income / profits within 2-3 years of implementation, and thereby underpin an early expansion in investments in novel antimicrobials.

Based on the application of a voucher to an average top-10 product, we estimate an originator would secure an additional €543m in non-contested sales because of the 1-year extension.

There would be a cost to the generics industry of a year's delay on the order of €164m.

There would a cost to the health system too, which we estimate at €283m. We further estimate the patient + payer monetised loss would be on the order of €441m

Some vouchers may be sold rather than used directly by the developer of the antimicrobial and we have estimated the average sale value of a voucher at €360m.

Each year, about 33,000 Europeans die as a consequence of antibiotic-resistant bacteria. On average, a hospitalised patient with antibiotic-resistant infections costs an additional 10,000 to 40,000 USD. The expansion in the development and authorisation of novel anti-microbials should help to manage and even reduce AMR, with fewer hospitalisations and deaths, although it has so far not been possible to estimate the scale of these potential benefits, in order to compare with the social costs of the incentives for taxpayers and health payers.

C.2.7. Consider adapted system for authorisation of phages therapies and other alternative products

Same as A.2.3.

This policy element would support the development of phage therapies potentially increasing the number of companies willing to invest and develop these therapies which will in turn increase competition, reducing prices of these therapies. The use of phage therapies may also reduce healthcare costs/budgets since phages are an inexpensive natural resource present in the environment, and offer immense potential as an alternative when

| Assessment |
|---|
| antibiotics are rendered ineffective due to bacterial resistance . Finally, by reducing the use of antibiotics it would help reduce the presence of antibiotics in the environment. |

### Summary assessment of prudent use of antimicrobials policy

Option C would be expected to catalyse an improvement in prescribing practices and stewardship by combining the stewardship measures set out here and under Policy Option B with the addition of an AMR lifecycle action plan.

Option C would provide substantive direct support for innovation, through the introduction of a transferable voucher, which would reinforce the investments of global MNCs active in the development of novel antimicrobials. The adaptation of the system for the authorisation of phage therapies may catalyse increased investment in this emerging and innovative technology.

*Table 54 Option C – Summary assessment of the proposed incentives for prudent use of antimicrobials*

| Policy elements | COB | Admin | SMEs | CTI | Internal Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.2.1 | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- | +/- |
| C.2.2. | + | - | + | +/- | +/- | + | - | + | +/- |
| C.2.3 | +/- | - | +/- | +/- | +/- | +/- | - | + | + |
| C.2.4 | - | +/- | +/- | +/- | +/- | +/- | - | + | + |
| C.2.5. | +/- | +/- | +/- | +/- | +/- | +/- | - | + | + |
| C.2.6. | +++ | -/+ | +++ | ++ | -/+ | +++ | --- | + | +/- |
| C.2.7 | + | +/- | +/- | + | + | + | - | + | + |
| Overall impact | +++ | - | +++ | ++ | +/- | +++ | --- | ++ | + |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

### *Assessment of synergies and tensions within the Policy Block*

Within the AMR Policy Block, the policy elements proposed under Policy Option C are largely complementary to each other, with the mandating of the use of the Central Procedure dovetailing with the proposal for EMA create a PRIME-like scheme for AM products. The Transferrable Voucher would reward antimicrobial innovators with an additional period of regulatory protection for their other medicines.

The adaptation of the system for the authorisation of phage therapies is a further complementary initiative that recognises the potential for this emerging and innovative technology to make a substantial contribution to combatting AMR. Moreover, the proposals on prescribing practices, package size, and disposal all work well together in supporting more prudent use. The expansion in the scope of the existing surveillance system would also provide an important means by which to track progress in environmental management across the EU. Lastly, the AMR PLCM would provide a framework for the optimal use and good stewardship of individual medicines.

### *A.5.3. Policy Block C (C.C): Future proofing*

Option C is a refinement of the current arrangements, with seven principal interventions that are discussed in the table below.

*Table 55 Option C – Assessment of the proposed measures for Future Proofing*

| |
|---|
| C.3.1. Adapted regulatory framework framework (*e.g. adapted requirements, authorisation procedures, collection of post-authorisation monitoring data*) for certain categories of novel products/technologies (e.g. personalised medicine, medicines combined with self-learning artificial intelligence, medicines that contain or consist of GMOs, platform technologies) or low volume products (hospital preparations) on the basis of well-defined conditions and respecting the principles of quality/safety/efficacy. Such frameworks could be adapted or expanded through delegated acts to set the technical framework that can be adapted to emerging scientific and technical advances (adaptive framework). Where applicable, such delegated acts should be developed in close coordination with other relevant competent authorities such as e.g. medical devices, IVDs or substances of human origin. |
| C.3.1 has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. It would also address the issues of current technological advancements that are not adequately legislated for and provide the legislation with a mechanism of keeping pace with technology through both facilitating adaptation and drawing on the expertise of deeply engaged stakeholders with in-depth technical knowledge of emergent areas. However, there would be an associated increase in administrative burden due to a likely expansion of the number of specific non-legislative (soft law) tools that would require development, maintenance, review etc. and ongoing need for feedback loops, iteration and adopting delegated acts. EMA and the regulators need to stay in control and ensure that the soft law tools are meeting the overall objectives of the legislation since the incentives and alignment of all stakeholders (some of whom have valuable technical expertise that this framework is designed to harness) is not implicit |
| C.3.2 Clinical trials: a risk-based approach is applied to determine when a specific GMO assessment is required. Where required, the assessment of the GMO aspects of investigational medicinal products is performed by EMA, within the maximum timelines defined in the Clinical Trial Regulation (centralised assessment). |
| This is the same as A.3.2<br>Clinical trials for investigational medicinal products (IMPs) for human use that contain or consist of GMOs are subject to both clinical trials and GMO legislations under national competences. This causes delays in clinical trials as the directives are not uniformly interpreted or applied between MSs and is especially problematic for clinical trials that are conducted over multiple MSs. These differences in interpretations also impact on the authorisation of GMO-containing medicinal products that fall under the mandatory scope of the centralised procedure creating complexities for developers as different MSs have different requirements and stakeholders involved, ultimately causing regulatory burdens and delays in market authorisations.<br>A.3.2 has potential to improve the efficiency of GMO assessment and thus accelerate authorisation of GMO-containing medicinal products by focussing regulatory efforts on GMO containing medicines that pose the greatest threat to the environment. A centralised approach to GMO assessment has already been adopted by the United States where the review of medicinal products containing GMOs has been centralised within the FDA to improve efficiency and regulatory agility. |
| C.3.3 Adapt certain definitions, including that of medicinal product and *delink scope from industrial process* to address technological developments, gaps/borderline questions, taking into consideration the views of regulatory authorities for other relevant legal frameworks (e.g. medical devices and blood, tissue and cells) - linked to scope of the legislation. |
| C.3.3 has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. Delinking scope from industrial process would immediately bring under regulation several potentially excluded products and processes – most notably novel manufacturing such as bedside such as pharmacoprinting. It would be important that upon their being brought in scope the GMP was able to adequately accommodate them or that sufficient alternative tailored guidance was available. Addressing gaps in the legislation would impact positively on patient safety though could cause a (likely short term) reduction or delay in access while adaptations for compliance to greater regulation were made. There would be additional regulatory burden to implement the extended scope of the legislation. However, long term the efficiencies and predictability are anticipated to increase investment and innovation, reduce the time to access and improve patient safety. |
| C.3.4. For specific cell-based (ATMP) medicinal products adapted regulatory requirements under the pharmaceutical legislation to facilitate production in the hospital setting (improved "hospital exemption" mechanism) and respecting the principles of quality/safety/efficacy. [*link with revision of BTC legislation*] |

ATMPs prepared "on a non-routine basis" for individual patients can by granted a hospital exemption by individual member states and can then be produced in the hospitals, exempt from the legislation scope which would require market authorisation and following GMP. This reflects a large proportion of ATMP development being undertaken by non-commercial entities (hospitals, research institutions, academia etc) for small patient numbers and was anticipated to increase ATMP development, improve timely access to ATMPs at affordable prices. The granting of the exemption has a lower evidence burden (including for safety and efficacy) than market authorisation and production of ATMPs in the hospital setting is not as strictly regulated in terms of batch-batch or patient-patient quality, safety and efficacy consistency.

Our understanding is that C.3.4 responds to this issue by the legitimising of hospital production increasing regulation such that it is more robust. In the context of ATMPs this would go alongside and require amendments to the hospital exemption which may include increased requirements of efficacy and safety demonstration in order to be granted, EU central oversight to harmonise pharmacovigilance across the same products, increased clarity to minimise differences in interpretation. In the case these were enacted then limitations of the number of patients treated could be removed thus facilitating hospital production under the new legitimate production method.

Increased patient safety through greater evidence burden for the exemption and then more consistent hospital production

More hospital production as patient numbers can be increased once this is removed from the exemption – better access and more data though we may expect a short-term reduction in ATMP access as production comes under regulation. Simultaneously as such an increase in production may make the market less attractive for commercial developers there could be a further withdrawal by them and potentially less ATMPs being picked up for MA as spin-offs by more commercial actors. Conversely, we may see commercial actors becoming more involved in development if they are able to access the hospital production route rather than MA – this may support more public-private partnerships.

There is some risk that research by SMEs, academics, and other non-commercial entities (currently the main stakeholder in ATMP development) reduce their activities as the costs increase through the need to have trial data and GMP manufacturing capability in order to be granted hospital exemption.

More transparent and predictable which may also encourage investment – by both commercial and non-commercial entities.

C.3.5. For specific products (named in annex – e.g. keratocytes etc.) less complex cell-based medicinal products to be defined on the basis of clear risk-based approach criteria - two sub-options could be explored in this regard:

C.3.5a. adapted requirements within the pharmaceutical legislation and authorisation by pharmaceutical national competent authorities (NCAs);

C.3.5b. to provide for a mechanism to exclude these medicinal products from the scope of the pharmaceutical legislation (in consultation with relevant authorities) and transfer them under the blood tissue and cells (BTC) legislation with authorisation by BTC NCAs

There are significant regulatory hurdles for less complex cell-based products (such as 'legacy products' existing before ATMPs) that are classed as ATMPs and subject to related standards. Many of these products could be produced in hospital settings. Additionally, there are borderline issues between the BTC and ATMP frameworks with some differing interpretation and classification between member states including some delineation reliant on the presence of an industrial process, no definition of which currently exists.

In theory, C3.5.a and C.3.5b should bring greater clarity around borderline products and simplify legislation for the less complex cell based medicinal products which would bring efficiencies and predictability. However, since both elements involve processes conducted at member state level there exists a potential for heterogenous interpretation and application. Such an outcome could impact negatively on patient safety as well as further exacerbate existing issues around ATMP classification and differentiation from BCT.

Depending on how C3.5.a and C.3.5b are implemented these measures may represent an increased regulatory burden for NCAs.

C.3.6. Introduction of a regulatory sandbox environment, especially in the context of the approval and oversight of complex/cutting-edge products especially those linked to the concept of a 'medicinal product'

We understand the purpose of the regulatory sandbox environment is to create an 'agile, evidence-based and resilient framework' which fosters competitiveness, growth, sustainability, and regulatory learning' to accelerate innovation of complex/cutting-edge medicinal products.

| |
|---|
| Sandboxes are increasingly being used in healthcare settings[100]. This has been inspired from the success of first regulatory sandboxes in the FinTech sector, which have helped businesses to attract investment and increase speed to market by 40% compared to the regulator's standard authorisation times[101]. Thus, sandboxes have the potential to facilitate EU patients getting faster access to complex /cutting edge medicinal products. |
| C.3.7. Create a central *classification mechanism* for advice on whether products are medicines or not, building on the current EMA Committee for Advanced Therapies (CAT) mechanism for ATMPs to all medicinal products (borderline products) in close coordination with other concerned authorities in particular in the frameworks of medical devices and substances of human origin. |
| This is the same as B.3.4.<br>Medicines are increasingly being used in combination with a medical device, usually to enable the delivery of the medicine. However, these combinational products have brought regulatory difficulties for NCAs in terms of uncertainty whether they should be classified as a medical product or medical device and what regulatory framework applies.<br>C.3.7. would improve consistency of the classification of borderline products and the resulting choice of the most appropriate pathway through the EMA committee structure. This should harmonise coordination between concerned authorities in particular in the framework of medical devices and substances of human origin, and thereby deliver some small efficiency gains and avoid assessment committees being distracted from their assessment work by definitional questions. It may also improve the overall timeliness of assessments. The creation of a central screening mechanism may be timely as more definition questions arise for example, 1 in 4 centrally approved medicines typically include a medical device component. Success would depend on EMA finding the capacity to deliver relevant advice at speed. |

*Table 56 Option C – Summary assessment of future proofing*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.3.1 | ++ | + | + | ++ | + | ++ | --- | + | +/- |
| C3.2 | + | + | +/- | + | + | ++ | - | + | +/- |
| C.3.3 | + | + | + | + | ++ | + | +/- | ++ | +/- |
| C.3.4 | +/- | - | +/- | +/- | +/- | + | - | + | +/- |
| C3.5a. | + | + | +/- | +/- | +/- | +/- | - | + | +/- |
| C3.5b. | + | + | +/- | +/- | +/- | +/- | +/- | + | +/- |
| C3.6 | + | +/- | ++ | + | + | ++ | --- | + | +/- |
| C3.7 | + | + | + | + | + | + | +/- | + | +/- |
| Overall impact | + | + | + | + | + | + | - | + | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

[100] European Commission. (2021). *Proposal for a regulation of the European Parliament and of the Council laying down harmonised rules on artificial intelligence (artificial intelligence act) and amending certain union legislative acts COM/2021/206 final*. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52021PC0206

Leckenby, E., Dawoud, D., Bouvy, J., & Jónsson, P. (2021). The Sandbox Approach and its Potential for Use in Health Technology Assessment: A Literature Review. In *Applied Health Economics and Health Policy* (Vol. 19, Issue 6, pp. 857–869). Adis. https://doi.org/10.1007/s40258-021-00665-1

[101] FCA. (2017). *regulatory-sandbox-lessons-learned-report*; FCA. (2019). *The Impact and Effectiveness of Innovate*.

### Assessment of any synergies and tensions within the Policy Block

A tension exists in this block between promoting business – particularly around ATMP development by commercial entities – and the recognition that the majority of ATMP development is currently undertaken by academic, research and SMEs who are non-commercial and unsuited to be MAHs but represent the major stakeholder in this area. In this context promoting business, incentives and patent protections for commercial entities does not necessarily go hand in hand in with promoting innovation.

Future proofing elements in this policy options related to reducing regulatory burden to promote innovation and access: Adapted regulatory framework for certain categories of novel products/technologies (C.3.1); adapt definitions, including that of medicinal product and delink scope from industrial process (C3.3); risk-based classification of less complex cell-based medicinal products (C3.5); and creating a central classification mechanism for borderline products (C3.7) will add clarity and streamline existing legislative pathways that complement with horizontal measures such as streamlining of procedures, including avoiding duplicative processes (including GMO requirements, prioritisation of applications, better coordination within the regulatory network; streamline procedures to facilitate efficient interaction and synergies between different but related regulatory frameworks e.g. Medical Device (for certain type of products) and Health Technology Assessments and create an expert group to give advice/guidance on UMN – cross sector involving health technology assessment bodies (via the Coordination Group of HTA bodies set up under the new HTA Regulation), pricing and reimbursement bodies, patients, and academic representatives. There are also synergies and complementary measures around definitions with security of supply measures (definitions of critical medicine, critical shortage, critical medicine) as well as additional measures in manufacturing quality that would also focus on adapting to new manufacturing processes.

Future proofing elements in this policy element related to improved mechanisms/approaches for innovation to promote access to novel medicines: Introduction of regulatory sandboxes (C.3.6) will provide an adaptive mechanism to support novel innovation approaches to develop medicines. Adapted regulatory requirements to improve use of HE mechanism will facilitate production of non-commercial cell based (ATMP) medicinal products. While a risk-based approach for GMO assessments (C3.2) will focus regulatory efforts on assessment of GMOs posing highest risk to the environment. Together these elements will facilitate the development of novel medicines, GMOs (ATMPs) that have high potential to address UMNs. Element C1.2 also has good synergies in the support of non-commercial entities and making more robust hospital-based manufacturing processes.

#### *A.5.4. Policy Block D (C.D): Access*

### Assessment of the key impacts for the policy elements

Option C incorporates two elements that were previously discussed in Options A (facilitating multi-country packs) and B (Requirement to include small markets in MRP/DCP applications) respectively, but also introduces two new elements.

| C.4.1. Conditional marketing authorisation: UMN incentives are only granted upon switching to standard MA |
|---|
| This measure introduces a conditionality on the granting of the incentives proposed within Block A. It is assumed that this pertains specifically to the granting of an additional period of data protection for products with a demonstrated ability to address an UMN (elements A.1.3, B.1.5 and C.1.5). As such, this element does not introduce *new* impacts but rather limits the extent to which the expected impacts linked to these elements may materialise. The intent of C.4.1. is to further incentivize the generation of post-authorisation evidence for conditionally approved products and to ensure that their (cost-)effectiveness and safety can be sufficiently established. Thus, introduction of this conditionality may be expected to be beneficial for authorities tasked with |

this assessment, as well as for health systems and patients who receive greater assurances that incentives are not granted to products not deserving of these.

C.4.2 Facilitate 'multi country packs' with labelling to allow their placing on the market in several Member States with the same packaging and pack sizes

Same as A.4.1

Currently, information on the pack (outside and inside) must be in the official language(s) of the MS where a product will be placed on the market, bar a few exceptions for certain products that are not intended to go directly to a patient. This language requirement, along with other potentially country-specific requirements, means that MAHs must produce packs specifically designed for each market. This increases production costs and may make smaller markets, where these costs cannot sufficiently be offset by revenues, commercially unattractive. Additionally, country-specific requirements can hinder the movement of medicines between different EU markets when products need to be repacked and relabelled, to meet all requirements of the importing country.

Facilitating 'multi-country packs' may result in more products being placed on a greater number of markets, in particular smaller or less economically attractive markets. In addition, medicines can be moved between EU countries more easily to mitigate or resolve shortages. This would improve security of supply and mitigate some of the risks resulting from product unavailability (e.g. treatment interruption, suboptimal treatment with alternatives). It will, however, be important to ensure that use of multi-country packs does not limit the ability of patients and healthcare providers to access information regarding, for instance, the correct use and safety profile of medicines. No studies were identified that detail experiences with multi-country packs as a way to overcome access challenges and that thus could inform an estimation of impact.

In economic terms, it is expected that multi-country packs would result in a cost saving to MAHs by reducing the number of different presentations they need to produce and streamlining production lines. The magnitude of these savings will depend primarily on the number of countries and languages included, whilst the size of the markets reached by multi-country packs will further influence the profit potential for the MAH.

In theory, multi-country packs may have the added benefit of facilitating joint procurement between countries. Several initiatives already exist whereby smaller countries engage in joint procurement to increase their purchasing power. Such initiatives have the potential to negotiate lower prices. A 2020 study for WHO shows that whilst these initiatives hold promise, they often take months or years of cooperation before tangible results are achieved. The study did not specifically look at the role of multi-country packs in facilitating joint procurement.

**C.4.3 If a medicinal product is appropriately and continuously supplied in all MS (unless it is demonstrated that a certain MS does not wish supplies) within a period of 2 years from MA and not later withdrawn before the additional exclusivity kicks in, then the product receives an additional 2 years of data protection**

This pivotal element seeks to encourage developers of innovative medicines to place products on all EU markets by offering a 2-year extension of regulatory data protection in return for doing so within two years of authorisation. To avoid potential abuse of the incentive and simultaneously address problems with access and continuity of supply, the incentive is linked not simply to market entry but to whether the product is appropriately and continuously supplied (subject to MS electing to reimburse / accept the product).

This element will complement the decision to reduce the standard period of regulatory data protection from 8+2 years currently to 6+2 years in future, with most MA holders being in a position to launch their new products in all member states willing to reimburse those medicines. This condition will bring the overall RDP back to the current 10 years (6+2+2) for the great majority of products.

We assume the 10-12 products annually may chose or fail to comply with the condition 'all markets within 2 years' and that these MAHs will see a loss of income (c. 22%; €352m-€422m a year) on those products, as a result of earlier generic entry (from year 8). We assume the cost of servicing say 25 EU markets on average rather than say 15 (more typical currently) would be cost neutral, with the higher sales volumes in the additional 10 smaller markets offsetting the additional marketing, distribution and other costs associated with smaller / marginal markets. EU health systems will also save money from earlier competition (€210m-€270m a year).

There are some practical issues to be tackled in the final detail design of this proposal. The element raises several questions as to how this should be operationalised. The first relates to the clock start. As most innovative medicines are approved via the centralised procedure, the most likely start time would be the date of central approval by the EMA. It has, however, not been specified whether medicines authorised via a national route would also be able to qualify and, if so, which date of authorisation should be considered.

Second, it is not clear how the measure would allow for the introduction of 'clock stops' to accommodate variability in the duration of pricing and reimbursement decision-making processes by public authorities. In the annually published results of the W.A.I.T. survey, conducted by EFPIA, it is estimated that the average time for a centrally approved medicine between marketing authorisation and the date at which products gain access to

the reimbursement lists, varies from 133 days in Germany to over 800 days in Bulgaria, Poland and Romania.[102] In these results, however, it has not been specified to what extent such differences are due to factors on the site of the MAH and of the public authority respectively. It is thus difficult to predict by how much an incentive for MAHs alone would be able to shorten this period if authorities are unable or unwilling to approve reimbursement within the required timeframes. This issue has not been discussed in consultations with public authorities and therefore it is not possible to indicate whether a two-year window would be sufficient.

Questions may also be asked about how to define 'appropriate and continuous' supply and how to apply this concept in determining whether eligibility criteria have been met. The concept exists in Article 81 of Directive 2001/83/EC which requires MAHs and wholesale distributors of a medicine that is placed on the market to ensure "appropriate and continued supplies", within the limits of their responsibility, to cover the needs of patients. This concept has, however, been interpreted differently in different countries and offers limited guidance on how to establish whether an MAH (or wholesaler) has acted appropriately to fulfil its obligations. It is therefore to be expected that similar difficulties will be encountered in its application in the context of the here proposed element, particularly if this assessment needs to be provided by the Member States where the products have been placed on the market.

C.4.4. Requirement to MAH applying for MRP/DCP to include small markets (in particular address the post-BREXIT challenges) or possibility for MS to opt-in a pending MRP/DCP procedure

Same as B.4.4

Most generic medicines are currently approved through the MRP/DCP route . Because of this, these products would not fall within the scope of the requirements imposed by B.4.2 and B.4.3. By also extending greater obligations for inclusion of smaller markets in the application for approval via the MRP/DCP, the Commission aims to increase access to a wider group of products, in particular generic medicines, than would be achieved via marketing obligations on centrally approved medicines alone. It is assumed that the proposed element intends only to require the applicant to include specific countries into the MRP/DCP application, such that there is a valid MA in these markets, but does not require the applicant to directly place products on these markets.

Requiring MAHs applying for an authorisation via the MRP/DCP route to include specific markets – or allowing countries to opt-in – will enable these countries to obtain medicines more easily from other EU MS (through parallel distribution), even when the MAH does not place the product directly on the market. This may have the effect of increasing access to medicines that are not within the scope of the CP, especially generic medicines. This, in turn, may be expected to positively affect both health outcomes for patients and the affordability of treatment by increasing access to low-cost generic versions. It will also improve security of supply for included countries by facilitating redistribution in case of shortages.

### Summary assessment of the principal costs and benefits by impact type

Table 57 presents a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under Option C, by impact type. Whilst the impact of some of the individual elements has been detailed previously under Options A and B, the introduction of new ones, as well as the new combination of elements will have intrinsically different synergies and tensions and thus result in a different assessment of the overall impact.

*Table 57 Option C – Summary assessment of access elements*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.4.1 | +/- | +/- | +/- | +/- | +/- | ++ | ++ | ++ | +/- |
| C.4.2 | ++ | + | +/- | + | ++ | +/- | + | + | +/- |
| C.4.3 | - | - | +/- | -- | + | +/- | ++ | ++ | +/- |
| C.4.4 | --- | -- | - | -- | + | - | ++ | +++ | +/- |
| Overall impact | --- | --- | -- | -- | ++ | +/- | +++ | +++ | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and

[102] https://www.efpia.eu/media/636821/efpia-patients-wait-indicator-final.pdf. Last accessed 23 May 2022.

production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

- The proposed elements impact different groups of industry stakeholders differently. For innovative medicine developers, the package of measures is skewing positively, by introducing a new incentive for market placement and removing some barriers to operating in smaller markets by facilitating multi-county packs. At best, these elements will enable innovators to increase their operating profits whilst on the other hand there are no new obligations introduced that could cause harm to their cost of business. Generics manufacturers on the other hand are not likely to benefit from the new incentive, as their products are normally not under regulatory protection, yet face a new requirement to include smaller markets in their MRP/DCP applications. Additionally, the incentive offered to innovative developers means a longer exclusion from the market for generic companies. Jointly, these measures thus most likely represent a substantial net negative for generic manufacturers.
- Inclusion of additional countries, in particular smaller MS, in the MRP/DCP application (C.4.4 will facilitate the movement of medicines between markets where the product has been authorised. This measure is substantially synergistic with the measure to facilitate use of multi-country packs (C.4.2). Jointly, these measures may be effective in facilitating the movement of medicines within the EU internal market to countries that are comparatively underserved or where medicines are in shortage.

### Assessment of any synergies and tensions within the Policy Block

As under Options A and B.

### *A.5.5. Policy Block E (C.E): Competition*

### Assessment of the key impacts for the policy elements

Table 58 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements.

*Table 58 Option C – Assessment of the proposed measures for competition*

| **Description** |
|---|
| C.5.1 New simpler regulatory pathway for generics (adapted EMA/CHMP working methods, shorter approval timelines, potentially distinguishing between complex generics/biosimilars – reducing requirements for known biologics) |
| As described for A.5.1.<br>The key impact from a simpler regulatory pathway with shorter approval times will be faster availability of generics to patients. It should create more clarity and potentially less administrative burden for marketing authorisation applicants, encouraging more applications and increased development activity for generics.<br>We assume that generics will be on the market soon after approval and access to generics will be similar in all member states. The latter assumption has been adopted for ease of analysis as generics market penetration varies considerably across member states and would add uncertainties to our assessment. |
| C.5.2 Interchangeability of biosimilars with their reference product will be generally recognised in guidance or e.g. through a recital in the legislation and will be scientifically assessed as part of the product assessment and indicated in the summary of product characteristics (SmPC, product information) to inform healthcare professionals and their patients as well as downstream decisions makers |
| As described for B.5.2.<br>Interchangeability, switching (by prescriber) and substitution (by pharmacy) of a reference medicine by its biosimilar currently fall within the remit of EU Member States. Guidance on interchangeability from one originator (reference) or biosimilar product to another at the EU level would enable all member states to make decisions on whether to allow switching and/or substitution for certain products, especially those countries where the relevant technical capacity is not available. There is potential to pool the best expertise from across the EU if product |

| Description |
|---|
| assessment is done as part of the centralised procedure, reducing burden on individual member state authorities. Inclusion of the guidance in a recital in the legislation and product information (SmPC) would inform prescribers, patients, and decision makers about interchangeability of specific products, potentially increasing uptake of biosimilars. This could improve access to biologics for patients and reduce health system costs if cheaper biologics were switched or substituted for more expensive ones.<br>It is not clear if additional data will be requested for the scientific assessment of interchangeability e.g. switch studies. Our assumption is that no additional data will be required – a study by Kurki et al. (2021) which analysed post-marketing surveillance data suggests that biosimilars approved in the EU are highly similar to and interchangeable with their reference products. A recent qualitative study also shows that European and UK regulatory, legal and policy experts do not see any added value in additional data or switching studies. |
| C.5.3 Broader Bolar exemption – allow additional beneficiaries (companies, producers of active pharmaceutical ingredients (APIs) and non-industry actors) to conduct studies/trials |
| Overall, the broader Bolar exemption is likely to increase legal certainty, access to medicines, cost savings and research activity in the EEA compared with a narrower exemption.[103] |
| C.5.4 Extend Bolar exemption beyond generics – Allow repurposing studies/comparative trials without infringing patent rights |
| Overall, the extended Bolar exemption is likely to increase legal certainty, access to medicines, cost savings and research and innovation activity in the EEA compared to a narrower exemption.[82] |
| C.5.5 Duplicates restricted to cases of intellectual property protection or co-marketing |
| As described for B.5.6b.<br>There will be a reduction in barriers to competition and monopolisation of the market by the first generic/biosimilar of an originator product to receive an MA. Consequently, there will be no delay in the second generic/biosimilar coming onto the market once it receives approval. This will mean greater consumer choice and price competition. |

## Summary assessment of the principal costs and benefits by impact type

Table 59 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block E under Policy Option C and for each impact type.

*Table 59 Option C – Summary assessment of the proposed measures for competition*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.5.1 | + | + | + | + | + | + | + | + | -/+ |
| C.5.2 | -/+ | -/+ | -/+ | + | + | -/+ | ++ | ++ | -/+ |
| C.5.3 | + | + | -/+ | + | + | + | ++ | ++ | -/+ |
| C.5.4 | + | + | -/+ | + | + | + | ++ | ++ | -/+ |
| C.5.5 | -/+ | -/+ | + | + | ++ | + | ++ | + | -/+ |
| Overall impact | + | + | + | + | ++ | + | +++ | +++ | -/+ |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and

[103] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Some of the key expected impacts are as follows:

- Increased international competitiveness through creation of a more favourable regulatory environment for generics/biosimilars (simplified generics pathway) and broader scope of activities and actors covered under the Bolar exemption. The broader Bolar exemption will increase the share of EU-based API producers and API manufacturing jobs and lower costs of supply for European generics.[104] The cost savings would be more pronounced for European generics manufacturers of specialised products e.g. for oncology or central nervous system
- Improved consumer choice and competition through availability of both generics/biosimilars and originators on the market (including guidance on interchangeability), resulting in lower prices and improved access for patients across member states. Modification of the duplicate regime will mean originator companies will not be able to severely undercut the price of potential biosimilar competitors through a duplicate authorisation for an autobiological while allowing the reference originator product to maintain a high price.[105]
- The extended scope of the Bolar exemption will increase returns to innovation and therefore increase incentives to innovate for European R&D based pharmaceutical companies in countries that currently have a narrow Bolar scope. This would increase R&I for generics and biosimilars and can be expected to lead to an increase in the number of skilled jobs[84]
- If the extended Bolar exemption leads to more clinical trials in a country, this will have impacts on access as it has been shown that new medicine adoption is wider in countries where the clinical trial was run[91]
- A very high likelihood of positive impact on patients through making medicines more readily available and reducing costs for health systems (generics represent around 80% cost reduction compared to originators, and entry of a generic also reduces price of the off-patent medicine by 61%[106]; biosimilars are 20% cheaper[107] compared to originator products)

### Assessment of any synergies and tensions within the Policy Block

There is synergy with the horizontal measure of streamlining and harmonisation with making the regulatory pathway for generics simpler. Changes to the Bolar exemption will have synergy with elements introduced to improve access, but may have some negative implications for innovation activity if ROI figures change for originators. Change to the duplicates regime improves background conditions for timely availability of biosimilars on the market and thus access.

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[104] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

[105] https://www.biosliceblog.com/2019/11/update-on-eu-duplicate-marketing-authorisations/

[106] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

[107] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilarsv

## Assessment of the key impacts for the policy elements

Table 60 presents our assessment of the key impacts of each of the proposed measures, drawing on our consultations, desk research and targeted literature review.

*Table 60 Option C – Assessment of the proposed measures for Supply Chain Security*

| **Assessment** |
|---|
| C.6.1. Introduce EU definition of a shortage, including a critical shortage and critical medicine |
| The measure has the potential to harmonise numerous definitions of shortages that exist across the EU. The clarification of criticality criteria can further help in making changes in shortage notification to cover shortages for most critical medicines. Overall, many stakeholders, and particularly industry representatives have advocated for the adoption of the concept of 'product criticality' into definitions of shortages and regulatory measures aimed at notification and prevention of shortages. The study of medicines shortages also called for the introduction of criticality criteria and further measures associated with it.[108]<br>The clarification of shortage criticality criteria can further help in making changes in shortage notification to cover the most impactful shortages. |
| C.6.2. a) Increase notification period to 12 months for all withdrawals of products that have been on the market for more than two 2 years<br>b) Notification at least 6 months in advance or as soon as identified for all shortages (non-withdrawal)<br>c) Introduce a common template for reporting withdrawals and shortages including details of root causes, alternatives medicines and impact. |
| This option differentiates between planned (permanent) market withdrawals and temporary supply disruptions, setting different notification timeframes for each. There is more explicit recognition of the fact that not all shortages can be foreseen 6 months in advance. It is uncertain whether this element will result in earlier notification than presently the case, given that most shortage notification are currently made with less than 2 months' notice, citing 'exceptional circumstances'. There is no clear reason why extending the notification period would remedy this situation. Where potential shortages are notified more in advance, these situations often are resolved before they result in an actual shortage. Extending the notification period may thus increase the number of 'false alarms'. There is also a risk that a longer notification period will increase the administrative burden on both MAHs and public authorities without clear benefits.<br>In some countries, parallel distributors also fall under a notification obligation. In consultation, this industry has indicated that a 6-month notification requirement would not be possible to meet since they typically do not hold stocks for more than 2-3 months.<br>Earlier notification of planned withdrawals (element a), however, may be more feasible and provide authorities more time to identify and source alternatives.<br>The obligation to utilise a common reporting template (Element c) is received positively by the stakeholders. Common data collection approaches, particularly if linked to a standardised reporting portal and automatic sharing of information between MS could, in the longer term, result in cost savings for authorities. Greater standardisation of information may also enable a better understanding of the causes of shortages and allow for the development of better-tailored policy approaches to address the issue of shortages. |
| C.6.3. Stockpiling requirements for MAHs for unfinished critical medicines, as appropriate |
| Some further elaboration is needed to determine criteria to establish what constitutes 'as appropriate'. More detailing is also needed about the expected quantity of such stock, what state the product needs to be in (e.g. intermediates or finished but unlabelled/unpacked products), at what level the stock will be held (e.g. EU, national, regional), who has ownership and responsibility for the stock (e.g. MAHs, wholesalers or authorities) and whether stock may be redistributed according to need. All such factors may strongly influence the operational feasibility of this measure and its acceptability to involved stakeholders.<br>Among wholesalers there is a sense that a limited level of additional reserve stockholding (~2-3 weeks) – with reserves dynamically rolled into normal stock – for critical measures may be a cost-effective measure against supply disruptions, holding larger volumes of stock is both unfeasible and unnecessary.<br>It is expected that the costs of increased stock holding will either need to be shared between MAHs and public authorities, or if not, that MAHs will seek to recoup the increased costs by raising prices. For generic |

[108] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages*

| |
|---|
| manufacturers, whose products are typically under strict price regulations and caps, this may not always be possible. Among generic manufacturers, there is therefore a fear that in the absence of a balanced cost/risk sharing arrangement, companies may be unable to continue operating in markets where these stock obligations apply. |
| C.6.4 (as in A.6.3.) Marketing authorisation offered for transfer to another MAH before a permanent withdrawal |
| Requiring a MAH to offer the MA to another party before allowing it to withdraw the product from a specific market could delay the original MAH's withdrawal decision, as it seeks to avoid enabling its own competitors.<br>Hypothetically, requiring MAHs to offer the MA to another manufacturer could benefit such manufacturers who are enabled to market a product that already has an established patient base. However, as indicated previously, a large proportion of product withdrawals can be traced to low product-level profitability[109]. It is not clear to what extent a MA transfer could effectively address these underlying profitability issues. Such transfers would only be feasible/interesting in case a product remains commercially interesting for the new MAH or if commercial viability is not required for another party to take over the MA (e.g. in case of transfer to a not-for-profit entity).<br>The study team has identified no experiences with similar measures that could inform a (quantitative) estimation of potential impact. Moreover, the EU trade association for the generics industry (Medicines for Europe) has indicated that it considers this proposal unconstitutional and not compliant with the proportionality requirements of EU treaties. It indicates that permanent withdrawals for commercial reasons are often necessitated by national market conditions, such as pricing and reimbursement policies (e.g. price cuts, reference pricing, claw backs and rebates), that are imposed by Member States and over which the MAH has no control. Mandating that the MAH offers the authorisation to another party before allowing it to withdraw is therefore considered a form of regulatory expropriation in violation of Art. 16 of the European Charter of Fundamental Rights. |
| C.6.5. Marketing authorisation holders to have shortage prevention and mitigation plans for all medicines. |
| Early identification of risks to the security of supply and of possible mitigation steps could reduce the occurrence and impact of supply disruptions. Fewer medicine shortages, as well as faster and more effective mitigation of the impact of shortages when these occur, improves patient access to (critical) medicines and leads to better health outcomes. The health system experiences fewer costs associated with dealing with medicine shortages.<br>Depending on the level of detail required and the degree to which risk mitigation steps (e.g. contractual agreements with backup suppliers) are expected, MAHs may make additional costs not only in drawing up the plans but also in implementing the actions therein specified.<br>Industry representatives have indicated that an important condition for the submission of shortage prevention plans would be that the company retains ownership of the plan, and that information remains confidential, as this could be commercially sensitive. In consultations, industry stakeholders have strongly opposed applying this measure to all authorised medicines rather than limiting it to critical medicines and those medicines at high risk of shortage. Amongst these stakeholders the measure is widely viewed as unnecessary, impractical, and burdensome as these plans would need to be regularly updated to remain relevant. It is expected this will create a very significant administrative burden for both regulators and MAHs.<br>There is greater support for this measure should it be limited in scope to critical medicines and products at risk of shortage. Even under these circumstances, however, industry stakeholders note that MAHs may not be able to offer alternatives as this is the responsibility of physicians and prescribers. |
| C.6.6. Monitoring of supply remains at MS level, with information exchange at EU level for critical shortages based on national monitoring, using a common methodology/format to ensure compatibility & exchange at EU level. |
| This policy element is economically advantageous for MAHs and NCA as it builds upon the existing system of national monitoring. The implementation of the element is also feasible: existing initiatives and networks such as SPOC can be used for the purposes of the exchange. However, countries would still need to adopt the definitions of critical medicines in order to make the exchange efficient. |
| C.6.7 Expanded requirements for key suppliers and back-ups to diversify supply chain for critical medicines |
| C.6.7. aims to force MAHs to diversify their supply chains to prevent shortages and thus improve the availability of medicines and overall patient outcomes.<br>Requiring more diverse supply chains most likely will result in increased production costs as MAHs may need to procure goods and services from less economically advantageous suppliers. These costs could be substantial, although no data was collected that would allow this impact to be quantified. There may be additional payments to backup suppliers, to reserve goods and space on production lines, even if not needed. |

[109] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages* (Issue December).

These additional costs occurred by the pharmaceutical industry may result in higher medicine prices and greater costs to health systems and patients. If requirements are introduced by individual MS rather than at the EU level, this could discourage MAHs from operating in markets with such requirements and contribute to inequitable access to medicine.

Importantly, the measure may not be feasible to implement for many medicines, for which globally a limited number of API and raw materials manufacturers exist, meaning that it may not be feasible for MAHs to sufficiently diversify their supply chains. Separate measures would be needed to enable this, e.g. economic incentives for industry to increase the manufacturing of APIs and raw materials.

C.6.8 Establish a mechanism of exchange of relevant information on supply chains between Member States to identify the supply chains bottlenecks and vulnerabilities

It is assumed this refers to sharing of information about the structure of supply chains, including the upstream aspects such as production and sourcing of raw materials and APIs, e.g. identifying the number, location and production capabilities of suppliers. Whilst improved insight into these structures certainly would be beneficial to understand which products may be at higher risk for supply disruptions, it is unclear who would be expected to provide the information or how it would be used. MAHs likely will consider such information commercially sensitive. It is, however, also unlikely that NCAs would be able to collect such information without the input from MAHs and other parties that make up the supply chain. It is thus difficult to understand the foreseen impact pathway and the actions needed to implement these policy elements. Consequently, we are presently not able to predict their potential impacts.

C.6.9. (same as B.6.8) Increase transparency of the supply chain, including:

1. active supply sites for all medicines,
2. volumes supplied, incl. supply quotas and remaining stocks for critical medicines upon request of NCA's/ EMA,
3. parallel traders and wholesalers' transactions for critical medicines upon request of NCAs/ EMA.

Improved transparency of the supply chain, at least for public authorities, has the potential of improving the security of supply by better matching supply and demand.

MAHs and parallel distributors each have a clear commercial interest in keeping (aspects of) information about their transactions confidential and are not generally welcoming of disclosing this to the other. For instance, parallel traders fear that full public disclosure of information about their transactions will render their trade practically impossible by allowing MAHs to throttle their supply to the level where no surplus is created.

For these parties to agree to share information with public authorities, it will be essential that strong agreements are made about what information is disclosed, for what purposes, how this will be used and who has access to it. Without this, it is unlikely that industry will cooperate. Mandatory disclosure of commercially sensitive information could furthermore distort competition between MAHs.

It may be assumed that regular sharing of information between supply chain actors and authorities – particularly when not done though an automated system – entails substantial administrative costs on all sides.

## Summary assessment of the principal costs and benefits by impact type

Table 61 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block F under Policy Option B and for each impact type.

*Table 61 Option C – Summary assessment of Policy Block F (Security of Supply)*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.6.1 | +/- | + | +/- | +/- | +/- | +/- | +/- | + | +/- |
| C.6.2 | -- | -- | +/- | +/- | +/- | +/- | +/- | ++ | +/- |
| C.6.3 | -- | -- | +/- | -- | +/- | +/- | - | + | -- |
| C.6.4 | - | - | +/- | - | +/- | +/- | +/- | ++ | +/- |
| C.6.5 | - | -- | +/- | -- | +/- | +/- | + | ++ | +/- |
| C.6.6 | +/- | + | +/- | +/- | +/- | +/- | + | ++ | +/- |
| C.6.7 | --- | --- | -- | -- | - | +/- | +/- | ++ | -- |
| C.6.8 | +/- | +/- | +/- | +/- | +/- | +/- | + | ++ | +/- |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| C.6.9 | +/- | -- | +/- | -- | - | +/- | + | ++ | +/- |
| Overall impact | -- | -- | +/- | - | - | +/- | ++ | +++ | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

### Assessment of any synergies and tensions within the Policy Block

Similar to Option B, several policy elements (C6.6. and C.6.7) are dependent on element C.6.1. (Introduce EU definition of a shortage, including a critical shortage and critical medicine). Overall, the elements are synergistic and do not contradict each other.

*A.5.7. Policy Block G (C.G): Quality and manufacturing*

### Assessment of the key impacts for the policy elements

Table 62 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on desk research and targeted literature review.

*Table 62 Option C – Assessment of the proposed measures for quality and manufacturing*

| **Assessment** |
|---|
| C.7.1. Strengthen the oversight of the sites within a supply chain (including distributors and APIs manufacturing/importing sites) by extending the scope of mandatory inspections and modifying provisions on inspections (frequency, content, triggering points) |
| This measure will strengthen end-to-end oversight of the supply chain and could improve GMP/GDP compliance. However, it would impose significant additional burden on businesses and competent authorities. It would substantially increase the workload of inspectors (because of the extended scope and depending on the modified provisions), which would need to be met with more resources. |
| C.7.2. Stronger EMA role in ensuring proper oversight of the manufacturing sites via adapted IT tool and by increased role in coordination of inspections, including in setting up multinational inspection teams |
| The proposed policy element would have efficiency benefits with regard to oversight of manufacturing sites in the long term through better data management, transparency, resilience, and interoperability. However, this effect would depend on the quality, content and implementation of the IT tool, and would require additional resources in the short term. A stronger role for the EMA and setting up of multinational inspection teams would allow harmonisation of approaches. The latter would promote knowledge exchange and efficiency, benefitting national competent authorities. In the short-term, there may be high costs involved in restructuring capabilities. |
| C.7.3. Reinforcing Member States GMP and good distribution practices (GDP) inspections capacity by setting up a mandatory joint audit scheme |
| Same as B.7.2.<br>This policy element has the potential to increase inspection efficiency through more cooperation and knowledge transfer. This may have a positive effect on manufacturing and distribution practices within the EU and globally, which would ultimately positively impact public health in the long-term. |
| C.7.4. Adaption of legislation/inclusion of specific provision covering new manufacturing methods (decentralised, continuous manufacturing, etc). to ensure levels of quality and safety equivalent to current methods |
| Same as A.7.3<br>The proposed measure has the potential to bring several product categories that are currently excluded from the legislation into the fold and provide regulatory certainty to manufacturers. These include magistral formulae (pharmacy-based preparation for an individual patient), radionuclides in sealed sources, hospital-manufactured medicines, and single-batch medicines. In addition, manufacturing methods such as decentralised manufacturing (where manufacturing occurs at different locations) and 3D printing-based methods could be accommodated.<br>Covering new manufacturing methods in the general pharmaceutical legislation has the main advantage of helping to standardise the methods themselves, quality control of the methods and resultant products and associated regulatory pathways at the EU level. Thus, there is a harmonisation benefit. Moreover, |

| Assessment |
|---|
| accommodating new technologies sends a positive signal to innovators as well as companies and will encourage more innovation and research activity and adoption of the new methods. There will be further knock-on effects on competition, competitiveness, and access to medicine. If greener manufacturing methods are used there will be an impact on environmental sustainability, but the likelihood and extent of that is unclear.<br>With more certainty over the manufacturing methods and the resultant products as well as more medicine developers adopting these methods, we could imagine a very high increase in the number of new therapies in comparison to the baseline. |

### Summary assessment of the principal costs and benefits by impact type

Table 63 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block G under Policy Option C and for each impact type.

*Table 63 Option C – Summary assessment of the proposed measures for quality and manufacturing*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.7.1 | - | - | - | - | - | -/+ | - | +/- | +/- |
| C.7.2 | + | + | +/- | +/- | +/- | +/- | + | +/- | +/- |
| C.7.3 | +/- | +/- | +/- | + | +/- | +/- | + | +/- | +/- |
| C.7.4 | -/+ | -/+ | -/+ | + | + | + | -/+ | + | -/+ |
| Overall impact | -/+ | -/+ | - | + | +/- | + | + | + | -/+ |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Extending the scope and modifying provisions of inspections and expanding oversight to all sites within a supply chain (including distributors and API manufacturers) could create additional transaction, compliance and administrative costs which could put a large burden on SMEs in particular. Moreover, NCAs will need additional inspection capacity and training to accommodate the changes in the scope, provisions and actors. On the other hand, a mandatory joint audit scheme for member states and stronger coordination of inspections by EMA will create efficiencies and savings for NCAs (and to some extent for businesses in the long term).

Adaptation of the legislation or inclusion of specific provisions to accommodate new manufacturing methods will improve international competitiveness, encourage greater research and innovation, and increase choice and competition in the sector. It would also have a direct impact on patients by making more treatments available and require additional transaction, compliance and administrative costs for oversight (both for businesses and NCAs). The measures to improve oversight of manufacturing but the quality standards are already high so there is unlikely to be greater added benefit to public health.

### Assessment of any synergies and tensions within the Policy Block

Policy elements C.7.1, C.7.2 and C.7.3 have synergies with regard to enabling stronger supply chain oversight through different mechanisms.

### *A.5.8. Policy Block H (C.H): Addressing environmental challenges*

#### Assessment of the key impacts for the policy elements

Table 64 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

*Table 64 Option C – Assessment of the proposed measures for addressing environmental challenges*

| **Assessment** |
|---|
| C.8.1 Include assessment of the environmental risk of manufacturing into ERA, including main supply chain actors (API, raw materials) |
| This measure represents considerable additional burden for medicine developers and supply chain actors, and public authorities in terms of compliance and administration costs and review costs respectively. On the other hand, it will allow tracking of the environmental risks of manufacturing across the supply chain providing a more comprehensive assessment of the potential environmental impact of a new medicine. For example, if risk associated with active pharmaceutical ingredient discharges from manufacturing sites is included in the ERA, it would increase the relevance of the assessments by including a part of the life cycle of the product responsible for the highest environmental concentrations detected.[110] |
| C.8.2 Strengthen the ERA requirements and conditions of use for medicines, while taking stock of research under the innovative medicines initiative (IMI) |
| The proposed measure should enable robust assessment of the environmental risks of pharmaceuticals as well as promote prudent use, supporting sustainable consumption and helping to minimise the environmental footprint of medicines. However, this may place slight additional burden on public authorities for reviewing ERA submissions (in case of additional data requirements) and monitoring medicine use (if required) as well as on businesses and other stakeholders responsible for complying with said requirements and conditions. |
| C.8.3 Advisory role of EMA on ERA and green manufacturing aspects and quality (e.g. with relation to generics) |
| Constitution of a new advisory body/bodies and ongoing costs of providing advice will be the main drivers of administrative burden for EMA. However, the advice will help companies to better address ERA requirements and adopt green manufacturing practices, which will in turn aid pharmaceutical sector businesses to be more sustainable. |
| C.8.4 Include the AMR aspects into GMP to address the environmental challenges |
| This measure would help minimise amounts of antibiotics entering the environment via manufacturing and thus prevent emergence of AMR from pharmaceutical manufacturing. Recent evidence indicates the presence of a selection pressure for AMR within environments receiving wastewater from antimicrobial manufacturing, as opposed to environments receiving wastewater from municipal sewage treatment plants (containing antibiotics from human use) that do not receive waste from antimicrobial manufacturing.[111]<br>There would be the additional costs for businesses to comply with the AMR requirements in GMP and data requirements and for public authorities for enforcement of the requirements. This could present barriers for smaller actors.<br>The KPI would be amount of an antibiotic in waste and wastewater in µg/l. Suggested annual mean value for an erythromycin environmental quality standard (EQS) is 0.2 µg/l.112<br>For the current impact assessment, we would assume that compliance with the measure will result in levels below the EQS and thus there is a high likelihood of impact on sustainable production (environmental impact). |

[110] Eeb. (2018). Policy options for regulating pharmaceuticals in the environment.

[111] WHO Expert Committee. (2020). *Annex 6 Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance*.

[112] UBA – Umweltbundesamt (Hrsg.) (2018) Empfehlungen zur Reduzierung von Mikroverunreinigungen in den Gew ssern,Hintergrund, Februar 2018, Dessau-Ro lau, https://www.umweltbundesamt.de/sites/default/files/medien/1410/publikationen/uba_pos_mikroverunreinigung_final_bf.pdf

### Summary assessment of the principal costs and benefits by impact type

Table 65 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block H under Policy Option C for each impact type.

*Table 65 Option C – Summary assessment of the proposed measures for addressing environmental challenges*

| Policy elements | COB | Admin | SMEs | CTI | Int Mar | I&R | PA | H&S | Sust |
|---|---|---|---|---|---|---|---|---|---|
| C.8.1. | - | - | - | - | - | +/- | - | + | ++ |
| C.8.2. | +/- | +/- | - | - | - | +/- | +/- | + | ++ |
| C.8.3. | +/- | +/- | +/- | +/- | +/- | +/- | - | + | + |
| C.8.4. | - | - | - | - | +/- | +/- | - | + | + |
| Overall impact | - | - | - | - | - | +/- | - | + | ++ |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

The key impact of the measures to address environmental challenges in Policy Option C are expected to be increased sustainable production and waste management owing to improved ERA, inclusion of AMR in GMP and green manufacturing. This may have an indirect effect on public health local to manufacturing sites due to reduced emissions and the possibility of fewer AMR strains emerging.

There may be additional burden on SMEs to meet the new requirements either in terms of administrative costs or need for specialised expertise with implications on competitiveness and the internal market. Similarly, the EMA and NCAs may require additional capacity or incur greater administrative burden in reviewing and assessing products based on the additional requirements for ERA and GMP.

### Assessment of any synergies and tensions within the Policy Block

There are no major synergies or tensions within this block for Policy Option C. Policy element C.8.1. is in line with elements in other blocks that aim to increase transparency and obligations about supply chain actors, but conflicts with the horizontal measure aimed at simplification. C.8.2. has synergy with the horizontal measure aiming to strengthen and harmonise ERA across member states, while reducing duplication of testing. C.8.4. has complementarities and synergies with measures to restrict and monitor use of antimicrobials, especially B.2.4. (Stricter rules on disposal) and B.2.8 (Establish monitoring system for data collection on human antimicrobial consumption and use and potentially on the emission of APIs to the environment). However, there is a risk of duplication of effort/data in the GMP/environment reporting requirements for companies, which should be covered in the revision.

The additional advisory role of the EMA has potential synergy with the measures to strengthen ERA and modify GMP and could support industry in smooth transition to and harmonised implementation of the new requirements.

## Assessment of the key impacts for the policy elements

Table 66 presents our broad assessment of the likely costs and benefits of the proposed policy element, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

*Table 66 Option C – Assessment of the proposed measures for COVID-19 lessons learnt*

| **Assessment** |
|---|
| C.9.1. Refusal of immature marketing authorisation applications |
| Same as B.9.1<br>The most significant efficiency gains would be for public authorities, which could save time currently spent on assessing immature applications and resolving internal differences of opinion as regards their evaluability or suitability for processing through the CMA pathway. As per baseline, we assume that there could be 2 to 3 marketing authorisation applications every year that do not initially request a CMA despite not containing enough data for standard marketing authorisation. This would likely lead to 2 to 3 immature marketing authorisation applications refused every year in the first one or two years, possibly increasing to 5 to 10 refused applications every year in the next 3-5 years as the evidentiary threshold is established. Industry would begin to recalibrate the acceptable levels of evidence in parallel and the numbers of weak applications should fall back to some minimum within 5 years, perhaps never quite falling below 2-3 a year over the remaining years through to 2035.<br>Overall, assuming an average annual reduction of 3-5% in the total number of applications for assessment and 100-120 applications annually, which are increasing at 5-10% a year (as per EMA annual report 2020), cutting assessments by 3-5% might result in a reduction of EMA / NCA costs of 2-3% (the work of the EMA committees is a major cost driver).<br>There could be a negative impact on cost for developers that are currently submitting immature marketing authorisation applications for valid reasons. For example, addressing an UMN may be difficult in terms of conducting large clinical trials. This may discourage developers of medicinal products for UMN if it is not combined with other policy elements. On the other hand, less immature data means HTA bodies and P&R authorities would be more able to assess therapeutic value, which could have a positive impact on access and affordability. Thus, the impact on healthcare systems could be negative (less developers working on UMN) and positive (more streamlined and coherent procedure leading to faster market launch). |

## Summary assessment of the principal costs and benefits by impact type

Table 67 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block I under Policy Option C and for each impact type.

*Table 67 Option C – Summary assessment of the proposed policy elements for COVID-19 lessons learnt*

| **Policy elements** | **COB** | **Admin** | **SMEs** | **CTI** | **Int Mar** | **I&R** | **PA** | **H&S** | **Sust** |
|---|---|---|---|---|---|---|---|---|---|
| C.9.1. | - | +/- | - | - | +/- | +/- | + | +/- | +/- |

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

# Overview of proposed horizontal measures

## A.6. Introduction

The impact assessment identified the need to improve the flexibility of the regulatory framework, to futureproof the system and ensure its effectiveness over the next 15-20 years.

In response, the EC and the wider regulatory 'family' has developed a long list of proposals for improving efficiency of the regulatory system, which are listed below in Table 68. The impact assessment has explored each of these areas through our consultations and wider desk research, which suggest there may be substantial opportunities for streamlining and reducing regulatory burden.

The initial assessment of this long list is shown below and has been used to identify a series of 10 pivotal horizontal measures, which have been the subject of a more detailed assessment and cost benefit analysis.

*Table 68 Original long list of horizontal measures that have been considered by the IA study*

| **Streamlining proposals** |
|---|
| Abolish the sunset clause for all medicinal products |
| Abolish requirement for renewal of marketing authorisation for all medicinal products |
| Abolish the additional monitoring requirement and accompanying black symbol. |
| Abolish risk management plans for generics, biosimilars, hybrid and informed consent products |
| Certification of active substance master file (ASMF) |
| Shorter timeline for MRP and DCP – what is the impact bearing in mind the market protection period? |
| Repeat use procedure (RUP) – legal basis for administrative zero-day MRP/RUP to prevent or address shortages |
| Establish legal basis for a platform for EMA to facilitate alignment of evidence requirements |
| Building in structured exchanges to ensure that the advice given is taken into account by the other bodies |
| Efficient governance of European Medicines Regulatory Network |
| Digitalisation through electronic submissions, variations to MA (see below) |
| Electronic submission of applications or registrations by companies. |
| Legal basis for Electronic Product Information (i.e. electronic labelling and package leaflet |
| Streamline procedures to facilitate efficient interaction and synergies between different regulatory frameworks |
| Closing potential gaps in Benefits/Risk of combination products where medicinal products have the primary role |
| Introducing joint scientific advice for developers of combination products |
| Data sharing for centrally authorised medicines with downstream decision makers |
| Increase collaboration between MS and trusted strategic partners to ensure better supervision |
| Additional leverage of regulators on summary of product characteristics (SmPC) |
| Increase or optimise the regulatory support to SMEs, academia and public innovators |
| Address availability issues related to radiopharmaceuticals |
| **Empowering new concepts** |

| Streamlining proposals |
|---|
| Strengthen the environmental risk assessment (ERA) |
| Empower regulatory authorities to access raw data |
| Use experts outside national competent authorities to ensure capacity and expertise for assessment |
| Opening certain procedures for third country participation to strengthen global attractiveness |
| Adapt where necessary the regulatory system to support the use of new concepts including real world evidence |
| Information from application dossiers available to authorities |
| Introduce an EU-wide centrally coordinated process for early dialogue |
| Create an expert group to give advice/guidance on UMNs |
| Creation of an emergency use authorisation (EUA) at EU level |

Table 69 presents our light touch assessment of each of these horizontal measures. There are 10-15 specific examples of proposals that would abolish certain current procedures, which have been found to be of limited effectiveness as regards their original objectives (e.g. the sunset clause and medicines shortages) or otherwise largely duplicative (e.g. risk management plans for generics). There are a similar number of proposals to improve the level of coordination, integration and harmonisation of the many working parts of the overall regulatory ecosystem, which are often intertwined with proposals to make fuller use of digital solutions across the system. There are also several measures that relate to growing concerns around new types of products and production processes, which are raising questions about where they fit in the overall regulatory architecture. Challenges are particularly evident around: Advanced therapy medicinal products (ATMPs); Combinational products; Products containing genetic modified organisms (GMOs).

Several concepts overlap with the issues raised through the IA consultations, and these are addressed briefly here and in the main body of the IA report (e.g. the abolition of the need to renew marketing authorisations after 5 years). Most of the individual proposals will only be considered here in this technical annexe.

## A.7. The strengths and weaknesses of the various proposals

Table 69 presents our qualitative assessment of the 20 or so streamlining measures and Table 70 presents our assessment of a further 10 horizontal measures that relate to new regulatory concepts and structures.

The treatment has included a brief review of what was found in the related evaluation of the EU general pharmaceutical regulation and the Impact Assessment consultation and literature review. Column three provides a synopsis of any advice or feedback from the Impact Assessment stakeholder workshop, and in particular Break Out Group 4, which focused on regulatory burden and flexibility. The final two columns provide qualitative reflections on the likely direction and intensity of future costs and benefits. The study team has sought to identify data and studies that would help to quantify and monetise these impacts, however, the proposals are so particular in their design, that we have been unable to find any relevant data or statistics to support a more granular cost benefit analysis. This absence of data holds even where proposals relate to major development initiatives (e.g. the EMA's digital transformation

programme, which is being implemented by around 80 FTEs) or existing legislative activities that have been evaluated (e.g. the EMA's international cooperation programmes and joint inspections have been evaluated, but no attempt was made to quantify costs or benefits).[113]

We have assessed each proposal against the current situation (baseline) using the same 7-point scale used in the assessment of the policy options, however, with such highly particular measures and no or few data, these assessments have had to be more cautious. We have had to be content for the most part in signalling the direction of costs or benefits with a single plus or minus, as there is simply no basis for determining likely real costs or benefits. In two or three instances, we have assigned two pluses or two minuses, where the proposal relates to a process or activity that is extensive and where our evaluation or impact assessment have picked out the issue as a source of substantial additional costs, time delays or other inefficiencies.

Based on our assessment of this long list, the biggest opportunities for efficiency gains appear to relate to the abolition of various redundant procedures (e.g. 5-yearly renewals), increased integration and collaboration among regulators within and beyond the EU and the need to pursue digitisation in a more determined and holistic manner.

Several points emerge from our assessment of this long list of proposals, whereby the feedback from our wider consultations and literature reviews suggests that these proposals may need to be appraised finally based on a more strategic view of the organisation and resourcing of the overall ecosystem. We see a risk in principle that this elemental approach could lead to piecemeal implementation of the easier fixes, and miss the opportunity to achieve more substantive and lasting improvements:

- The overall system is complex and in danger of becoming more so, and that creating new coordination units or advisory structures is likely to add to the costs and the confusion, without bringing any substantive improvements in functional effectiveness. Our consultations revealed widespread criticism by industry as regards the complexity, rigidity and levels of duplication that the experience with the current system. While these stakeholders can offer numerous examples of difficulties experienced or delays in decision making, they were unable to quantify these inefficiencies overall. Their concerns are echoed by the regulators too, who point to the challenges of fragmentation and resourcing that accompany the EU regulatory model, as compared with the more centralised and integrated US system. There are also concerns being expressed publicly by the chair of the CHMP who told the DIA Europe 2022 conference delegates that the EMA struggles to do its job as a result of its limited resources and its reliance on experts from national regulators to carry out a large part of the work of the committees, given these experts have day jobs and may not be available or allowed to invest the time needed. He noted the duplication of regulatory work across the EU, with numerous regulators carrying out their own reviews of the same products, between sectors and across countries, even within the EEA. The concerns about resourcing, complex committee structures and organisational efficiency were underlined in another presentation, by the head of the EMA's regulatory science and innovation task force, noting problems with approval times. He commented on the use of the clock-stop methodology, which was hiding issues with turnaround times. He also cited the study carried out for EFPIA looking into the 67-day

[113] https://www.ema.europa.eu/en/documents/other/programme-rationalise-international-good-manufacturing-practice-inspections-active-pharmaceutical/active-substance-manufacturers-terms-reference-procedures-participating-authorities_en.pdf

decision making process (33-198 days in practice)[114] at the EC for the issuing of a marketing authorisation decision following the CHMP opinion, and whether it could be shortened.

- The many proposals for organisational reform and digitalisation should be considered together, in the round, with a view making a step change in the level of systemic integration, data sharing, collaborative working and the findability of relevant data and information from across the system.
- Many of these proposals have merit and could be taken forward to the benefit of the system overall, however, it is not clear that many should be a matter for the regulation specifically, inasmuch as they have no need to be detailed specifically in the primary legislation and possibly not even in the accompanying technical guidelines and other 'soft law.' Most of the proposals are about the organisational coherence and dynamism of the whole regulatory system and its integration with other contiguous areas of regulator interest in the health, environment, innovation, and industrial policy realms. There is a risk that hardwiring these elements in the legislation will reduce the long-run effectiveness of the overall ecosystem, adding costs rather than adding speed, efficiency, and agility.

*Table 69 Qualitative assessment of proposals for streamlining*

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| Abolish the sunset clause for all medicinal products | Evaluation revealed feedback suggesting this procedure had not been used greatly<br>EMA monitors withdrawals (I think), which relate to all regulatory pathways and can be triggered by EU / MS regulators | Industry sees little added value in this procedure, which would create some small savings<br>National regulators are more positive about having an ability to formally register that a medicine has been withdrawn and thereby close a file | No quantitative data identified<br>No substantive costs expected (+/-) | No quantitative data identified<br>Would reduce costs to a very limited degree for MAHs (+) |
| Abolish requirement for renewal of marketing authorisation for all medicinal products | Evaluation confirmed this was problematic<br>IA feedback | Almost universal support for this proposal<br>The 2-3 environmental groups in the room disagreed | No quantitative data identified<br>No substantive costs expected (+/-) | No quantitative data identified<br>There would be substantial time-related cost savings for regulators and industry (++)<br>(could we use pharmacovigilance fees as a proxy?) |
| Abolish the additional monitoring requirement and accompanying black symbol. | Eval: No feedback<br>IA: not asked<br>The EMA maintains a current list of | The EFPIA delegation suggested they would be supportive of this proposal | No quantitative data identified<br>No substantive costs expected (+/-) | No quantitative data identified<br>There would be time-related cost savings for |

[114] https://www.vintura.com/news/every-day-counts-improving-regulatory-timelines-to-improve-time-to-patient-access-across-europe/

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| | medicines subject to additional monitoring (c. 375) and black label | No other delegates offered any remarks | | regulators and industry (+)<br>(could we use pharmacovigilance fees as a proxy?) |
| Abolish risk management plans for generics, biosimilars, hybrid and informed consent products, unless the reference medicinal product has requirement for additional risk minimisation measure in its risk management plan or unless specifically requested for generics etc. | Eval: No feedback<br>IA: asked as part of a composite question, which received a very strong positive response from industry (and regulators | RMPs for generics were not discussed in BG4 | No quantitative data identified<br>The introduction of a risk-based approach to the development of RMPs should not create any meaningful additional costs, beyond the initial costs to develop, pilot and refine a robust system (-) | No quantitative data identified<br>The introduction of a risk-based approach to the development of RMPs should deliver cost savings to the generics industry (++) |
| Certification of active substance master file (ASMF) – an independent procedure prior to application for marketing authorisation for generics | Eval: No feedback<br>IA: not asked | Medicines for Europe said they support this proposal 'very strongly,' but it didn't attract wider comments | No quantitative data identified<br>The design and implementation of this new certification system would create additional one-off / ongoing costs for regulators (-) | No quantitative data identified<br>A certified file may reduce the need for generics companies to prepare a separate document (+) |
| Shorter timeline for MRP and DCP – what is the impact bearing in mind the market protection period? | Eval: No feedback<br>IA: not asked | Not discussed | No quantitative data identified<br>Shortening timelines implies more resources and or further simplification of procedures by regulators (-) | No quantitative data identified<br>Industry generally benefits from shorter decision-making periods (+) |
| Repeat use procedure (RUP) – legal basis for administrative zero-day MRP/RUP to prevent or address shortages | Eval: No feedback<br>IA: not asked<br>The current RUP arrangements allow member states up to 90 days accept an assessment by the reference member state | Not discussed | No quantitative data identified<br>Creating this exceptional legal basis would require national regulators to develop / agree / implement 'emergency' assessment procedures, which will create additional costs | No quantitative data identified<br>Accelerated approval in an EU MS of an alternative medicine(s) authorised in another MS may help to address critical shortages, to the benefit of patients (+) |

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| | | | at the design stage and would create additional costs and risks at each time of use (-) | |
| Establish legal basis for a platform for EMA to facilitate alignment of evidence requirements through parallel scientific advice (building on mechanisms introduced by the HTA Regulation) | Eval: No feedback<br>IA: not asked<br>The chair of the CHMP presented a paper on regulatory governance at the DIA 2022 Conference, where he talked about duplication of efforts within EMA and between EMA and other regulators | Not raised as an issue by stakeholders | No quantitative data identified<br>There would be costs – and political challenges – involved in designing, setting up and maintaining a more open and integrated system for obtaining, sharing and reusing scientific advice across regulators (-) | No quantitative data identified<br>There could be substantial efficiency gains – and speed enhancements – across the system (++) |
| Building in structured exchanges to ensure that the advice given at each step of the development is known and taken into account by the other bodies (e.g. scientific advice given by EMA should be aligned with the authorisation processes of the clinical trials related to this advice). | Eval: No feedback<br>IA: not asked<br>Harald Enzmann chair of the CHMP presented a paper on regulatory governance at the DIA 2022 Conference, where he talked about duplication of efforts within EMA and between EMA and other regulators | Industry delegates cited the work done by their various representative bodies on the biggest opportunities for streamlining, from an industry perspective, which include<br>1. Iterative regulatory advice and agility<br>2. Expedited, flexible and dynamic assessment and decision-making pathways.<br>The top 5 issues were identified through a poll at the DIA 2022 Conference | No quantitative data identified<br>There would be costs – and political challenges – involved in designing, setting up and maintaining a more open and integrated system (-) | No quantitative data identified<br>There could be substantial efficiency gains – and speed – across the system (++) |
| Efficient governance of European Medicines Regulatory Network | Eval: No feedback<br>IA: not asked<br>The European Medicines Regulatory Network strategy to 2025 includes | Not discussed | No quantitative data identified<br>Strengthened coordination would bring some small additional costs (ongoing) for regulators, for | No quantitative data identified<br>Strengthened coordination may deliver more timely / effective / even contributions to the |

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| | a section on governance, operational excellence and sustainability. But no references to or expected scale of impact.[115] | | secretariat / governing body / individual members (-) | work of the network (+) |
| Digitalisation through electronic submissions, variations to MA (see below) | Eval: industry and regulators argue that the regulatory system had fallen behind on digital<br>IA: all stakeholders are strongly supportive of further digitalisation to improve timeliness, efficiency and consistency<br>The EMA is investing heavily in digital transformation, and is closely involved with wider projects on digital health. EMA Digital Business Transformation task force (17 FTE); EMA Data Analytics and Methods Task Force (62 FTEs)[116] | All stakeholders were supportive of the need for the regulatory system to exploit digitalisation more fully<br>Variations to the MA were noted as being a major source of administrative costs for industry<br>Several contributors signalled a note of caution around digitalisation: there is substantial work in hand already by EMA and others; and there is a need for a wide-ranging and holistic approach to digitalisation that goes far beyond the regulation.<br>Digitalisations also needs to be properly planned, funded and overseen | No quantitative data identified<br>The incremental improvement to the submission of applications and variations may be relatively low cost and could possibly be done without impeding wider ambitions<br>There would be some limited one-off costs involved with digitalisation of submissions (-)<br>The ongoing costs would be recharged as fees to applicants / MAHs, increasing charges by a small fraction (-) | No quantitative data identified<br>Improved portals for submissions and variations would provide efficiency gains / savings for applicants and MAHs (+++)<br>… and for regulators (+) |
| Electronic submission of applications or registrations by companies. This would cover not only applications for marketing authorisation and variations, but also possibly for manufacturing or wholesale distribution authorisation as well as registrations of manufacturers/importers of active substance and of brokers. | Eval: industry and regulators argue that the regulatory system had fallen behind on digital<br>IA: all stakeholders are strongly supportive of further digitalisation to improve | All stakeholders were supportive of the need for the regulatory system to more fully exploit digitalisation<br>Variations to the MA were noted as being a major source of administrative costs for industry | No quantitative data identified<br>The incremental improvement to the submission of applications and variations may be relatively low cost and could possibly be done without | No quantitative data identified<br>Improved portals for submissions and variations would provide efficiency gains / savings for applicants and MAHs (++)<br>… and for regulators (+) |

[115] https://www.ema.europa.eu/en/documents/report/european-union-medicines-agencies-network-strategy-2025-protecting-public-health-time-rapid-change_en.pdf

[116] https://www.ema.europa.eu/en/documents/report/final-programming-document-2022-2024_en.pdf

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| | timeliness, efficiency and consistency | Several contributors signalled a note of caution around digitalisation: there is substantial work in hand already by EMA and others; and there is a need for a wide-ranging and holistic approach to digitalisation that goes far beyond the regulation.<br><br>Digitalisations also needs to be properly planned, funded and overseen | impeding wider ambitions<br><br>There would be some limited one-off costs involved with digitalisation of submissions (-)<br><br>The ongoing costs would be recharged as fees to applicants / MAHs, increasing charges by a small fraction (-) | |
| Legal basis for Electronic Product Information (i.e. electronic labelling and package leaflet to replace the paper one for hospital administered products and products administered by healthcare professionals). | Eval: no feedback<br><br>IA: all stakeholders support the move to ePI | All stakeholders support the move to ePI, while noting it may take time and there are issues of digital access / literacy<br><br>People noted there is substantial activity in this space already, that needs to be learned from.[117]<br><br>The move to digital also creates opportunities for a more diverse / effective means by which to communicate stator information such that patients are more likely to see this information and understand it<br><br>It was suggested that the legislation should facilitate this trend by considering ePI equivalent to paper leaflets | No quantitative data identified<br><br>The numerous pilot initiatives being run at EU, member state and international levels suggest that while the electronic solution may be relatively simple to put in place, the creation of an integrated / safe system is likely to be costly / challenging (--) | No quantitative data identified<br><br>Electronic product information would provide numerous advantages in terms of the ease of access for the majority of patients with opportunities to improve readability and assistive technologies and to ensure information is kept up to date and in line with the SmPC(++) |
| Streamline procedures to facilitate efficient interaction and synergies between different but related regulatory frameworks e.g. Medical Device (for certain | Eval: No feedback<br><br>IA: Strongly positive feedback from | Delegates flagged the presentations by regulators at the DIA 2022 conference openly calling for reform of | No quantitative data identified<br><br>Devising and implementing new structures | No quantitative data identified<br><br>Improved interaction may reduce occasional |

[117] https://www.eahp.eu/practice-and-policy/ehealth-and-mhealth/ePIsurvey

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| type of products) and Health Technology Assessments. | industry and regulators on this aspect | structures and processes both within the core medicines regulators (EMA) and between EMA and others | to facilitate improved interaction would bring one-off costs and ongoing costs for regulators seeking to ensure that all actions / decisions are fully joined up with other affected regulators (-) | delays and duplication of effort (+) |
| Closing potential gaps in Benefits/Risk of combination products where medicinal products have the primary role | Eval: no feedback<br>IA: not asked directly<br>Stakeholders were strongly positive about the potential benefits of the introduction of coordination and advisory mechanisms to facilitate the timely / consistent assessment of the growing number of combination products | Delegates were supportive of the need for a regulatory ecosystem that didn't have gaps and was well-integrated (e.g. combinations with medical devices) and future proof (e.g. AI) | No quantitative data identified<br>The new mechanisms would bring additional costs for the EMA and other regulators (-) | No quantitative data identified<br>Closing gaps would help reduce some unnecessary delays in assessments for applicants (+) |
| Introducing joint scientific advice for developers of combination products | Eval: no feedback<br>IA: not asked | Not discussed | No quantitative data identified<br>The creation of a mechanism for providing joint scientific advice may create some additional costs for regulators with one-off costs to set up protocols and guidelines such that the structure / process can be implemented as necessary and consistently (-) | No quantitative data identified<br>The creation of a mechanism for providing joint scientific advice may reduce occasional difficulties working across committees and regulators, and thereby create some small efficiency gains for regulators and some time savings for applicants (+) |
| Data sharing for centrally authorised medicines with downstream decision makers in compliance with | Eval: no feedback<br>IA: not asked | Delegates acknowledged the importance of a holistic approach | No quantitative data identified | No quantitative data identified |

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| GDPR, taking into account commercially confidential information and the EHDS proposal | | to ehealth including data sharing | Setting up an EU-wide system to facilitate downstream access to authorised medicines data would be challenging and may be quite costly to implement and operate for EMA (fees charged to HTAs) (--) | Improved access to data by HTAs etc may facilitate their assessment processes and allow occasional queries to be answered by direct interrogation of those data. However, it is not clear how significant such data are to effective / expeditious decision making (+)<br><br>In the longer term, it may benefit MA holders through an ability to re-use large parts of a dossier for an HTA assessment from their submissions to the assessment agency (+) |
| Increase collaboration between MS and with trusted strategic partners to ensure a better supervision while saving resources by: developing collaborative inspection programmes and expanding the existing ones on API and sterile product manufacturing sites; increase the reliance on inspection reports from trusted authorities, e.g. US FDA, MHRA (concept paper on this); extra inspection capacity and build more efficient specialised inspector capability (concept paper on this) | Eval: no feedback<br><br>IA: not asked<br><br>There is substantial work ongoing, including for example the EMA-coordinated International Collaboration on GMP inspections, the ICMRA (International Coalition of Medicines Regulatory Authorities), and through the EMA's ad hoc work with non-EU regulators through its thematic topics or 'clusters.'[118] | International cooperation was not discussed at length during the workshop, however, there was an acknowledgement of the potential for reducing burden through greater cooperation internationally | No quantitative data identified<br><br>(the EMA has published several reviews of its international programmes, but none has sought to quantify the costs and benefits)[119]<br><br>The EU pharma legislation may need to explicitly approve the legitimacy of this global collaborative approach. Beyond providing the necessary permission, most of the relevant activities would | No quantitative data identified<br><br>The EMA's international collaboration on inspections states that there are important gains from increased cooperation and collaboration that derive from pooled resources, reduced duplication, greater consistency, and greater scope / reach of inspections.<br><br>There is an expectation that the revisions to the legislation will seek to extend the scope of EU interests in the performance of global supply chains and that the need for |

[118] https://www.ema.europa.eu/en/partners-networks/international-activities/cluster-activities

[119] https://www.ema.europa.eu/en/documents/other/programme-rationalise-international-good-manufacturing-practice-inspections-active-pharmaceutical/active-substance-manufacturers-terms-reference-procedures-participating-authorities_en.pdf

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| | | | fall outside the legislation.<br>Creating a more substantive international collaboration programme for inspections (etc.) would bring some additional design / set-up costs and would bring costs associated with the EMA's oversight / coordination of EU and EU MS participation in this global programme (-) | collaboration will become more urgent and demand greater reciprocity. This may become more of an international relations issue, however, it should also deliver efficiency and quality benefits for the system overall (+) |
| Additional leverage of regulators on summary of product characteristics (SmPC) based on evidence on safety and efficacy (i.e. to adapt the product information without full consent of the marketing authorisation holder). This adaptation could be during the assessment of the application for marketing authorisation or during post-authorisation procedures. | Eval: no feedback<br>IA: not asked<br>Our consultation did consider the potential benefits of a more harmonised and regular process for updating SmPC linked with older antimicrobials, which was viewed positively. | Not discussed | No quantitative data identified<br>The intensification / acceleration of the established process for notifying / updating SmPCs would bring additional costs for industry and for regulators (-)<br>The suggestion that regulators – or their agents – would update the product information without the consent of the MAH, even as a last resort, would be resisted by industry (--) | No quantitative data identified<br>With no view on the nature and extent of the problem, it is not possible to determine what benefits such a change would deliver, even qualitatively or directionally (+/-) |
| Increase or optimise the regulatory support to SMEs, academia and public innovators to bring their innovative products to market more efficiently. Similar measures for academic and public innovators be introduced as for SMEs, e.g. fee reductions, more advice | Eval: the evaluation found a positive view regarding the support provided to SMEs, in terms of both additional advice and fee reductions | Industry delegates underlined their wish for a much more agile and interactive regulatory system. They noted this dynamic approach was especially important for smaller businesses | No quantitative data identified<br>This would have some limited additional cost and resource implications for the EMA and its partner national regulators, in setting up and delivering | No quantitative data identified |

| Streamlining proposals | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| | IA: this question was not asked specifically | On a related matter, industry delegates signalled caution about the possible risks of regulators seeking to encourage engagement by non-commercial actors through the creation of less-rigorous pathways<br>The healthcare and academic communities did not offer a view on the needs / solutions for optimising support | additional, on-demand bespoke advice for SMEs, academics and non-commercial organisations (-)<br>Any further fee reductions would also<br>There may be limited additional demand for such services, so the ongoing costs | |
| Address availability issues related to radiopharmaceuticals. Better define the scope to avoid overregulation of radiopharmaceuticals as per defined in the evaluation. | Eval: no feedback<br>IA: not asked | Not discussed directly, beyond a short remark about these types of therapies having a potentially high environmental risk and needing to be considered by the pharma legislation based on benefit-risk to patients as well as to the environment | No quantitative data identified | No quantitative data identified |

*Table 70 Assessment of horizontal measures that may support new regulatory concepts and structures*

| Empowering new concepts | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| Strengthen the environmental risk assessment (ERA), as appropriate, and assess whether it should be part of the risk-benefit assessment; assess whether the introduction of risk mitigation measures, where needed, would be enough to address the environmental concerns; ensure no duplication of testing is carried out; aim at the harmonisation in the way ERAs are carried out in all Member States, while assessing what entails to have a common data basis, accessibility and transparency of environmental information for all products. | Stakeholder feedback revealed broad support for doing more with ERA<br>Public authorities, CSOs and health services believe this is important<br>Industry is slightly positive | Industry is supportive of a strengthened ERA, but suggests the assessment should be risk-based and focus on the APIs rather than product<br>Industry supportive of more harmonisation and more transparency (EPARs)<br>CSOs noted that there is less work done – and more gaps on older APIs – on pharma substances than in other sectors | No quantitative data identified<br>A strengthened ERA would bring additional limited costs for all MA applicants (-)<br>A more careful assessment of an expanded ERA and a fuller record of that assessment may bring limited additional costs for regulators (-) | No quantitative data identified<br>Greater transparency and reuse would avoid duplication of effort and bring some limited savings for industry and regulatory bodies (+)<br>Given the thicket of other applicable EU legislation, this initiative would not add much value from an environmental perspective (+/-) |

| Empowering new concepts | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| | | Industry noted that EU-based manufacturers are responsible for a fraction of all releases (2%); perhaps not the case globally<br><br>Industry noted that there is substantial other legislation that address these issues (inclusion in the pharma legislation is less relevant) | | |
| Empower regulatory authorities to access raw data, e.g. in cases where a regulatory submission include only aggregated data or to monitor the effectiveness following post-marketing authorisation. Competent authorities for medicines authorisation to access raw data of applicants or marketing authorisation holders to review/analyse this data themselves. | Eval: no feedback<br><br>IA: not asked | Not discussed directly<br><br>There was general support by industry and regulators and CSOs for the regulatory system to improve its management, re-use and access to regulatory data overall<br><br>Given the likely costs and risks to privacy / confidentiality, industry may object to the proposal that regulators should have the authority to insist on having routine access to raw data to support their own assessment work | No quantitative data identified<br><br>Some limited additional costs for industry that would follow a need to curate / archive 'raw data' securely enough to grant regulators managed access (-)<br><br>Some additional costs associated with regulators having to resource these occasional and ad hoc deep dives (-) | No quantitative data identified<br><br>The need to make raw data open to regulators may have a small positive impact on the curation of data and the consistency of the underpinning work processes (+)<br><br>There may be some limited gain for applicants if regulators can clarify at least some technical questions that arise during assessments from direct access to micro-data. However, there is a risk that such open and unguided access to data would be likely to generate more queries rather than fewer. (+)<br><br>There may be a timing benefit if queries can be resolved more easily and quickly through direct access. (+) |
| Use under certain conditions experts outside national competent authorities to ensure capacity and expertise for assessment | Eval: no feedback<br><br>IA: not asked directly<br><br>EMA / NCA resourcing pressures were | Not discussed directly<br><br>Delegates suggested that the EU regulatory model is under pressure and that | No quantitative data identified<br><br>Regulators would have to fund the creation and management of a large pool of | No quantitative data identified<br><br>A standing college of experts would help to reduce delays in assessments |

| Empowering new concepts | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| | raised in the consultation | resourcing issues are causing many delays and disadvantaging EU businesses | appropriately qualified experts and pay their fees (cf DG RTD's pool of expert evaluators that support the review of calls for proposals (-) | relating to capacity bottlenecks. It is unknown how often capacity is the root cause of significant delays (+)<br>External experts would help to reduce the unevenness of workloads across NCAs, with several EU member states providing a disproportionate share of capacity for scientific assessments (+) |
| Opening certain procedures for third country participation to strengthen global attractiveness | Eval: no feedback<br>IA: not asked | Not raised as an issue | No quantitative data identified<br>The scope or purpose is unclear, however, there would be additional costs to the regulators if this expands enquiries / applications overall (and that expansion tracks back to organisations with limited prior knowledge of the EU regulatory context (-) | No quantitative data identified<br>The scope or purpose is unclear, so benefits cannot be understood beyond the general notion of increased global attractiveness (+/-) |
| Adapt where necessary the regulatory system to support the use of new concepts including real world evidence, health data while keeping the standards of Q/S/E | Eval: no feedback<br>IA: RWE was raised in the consultation as being an important trend that will benefit regulatory systems in future<br>The EFPIA study on real-world data and real-world evidence found that companies are making use of RWD (84%) albeit less than half had used these data in | Industry delegates made clear they are advocates of regulators being open to new concepts including RWE<br>Regulators / CSOs did not offer a view on this question | No quantitative data identified<br>Regulators may incur some limited one-off costs associated with the development of new guidelines (-)<br>There may be some inefficiencies / delays initially as committees build experience of using these new concepts and calibrate the value of novel data sources. (-) | No quantitative data identified<br>Some timing and efficiency gains for MA applicants and MA holders, but impacts may be quite limited in the medium term as these data types are generally used as complements to other data<br>Should result in regulators being able to take more confident / speedier decisions on applications<br>Should improve quality / efficiency of post marketing |

| Empowering new concepts | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| | regulatory documents[120] | | | authorisation activities (+) |
| Information from application dossiers, including for nationally authorised products, as regards the manufacturing sites for finished products and APIs, available to authorities and make data held by regulatory agencies and manufacturers available using the EHDS framework. | Eval: no feedback<br>IA: not asked | Not raised as an issue directly, but as noted above there was general support across stakeholders for enhancing the use of digital solutions to facilitate increased data sharing and re-use<br>There was strong support for developing structures / platforms to facilitate increased worksharing | No quantitative data identified<br>There would be costs associated with such a system for industry, in ensuring its data are held and curated in a manner that would facilitate this more open approach (-)<br>There would be costs associated with the design and implementation of such a system for EMA and NCAs, even if it were inked with the existing EHDS infrastructure (-) | No quantitative data identified<br>This data sharing would be beneficial to post authorisation activities, providing improvements in speed / convenience of access, reuse and supporting collaborative working (+) |
| Introduce an EU-wide centrally coordinated process for early dialogue and more coordination among clinical trial, marketing authorisation, health technology assessment bodies, pricing and reimbursement authorities and payers for integrated medicines development and post-authorisation monitoring, pricing and reimbursement. When providing scientific advice to developers, at its scientific discretion EMA can take into account this early dialogue and coordination. | Eval: no feedback<br>IA: not asked | Industry delegates underlined their wish for a much more agile and interactive regulatory system. They noted this dynamic, interactive approach was especially important for smaller businesses<br>A delegate suggested that academia and SMEs should have access to early agile and maybe more informal advice (price is prohibitive for academia). They noted that the INTERACT meeting with the FDA is quite efficient for early discussion: a phone call with a simple briefing package allows for early brainstorming | No quantitative data identified<br>Early dialogue may place additional pressures on EMA finances and resourcing (and the regulatory network)<br>Doing this EU-wide would bring substantial additional costs (--) | No quantitative data identified<br>Early dialogue is seen by industry as a major opportunity to improve developers' abilities to deliver mature / comprehensive applications that are more likely to be assessed quickly (and positively). Doing it EU wide would be a strongly positive approach (++)<br>A more coordinated approach should result in some savings for national authorities (+) |

[120] https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.2103

| Empowering new concepts | Consultation | IA workshop (BG4) | Costs | Benefits |
|---|---|---|---|---|
| | | and then early directions in regard to potential classification and regulatory considerations | | |
| Create an expert group to give advice/guidance on UMN – cross-sector involving health technology assessment bodies (via the Coordination Group of HTA bodies set up under the new HTA Regulation), pricing and reimbursement bodies, patients, and academic representatives. | Eval: no feedback<br>IA: not asked directly | Not discussed | No quantitative data identified<br>Introducing a regulatory incentive specifically for UMNs will require the creation of an agreed set of definitional criteria or lists of UMNs. This will require additional guidance and possibly additional advice for assessment bodies.<br>A cross-sector working group may reduce the operational effectiveness and timeliness of such a body, from the perspective of medicines regulators specifically (-) | No quantitative data identified<br>The creation of a standing group to give advice on UMNs to multiple regulators and pubic bodies may produce some efficiency gains and support a more consistent implementation, with a potential for cost sharing across stakeholders (+) |
| Creation of an emergency use authorisation (EUA) at EU level as an additional tool to support faster use of medicines without a marketing authorisation during pandemic situation | Eval: no feedback<br>IA: not asked directly | Not discussed | No quantitative data identified | No quantitative data identified |

## A.8. Cost benefit analysis for the horizontal measures

### *A.8.1. Qualitative assessment of costs and benefits relating to the pivotal horizontal measures*

Table 71 presents an overview of the 10 pivotal measures and our qualitative assessment of the costs and benefits for each proposal, which we have analysed in Table 72 below.

*Table 71 Overview of the pivotal horizontal measures and their expected costs and benefits*

| Description | Qualitative assessment of costs and benefits |
|---|---|
| 1. **Streamlining of procedures**, including avoiding duplicative processes (including GMO requirements, prioritisation of | Benefits: the various streamlining procedures proposed would deliver direct cost savings to both industry and regulators. Abolition of risk management plans may be the |

| | |
|---|---|
| applications, better coordination within the regulatory network; renewal of marketing authorisation, PhV requirements – RMPs for generics + black symbol):<br>– Abolish the sunset clause for all medicinal products<br>– Abolish requirement for renewal of marketing authorisation for all medicinal products<br>– Abolish the additional monitoring requirement and accompanying black symbol.<br>– Abolish risk management plans for generics, biosimilars, hybrid and informed consent products, unless the reference medicinal product has requirement for additional risk minimisation measure in its risk management plan or unless specifically requested for generics etc.<br>– Certification of active substance master file – an independent procedure prior to application for marketing authorisation for generics | most beneficial to generics companies and national regulators. These various procedures bring occasional costs for most companies at some point in time (++)<br>Costs: the proposed abolition of various duplicative procedures should not result in any meaningful additional costs for any stakeholders. The creation of a certification system for the ASMF would bring one-off costs for the design and implementation of the enhanced procedure, falling on regulators |
| **2.** Enable an **accelerated mutual recognition procedure** (MRP) within the EU, Enable a (more) efficient Repeat Use Procedure, For EU authorities to reduce the administrative and cost burden submission of post approval changes<br>– Shorter timeline for MRP and DCP – what is the impact bearing in mind the market protection period?<br>– Repeat use procedure (RUP) – legal basis for administrative zero-day MRP/RUP to prevent of address shortages | Benefits: as accelerated procedure would benefit the generics industry directly and possibly health payers indirectly, with generic competition being brought forward by a month or so in a proportion of cases. A legal basis for a zero-day MRP may help to address critical shortages to the benefit of patients, where there is an alternative medicine(s) authorised in another MS but not in the MS in question. (++)<br>Costs: the accelerated MRP should be achieved through streamlining and harmonisation of procedures (and various improvements to digital infrastructure, worksharing and pan-EU data services), so should bring few if any additional costs for regulators. The zero-day RUP would require some limited one-off costs for the network / regulators to prepare a detail design and associated procedures that all member states would support. (--) |
| **3.** Efficient governance of European Medicines Regulatory Network: (not for assessment) formalize the structure of the network including role and tasks of Heads of Medicines Agencies; efficient cooperation of EMA committees – simplify processes of EMA committees when several are involved. Strengthen system of inspections to better use resources<br>– Increase collaboration between MS and with trusted strategic partners to ensure a better supervision while saving resources by :<br>– develop collaborative inspection programmes and expand the existing ones on API and sterile product manufacturing sites<br>– increase the reliance on inspection reports from trusted authorities, e.g. US FDA, MHRA (concept paper on this)<br>– support extra inspection capacity and build more efficient specialized inspector capability (concept paper on this) | Efficient governance<br>Benefits: more efficient governance of the regulatory network should reduce the average elapsed time between initial application and a recommendation, which will benefit developers by creating the potential for earlier market launch and patients indirectly. It should also bring efficiency gains for regulators. Better coordinated cross-border and international inspections should provide efficiency gains for regulators (+++)<br>Costs: Strengthened governance may bring some small additional costs for regulators associated with an expanded coordination function (-) |

| | |
|---|---|
| **4.** Streamline procedures to facilitate **efficient interaction and synergies between different but related regulatory frameworks** e.g. Medical Device (for certain type of products) and Health Technology Assessments.<br>– Closing potential gaps in B/R of combination products where medicinal products have the primary role<br>– Introducing joint scientific advice for developers of combination products<br>– BTC framework could be added as well. | Efficient interaction between related regulatory frameworks<br>Benefits: more efficient interaction across regulatory frameworks should reduce the average elapsed time between initial application and a recommendation for a proportion of applications (e.g. combination products), which will benefit developers by creating the potential for earlier market launch. It should also bring efficiency gains for regulators. (++)<br>Costs: Devising and implementing new structures to facilitate improved interaction among regulators would bring one-off costs associated with the design / implementation of those new structures and ongoing costs for regulators of running those coordination mechanisms seeking to ensure that all actions / decisions are fully joined up with other affected regulators (-) |
| **5.** Legal basis for the network to analyse real world evidence, **create computing capacity, store and manage large data sets and to share the data** with the HTA Coordination Group as set out in Regulation 2021/2282 and Pricing and reimbursement authorities, in compliance with GDPR, taking into account commercially confidentially information and the EHDS proposal. | Real world evidence and a pan-EU data service<br>Benefits: a more inclusive view of allowable data should help regulators with both the assessment of applications and various post-authorisation activities. The creation of an integrated online data service accessible by various types of health regulators should bring major efficiency gains for the system overall. (+++)<br>Costs: The EU and regulators may incur significant one-off costs associated with the creation of a new integrated data infrastructure for the regulatory system overall. There will be additional recurrent costs associated with the operation and maintenance of what would be a large and growing data set. (---) |
| **6.** Legal basis for **Electronic Product Information** (i.e. electronic labelling and package leaflet to replace the paper one for hospital administered products and products administered by healthcare professionals). | ePIL<br>Benefits: having a legal basis for ePIL would anticipate and reinforce a trend. Electronic product information would make it easier for healthcare professionals to access comprehensive and up-to-date information on products within different settings. There would be some small environmental benefit in terms of reduced use of paper and less waste, albeit manufacturers would need to run paper and electronic systems in parallel) (++)<br>Costs: manufacturers would incur one-off costs associated with the upgrading of their electronic publishing capabilities. But should otherwise be well placed to expand ePIL provision. Regulators and healthcare systems would incur one-off costs when negotiating the creation of a 'common' EU-wide infrastructure for ePIL and recurrent costs associated with its operation and maintenance. (---) |
| **7.** Electronic submission of applications or registrations by companies<br>– This would cover not only applications for marketing authorisation and variations, but also possibly for manufacturing or wholesale distribution authorisation as well as registrations of manufacturers/importers of active substance and of brokers. | Electronic submission<br>Benefits: manufacturers would see efficiency gains from the introduction of a fully digital submission platform. Regulators would similarly see efficiency gains from a move to digital submissions supporting the re-use of data across functions and committees and for example eliminating the need for committee members to work with large paper files. There would be an environmental benefit too from the reduction in the use of paper. This would provide a small but lasting benefit to the whole industry and to all regulators (++)<br>Costs: manufacturers may incur some very limited one-off costs associated with harmonisation of their data systems with any new templates. The regulators would incur one off costs in creating the new submission system and recurrent costs associated with its operation and maintenance. There |

| | |
|---|---|
| | is already substantial use of online submissions and digital solutions, so while there would be costs for all actors these should be relatively modest (-) |
| **8.** Increase or **optimise the regulatory support** to SMEs, academia and public innovators to bring their innovative products to market more efficiently | Optimise regulatory support SMEs and non-commercial<br><br>Benefits: SMEs would benefit from additional support / scientific advice tailored to smaller developers, which may help them to develop applications with more confidence and with a greater likelihood of a successful opinion. Non-commercial organisations would also benefit from tailored support, as they are likely to have even less experience and internal support when it comes to regulatory matters. Given the growing importance of small biopharma, this expansion in regulatory support could be highly beneficial to startups and innovative therapies. (++)<br><br>According to the latest EMA annual report, requests for scientific advice has been increasing at 5-10% year over the past five years (787 requests in 2020). In 2020, 25% of all requests for scientific advice came from SMEs. The EMA's review of SME support (2020) obtained feedback from 553 SMEs and found the very great majority (80%) judged themselves to be well appraised of the support on offer (fees and advice) and more than 90% judged the support / services to be relevant. The primary requests for improvements related to additional financial discounts and simplified applications<br><br>Costs: the EMA would incur additional costs associated with this expanded and tailored support. The numbers of users may not be especially high, which would contain costs, however, the amount of support required for an average request may be proportionately much greater than would be the case for most developers (-) |
| **9.** Adapt where necessary the regulatory system to **support the use of new concepts** including real world evidence, health data while keeping the standards of Q/S/E | Adapting the system to use new concepts<br><br>Benefits: this would deliver greater regulatory alignment with important developments, improving the speed of decision making and reducing regulatory costs. It would reward developers for using new and emerging types of data within their applications (++)<br><br>Costs: the EMA would incur additional one-off costs associated with the creation of new or expanded guidelines and working methods to tackle new concepts with confidence and consistently. (--) |
| **10.** Introduce an **EU-wide centrally coordinated process for early dialogue** and more coordination among clinical trial, marketing authorisation, health technology assessment bodies, pricing and reimbursement authorities and payers for integrated medicines development and post-authorisation monitoring, pricing and reimbursement. When providing scientific advice to developers, at its scientific discretion EMA can take into account this early dialogue and coordination. | Early dialogue with developers and across regulators<br><br>Benefits: early, iterative regulatory advice and dynamic assessment came out as the top two items on an industry poll (DIA Europe 2022 conference) as regards the areas where they would like to see improvements in regulatory performance. Early dialogue and more coordination should deliver efficiency gains for industry and regulators as well as faster decision making overall (+++)<br><br>Costs: the EMA may incur substantial additional one-off and recurrent costs associated with the move to a more centrally coordinated and dynamic assessment system, covering both the CP and distributed procedures and leading on coordination with other agencies (---) |

Lastly, in Table 72, we have summarised this preceding tabular presentation in a more visual, qualitative assessment of the benefits of each of the 10 pivotal horizontal measures, by key stakeholder group. From this perspective, the most promising horizontal measures – overall, for

all stakeholder groups – are the proposals to improve the governance of the European medicines regulatory network, the development of an integrated, pan-EU data architecture for the regulatory system and an EU-wide, centrally coordinated process for early dialogue.

*Table 72 Qualitative assessment of the benefits of pivotal horizontal measures, by key stakeholder group*

| | Business | EMA | NCAs | SMEs | Health Systems | Environmental |
|---|---|---|---|---|---|---|
| **Streamlining and de-duplication** | | | | | | |
| #1 Streamlining of procedures | H | M | M | H | L | L |
| #2 Accelerated MRP and more efficient RUP | H | L | H | L | M | L |
| #3 Efficient governance of the European Medicines Regulatory Network | H | H | H | H | M | L |
| #4 Facilitate more efficient interaction across regulatory frameworks | M | H | M | M | M | L |
| **Digitalisation** | | | | | | |
| #5 Legal basis to allow network to create an integrated, pan-EU health regulatory data service | M | M | H | H | H | M |
| #6 Legal basis for setting up ePIL system for healthcare professionals | L | M | M | L | M | M |
| #7 Electronic submission of applications | H | H | M | H | L | M |
| **Enhanced support and regulatory flexibility** | | | | | | |
| #8 Optimise regulatory support to SMEs and non-commercial organisation | L | M | L | H | H | L |
| #9 Adaptation of the regulatory system to support the use of new concepts | H | M | M | H | M | L |
| #10 EU-wide centrally coordinated process for early dialogue | H | M | H | H | M | L |

### *A.8.2. Overview of costs and benefits*

Table 73 presents an overview of the costs and benefits associated with the three major categories of horizontal measures identified through the impact assessment. This has been prepared in line with the better regulation guidelines, with the costs presented in line with the standard cost model.

It shows estimated total costs for the pivotal streamlining measures combined fall in the range €1.1bn to €2.5bn. We estimate the total benefits will fall somewhere in the range €2.8bn-€5.8bn. The benefits significantly outweigh the costs for both the lower and upper bound estimates.

The analysis suggests that the proposed streamlining measures are likely to deliver the greatest quantum of benefits, falling in the range €1.5bn-€3.1bn. By contrast the digitalisation measures are likely to be the costliest to implement, albeit with substantial benefits to the efficiency of the regulatory system overall. The analysis suggests the enhanced support measures are likely to be the most affordable (€72m-€108m), and while they will yield a lower overall benefit (€214m-€428m), it is the highest rate of return proportionately.

*Table 73 Overview of the costs and benefits associated with the horizontal measures*

| | **Businesses** | **Businesses** | **EMA** | **EMA** | **NCAs** | **NCAs** | **Totals** | **Totals** | **Totals** |
|---|---|---|---|---|---|---|---|---|---|
| | **one-off** | **recurrent** | **one-off** | **recurrent** | **one-off** | **recurrent** | **one-off** | **recurrent** | **15 years** |
| **Streamlining costs** | | | | | | | | | |
| Direct | | | | | | | | | |
| Enforcement | | | €1.8m - €3.6m | €3.5m-€7.5m | €15m-€30m | €30m-€60m | €16.8m - €33.6m | €33.5m-€67.5m | |
| Indirect | | | | | | | | | |
| Totals | | | | | | | **€16.8m - €33.6m** | **€33.5m-€67.5m** | **€519.3m-€1,046.1m** |
| **Streamlining benefits** | | | | | | | | | |
| Direct | | €15m-€30m | | €3.5m-€7m | | €30m-€60m | | €48.5m-€97m | |
| Indirect | | €55m-€110m | | | | | | €55m-€110m | |
| Totals | | | | | | | | **€103.5m -€207m** | **€1,552.5m -€3,105m** |
| | | | | | | | | | |

| | Businesses | Businesses | EMA | EMA | NCAs | NCAs | Totals | Totals | Totals |
|---|---|---|---|---|---|---|---|---|---|
| | **one-off** | **recurrent** | **one-off** | **recurrent** | **one-off** | **recurrent** | **one-off** | **recurrent** | **15 years** |
| **Digitalisation costs** | | | | | | | | | |
| Direct | | | | | | | | | |
| Enforcement | | | €20m-€50m | €4m-€10m | €100m - €300m | €20m-€60m | €120m-€350m | €24m-€70m | |
| Indirect | | | | | | | | | |
| Totals | | | | | | | €120m-€350m | €24m-€70m | **€480m-€1,400m** |
| **Digitalisation benefits** | | | | | | | | | |
| Direct | | €7.5m-€15m | | €7m-€14m | | €60m-€120m | | €75m-€149m | |
| Indirect | | | | | | | | | |
| Totals | | | | | | | | | **€1,117.5m -€2,235m** |
| | | | | | | | | | |
| **Enhanced support costs** | | | | | | | | | |
| Direct | | €1.6m-€2.4m | | | | | | €1.6m-€2.4m | |
| Enforcement | | | | €4.8m-€7.2m | | | | €4.8m-€7.2m | |
| Indirect | | | | | | | | | |
| Totals | | | | | | | | | **€72m-€108m** |
| **Enhanced support benefits** | | | | | | | | | |
| Direct | | €7.5m-€15m | | €1.75m-€3.5m | | | | €9.25m-€18.5m | |

| | Businesses | Businesses | EMA | EMA | NCAs | NCAs | Totals | Totals | Totals |
|---|---|---|---|---|---|---|---|---|---|
| | one-off | recurrent | one-off | recurrent | one-off | recurrent | one-off | recurrent | 15 years |
| Indirect | | €5m-€10m | | | | | | €5m-€10m | |
| Totals | | | | | | | | | **€214m-€428m** |

Our overall estimates are likely to be understated slightly, as there are likely to be further indirect benefits associated with these measures, and in particular the likelihood of shortening average times for the assessment of applications, which should flow through to marginally earlier access to new medicines and generic competitors for large numbers of EU citizens and patients. We were unable to push these estimates to the point where we were able to quantify the likely benefits to patients, which are likely to be relatively limited in depth but wide-ranging.

Given the scope and diversity of the proposed initiatives and the large numbers of actors that would be involved, we have had to rely on assumptions drawn from the wider literature, to make our monetary estimates. Given the many uncertainties involved with this process, we have used ranges throughout. Our logic and assumptions are detailed in Table 74.

*Table 74 Descriptive overview of the costs and benefits and assumptions associated with the horizontal measures*

| | Description of types of costs and benefits | Assumptions made in quantification | Notes on sources |
|---|---|---|---|
| Streamlining costs | | | |
| Direct | There should be few if any direct costs associated with the various streamlining measures, which would deliver efficiency gains to businesses | | |
| Enforcement | There should be few if any enforcement costs associated with the various streamlining measures, as the principal regulatory measures relate to the abolition of procedures that are duplicated elsewhere in the system | We have assumed the one-off indirect costs might amount to 0.5-1% of EMA annual expenditure (€365m in 2020) and NCA annual expenditure (€3bn), spread over 2-3 years. We have assumed recurrent annual costs would be slightly higher, 1-2%. | We have found no quantitative estimates of the likely costs of these proposed measures through our consultations or literature reviews, and have had to make assumptions about likely level of effort and multiplied this by EMA / NCA budgets |
| Indirect | There will be no substantive indirect costs from the proposed streamlining measures | | |

| | Description of types of costs and benefits | Assumptions made in quantification | Notes on sources |
|---|---|---|---|
| Streamlining benefits | | | |
| Direct | There should be direct cost savings to businesses and regulators from the streamlining measures | We have assumed that these refinements may save businesses 1-2% of their regulatory costs annually (15m-30m: c. €1.5bn based on McKinsey estimate of Regulatory Costs being c. 4.1% of BERD); EMA 1-2% and NCAs 1-2% | We have found no quantitative estimates of the likely benefits of these proposed measures through our consultations or literature reviews, and have had to make assumptions based on estimates of overall regulatory costs. |
| Indirect | There may be some limited indirect benefits in terms of accelerated procedures meaning applications are authorised several weeks earlier (CP / DCP), which may facilitate at least some new medicines being approved for sale earlier and some generics entering the market earlier. | We assume the average period taken to assess applications may be reduced by 2-4 weeks, albeit the bigger impact may be on outliers and enabling a greater proportion of all assessments to be carried out closer to the median time taken. We based this 10-20 day improvement on the fact that the EMA part of the assessment process is taking around 200 days on average (EMA annual report 2020) and the accelerated assessment takes around 140 days. If we assume 50% of the EMA positive opinions are approved and manage to come to market 2-4 weeks early, and we assume an average annual EU income for a medicine at 50m (c. €1m a week), that would amount to income of around €100m-€200m being brought forward. The market would be competed away 2-4 weeks earlier, so the total income may not change. But there could be first mover advantages as well as the time value of money, and so we might suggest that businesses will benefit by 5% of the value of this earlier cashflow (5m-10m). This accelerated process would apply to generics also, and given the relative scale of assessments (CP v DCP), the benefits for this group of businesses may be an order of magnitude higher (50m-100m) | We have found no quantitative estimates of the likely impact of these proposed measures, and have no good basis for approximating the nature and extent of the possible indirect benefits. We have therefore used a large range for our assumptions. |
| Digitalisation costs | | | |
| Direct | There should be few if any direct costs associated with | | |

| | Description of types of costs and benefits | Assumptions made in quantification | Notes on sources |
|---|---|---|---|
| | the various digitisation measures, which would deliver efficiency gains to businesses | | |
| Enforcement | There will be additional one-off costs for the EMA and other regulators in designing and implementing these various enhanced digitalisation measures | We have assumed the proposed online application system may cost a few millions to implement (c. €2m-€3m, the ePIL system may cost an order of magnitude more (c. €10m-€30m) and the integrated regulatory data system will be the most demanding and costly to design and implement and could cost several hundred millions across all regulators (€100m-€300m), perhaps €120m-€350m in total. We have assumed a split between the EMA (€20m-€50m) and NCAs (€100m-€300m). We have assumed these will be one-off costs - spread over several years - and may be associated with recurrent costs (operation, maintenance, depreciation) on the order of 25% of the one-off costs | We have no quantitative data on costs of benefits relating to the proposed digital measures, so have had to look at past activities for guidance. According to the EMA final-programming-document-2022-2024, the EMA Digital Business Transformation Task Force will have access to 17 staff to deliver its various digital projects, working across 7 areas, including ePIFs and electronic submissions. Annex 19 to the EMA annual report 2020 shows that the agency invested around €7m in Business-Related IT in 2019 and will spend around €20m in 2020. Annual IT spend has fluctuated substantially however, in line with various business development programmes. |
| Indirect | There will be no substantive indirect costs from the proposed digitalisation measures, as they will retain some aspects of paper-based systems (product leaflets) to minimise risks of digital exclusion (not all citizens have or wish to use digital platforms) | | |
| Digitalisation benefits | | | |
| Direct | The various digital initiatives proposed will save time and cost for both businesses and regulators | We have assumed that these refinements may deliver efficiency gains to industry equivalent to 0.5-1% of their regulatory costs. We have assumed an annual efficiency gain of 1-2% for both the EMA and the NCAs | We have found no quantitative estimates of the likely benefits of these proposed measures through our consultations or literature reviews, and have had to make assumptions based on the wider literature on digitalisation and productivity. An OECD review suggests that productivity gains for businesses from digitalisation range from 1-4% on average. Greater use of e-government - as proposed here - is seen to deliver benefits on the order of 1%. The OECD is careful to point |

| | Description of types of costs and benefits | Assumptions made in quantification | Notes on sources |
|---|---|---|---|
| | | | out that these figures can differ markedly across sectors and countries, we have therefore used a range of 0.5-1%. These digitalisation proposals will impact to a greater extent on the efficiency of the regulatory system. |
| Indirect | There may be some limited indirect benefits in terms of accelerated procedures meaning applications are authorised several weeks earlier, which may facilitate at least some new medicines being approved for sale earlier and some generics entering the market earlier. | | We have found no quantitative estimates of the likely impact of these proposed measures, and have no good basis for approximating the nature and extent of the possible indirect benefits |
| | | | |
| Enhanced support costs | | | |
| Direct | There may be some limited additional costs to businesses from greater use of advice or increased dialogue more generally | We assume this might cost business an additional €1.6m-€2.4m. The EMA is currently receiving around 800 requests for scientific advice and protocol-assistance. We have no data on the intensity of work involved in preparing the request or answering it, but no doubt a proportion will be formulated in hours while others may take several staff days to respond to. We have assumed an average of 1 staff day to prepare a request and 3 staff days to process the request (with a market value of c. €1k / staff day). We have further assumed that a more interactive approach to dialogue - and greater support for SMEs non-commercial organisations - may double of treble this level of activity, for industry and regulators. For business: 1.6m=800*1*1000*2 or 2.4m = 800*1*1000*2; For EMA: €4.8m=800*3*1000*2 or €7.2m=800*3*1000*3 | We have found no quantitative estimates of the likely costs of these proposed measures through our consultations or literature reviews, and have had to make assumptions about the likely level of effort based on EMA activity statistics. |
| Enforcement | There will be additional costs for regulators associated with the enhanced and extended support measures | We assume this might cost the EMA an additional €4.8m-€7.2m. The EMA is currently receiving around 800 requests for scientific advice and | We have found no quantitative estimates of the likely costs of these proposed measures through our consultations or |

| | Description of types of costs and benefits | Assumptions made in quantification | Notes on sources |
|---|---|---|---|
| | | protocol-assistance. We have no data on the intensity of work involved in preparing the request or answering it, but no doubt a proportion will be formulated in hours while others may take several staff days to respond to. We have assumed an average of 1 staff day to prepare a request and 3 staff days to process the request (with a market value of c. €1k / staff day). We have further assumed that a more interactive approach to dialogue - and greater support for SMEs non-commercial organisations - may double of treble this level of activity, for industry and regulators. For business: 1.6m=800*1*1000*2 or 2.4m = 800*1*1000*2; For EMA: €4.8m=800*3*1000*2 or €7.2m=800*3*1000*3 | literature reviews, and have had to make assumptions about the likely level of effort based on EMA activity statistics. |
| Indirect | There will be no substantive indirect costs of these enhanced support measures | | |
| Enhanced support benefits | | | |
| Direct | Industry - and SMEs in particular - should benefit from better and more dynamic advice avoiding queries on applications (delay) and rework to the same (cost); regulators should benefit from more mature applications that can be assessed more easily and quickly | We have assumed that these refinements may save businesses 0.5-1% of their regulatory costs annually (7.5m-15m: c. €1.5bn based on McKinsey estimate of Regulatory Costs being c. 4.1% of BERD); EMA 0.5-1%. We have assumed these measures will be of less benefit to NCAs than the more general streamlining and digitalisation measures, and so have not included a value for a benefit. | We have found no quantitative estimates of the likely direct benefits of these proposed measures |
| Indirect | There may be some limited indirect benefits, whereby faster assessments, on average, may facilitate at least some new medicines being approved for sale earlier and some generics entering the market earlier. | We assume the average period taken to assess applications may be reduced by 2-4 weeks. We based this 10-20 day improvement on the fact that the industry part of the assessment process is taking around 160 days on average (EMA annual report 2020) and 200 days for SMEs. If we assume 50% of the EMA positive opinions are approved and manage to come to market 2-4 weeks early, and we assume | We have found no quantitative estimates of the likely indirect benefits of these proposed measures |

| | Description of types of costs and benefits | Assumptions made in quantification | Notes on sources |
|---|---|---|---|
| | | an average annual EU income for a medicine at 50m (c. €1m a week), that will amount to income of around €100m-€200m being brought forward. The market would be competed away 2-4 weeks earlier, so the total income may not change. But there could be first mover advantages as well as the time value of money, and so we suggest that businesses will benefit by 5% of the value of this earlier cashflow (5m-10m). | |

### *A.8.3. Overview of costs and benefits relating to simplification and burden reduction*

This annex deals with horizontal measures, which are primarily designed to simplify the regulatory system and reduce burden on industry and regulators alike. This is done for reasons of good governance but also in part to create the financial headroom to introduce new legislative actions and procedures that will bring additional costs, in line with the one in one out principle. As such, the preceding sub-sections deal extensively with simplification and burden reduction.

Table 75 represents these data for the wo horizontal measures that relate most directly to simplification and burden reduction, specifically streamlining and digitalisation measures. The table summarises the balance of costs and benefits, and suggests that the measures as proposed may deliver a reduction in compliance costs and burden in the range of €1.2bn-€2.4bn for industry. More specifically:

- The proposed streamlining procedures will yield useful cost savings for European pharmaceutical businesses, with estimated cost savings falling in the range of €1bn-2.1bn over the next 15-years
- The streamlining procedures are estimated to be cost neutral for the EMA, with investments in additional coordination structures and the development of new protocols and procedures being mirrored by broadly equivalent savings, with the balance of costs and benefits estimated to fall in the range €-4m to €2m over the next 15 years
- The streamlining procedures are estimated to be slightly positive in efficiency / monetary terms, for the national competent authorities, with investments in additional coordination and new procedures being outweighed by savings, with the balance of costs and benefits estimated to fall in the range €15m to €30m over the next 15 years
- The proposed digitalisation measures will provide relatively modest financial savings to industry, given the primary focus is on the integration of regulatory systems and platforms across the EU and support for the re-use of data (e.g. the 'Once Only' principle of the EU digital strategy). Electronic submission will deliver industry cost savings. These are estimated at €112m-€225m over 15 years

- The proposed digitalisation measures will provide similarly modest financial savings to the EMA, given the substantial costs involved in the design and development of the new systems. The savings are estimated at €65m-€70m over 15 years
- The proposed digitalisation measures will provide relatively greater financial savings for NCAs, with the EMA shouldering more of the substantial costs involved in the design and development of the new systems. The savings across the whole EU regulatory network are estimated at €700m-€1,200m over 15 years

*Table 75 Overview of the costs and benefits associated with the horizontal measures related to simplification and burden reduction*

| | **Businesses** | **Businesses** | **EMA** | **EMA** | **NCAs** | **NCAs** |
|---|---|---|---|---|---|---|
| | **one-off** | **recurrent** | **one-off** | **recurrent** | **one-off** | **recurrent** |
| **Streamlining costs** | | | | | | |
| Enforcement | | | €1.8m-€3.6m | €3.5m-€7.5m | €15m-€30m | €30m-€60m |
| Indirect | | | | | | |
| **Streamlining benefits** | | | | | | |
| Direct | | €15m-€30m | | €3.5m-€7m | | €30m-€60m |
| Indirect | | €55m-€110m | | | | |
| Total savings | | €1,050m-€2,100m | | €-3.9m to €1.8m | | €15m-€30m |
| **Digitalisation costs** | | | | | | |
| Direct | | | | | | |
| Enforcement | | | €20m-€50m | €4m-€10m | €100m-€300m | €20m-€60m |
| Indirect | | | | | | |
| **Digitalisation benefits** | | | | | | |
| Direct | | €7.5m-€15m | | €7m-€14m | | €60m-€120m |
| Indirect | | | | | | |
| Total savings | | €112m-€225m | | €65m-€70m | | €700m-€1,200m |

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PART 1/6

**COMMISSION STAFF WORKING DOCUMENT**

**EVALUATION**

# Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

{SEC(2020) 291 final} - {SWD(2020) 164 final}

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# Glossary

| *Term or acronym* | *Meaning or definition* |
|---|---|
| Accessibility | A medicine becomes accessible to patients once it has been authorised, is being marketed, and can be reimbursed in a Member State. |
| Affordability | Relates to payments to be made by patients (out of pocket on healthcare or through co-payments) which can be described as affordability at micro level and to the sustainability of public funding of the healthcare sector raised through social security contributions or taxes (affordability at macro level). |
| ATMPs | Advanced therapy medicinal products |
| Availability | A medicine becomes available once it has been authorised in a Member State or centrally in the EU. |
| Biological medicine | A medicine whose active substance is made by or derived from a living organism. Biological medicines contain active substances from a biological source, such as living cells or organisms (human, animals and microorganisms such as bacteria or yeast). |
| Biomarker | Biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals. |
| Biosimilar | A biosimilar is a biological medicine that is very similar to another biological medicine which has already been approved. Biosimilars are approved if they meet the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines. |
| Cash benefits | Cash benefits are monetary savings associated with reduced hospitalisation and outpatient encounters as a result of reduced avoidable adverse drug reactions. |
| CAT | The Committee for Advanced Therapies is the European Medicines Agency's committee responsible for assessing quality, safety and efficacy of advanced therapy medicinal products (ATMPs) and following scientific developments in the field. |
| CBA | Cost-benefit assessment |
| CHMP | The Committee for Medicinal Products for Human Use is the Agency's committee responsible for human medicines. |
| Class waiver | Class waivers provide an exemption from the obligation to submit a paediatric investigation plan for a class of medicines, such as medicines for diseases that only affect adults. |
| CMA | Conditional marketing authorisation is the approval to market a medicine that addresses patients' unmet medical needs on the basis of data that is less comprehensive than that normally required. The available data must indicate that the medicine's |

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| | benefits outweigh its risks and the applicant should be in a position to provide comprehensive clinical data in the future. |
| COMP | The Committee for Orphan Medicinal Products is the Agency's committee responsible for recommending orphan designation of medicines for rare diseases. |
| Data protection | Period of protection during which pre-clinical and clinical data and data from clinical trials handed in to the authorities by one company cannot be referenced by another company in their regulatory filings. |
| EMA | The European Medicines Agency ('the Agency') is an EU agency founded in 1995 which is responsible for the scientific evaluation, supervision and safety monitoring of medicines, both human and veterinary, across Europe. (https://www.ema.europa.eu/en). |
| ERN | European reference networks (ERNs) are virtual networks involving healthcare providers across Europe. Directive 2011/24/EU on patients' rights in cross-border healthcare provides for the setting up of ERNs, 24 of which were established in 2017. The purpose of these networks is to facilitate discussion of complex or rare diseases and conditions that require highly specialised treatment, and concentrated knowledge and resources. |
| Extension of marketing authorisation | A change to a marketing authorisation which fundamentally alters its terms. Such changes may have to do with modifications of the active substance, the strength, the pharmaceutical form and/or the route of administration. |
| Generic medicine | A generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s). The generic can only be marketed after expiry of the data and market protection. |
| HTA | A health technology assessment (HTA) is the systematic evaluation of the added value of a new health technology compared to existing ones. It is a multidisciplinary process to evaluate the social, economic, organisational and ethical issues associated with a health intervention or health technology. The main purpose of conducting an assessment is to inform policy decision-making. |
| ICER | An incremental cost-effectiveness ratio (ICER) is a summary measure representing the economic value of an intervention, compared with an alternative (the comparator). An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of 'extra cost per extra unit of health effect' for the more expensive therapy versus the alternative. |
| Impact assessment | An impact assessment must identify and describe the problem to be tackled, establish objectives, formulate policy options, assess the impacts of these options and describe how the expected results will be monitored. The Commission's impact assessment system follows an integrated approach that assesses the environmental, social and economic impacts of a range of policy |

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| | options, thereby ensuring that sustainability is an integral component of Union policymaking. |
| Magistral/officinal formula | A medicinal product prepared in a pharmacy in accordance with a medical prescription or according to the prescriptions of pharmacopoeia and intended to be supplied directly to patients served by the pharmacy. |
| Medical condition | Any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome). |
| Marketing authorisation | The approval to market a medicine in one, several or all European Union Member States. |
| Marketing authorisation application | An application made to a European regulatory authority for approval to market a medicine within the European Union. |
| Marketing authorisation grant | A decision granting the marketing authorisation issued by the relevant authority. |
| Market protection | Period of protection during which generics cannot be placed on the market. |
| Neonatology | A subspeciality of paediatrics consisting of medical care for newborn infants, especially the ill and premature. |
| Non-cash benefits | Non-cash or intangible benefits are benefits expected from improved actual treatment, resulting in reduced mortality, improved quality of life and time saved by informal carers. |
| Oncology | A branch of medicine that specialises in the prevention, diagnosis and treatment of cancer. |
| Orphan condition | A medical condition, as defined above, that meets the criteria defined in Article 3 of Regulation (EC) No 141/2000; a life-threatening or chronically debilitating condition affecting no more than five in 10 thousand persons in the EU. |
| Orphan designation | A status assigned to a medicine intended for use against a rare condition. The medicine must fulfil certain criteria for designation so that it can benefit from incentives such as market exclusivity. |
| Orphan indication | The proposed therapeutic indication for the purpose of orphan designation. This specifies if the medicinal product subject to the designation application is intended for diagnosis, prevention or treatment of the orphan condition. |
| Orphan-likes | Orphan-like medicinal products which entered the EU market from the United States before 2000, when there was no special legislation in place. |
| Payer | An entity responsible for financing or reimbursing healthcare. |
| PDCO | The Paediatric Committee (PDCO) is the Agency's scientific committee responsible for activities associated with medicines for children. It supports the development of such medicines in |

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| | the European Union by providing scientific expertise and defining paediatric need. |
| PIP | A paediatric investigation plan (PIP) is a development plan designed to ensure that the data required to support the authorisation of a paediatric medicine are obtained through studies of its effect on children. |
| PUMA | The paediatric-use marketing authorisation (PUMA) is a dedicated marketing authorisation covering the indication(s) and appropriate formulation(s) for medicines developed exclusively for use on the paediatric population. |
| QALYs | Quality-adjusted life years (QALYs) refers to a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to one year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life and freedom from pain and mental disturbance. |
| Rare disease | Rare diseases are diseases with a particularly low prevalence; the European Union considers diseases to be rare when they affect no more than 5 per 10,000 people in the European Union. |
| Repurposed medicines | Existing medicines investigated for new therapeutic indications. |
| RSB | The Regulatory Scrutiny Board is an independent body of the Commission that offers advice to the College of Commissioners. It provides a central quality control and support function for the Commission's impact assessment and evaluation work. The Board examines and issues opinions and recommendations on all the Commission's draft impact assessments and its major evaluations and fitness checks of existing legislation. |
| SA | Scientific advice: the provision of advice by the Agency on the appropriate tests and studies required in developing a medicine, or on the quality of a medicine. |
| SmPC | A summary of product characteristics (SmPC) describes the properties and the officially approved conditions of use of a medicine. |
| SMEs | Micro, small and medium-sized enterprises |
| SPC | The supplementary protection certificate (SPC) is an intellectual property right that serves as an extension to a patent right. The patent right extension applies to specific pharmaceutical and plant protection products that have been authorised by regulatory authorities. |
| Sponsor | Legal entity responsible for submitting an application for orphan designation to the EU. |
| SWD | Staff working documents (SWDs) are required to present the results of all impact assessments and evaluations/fitness checks. |

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| Therapeutic indication | The proposed indication for the marketing authorisation. A medical condition that a medicine is used for. This can include the treatment, prevention and diagnosis of a disease. The therapeutic indication granted at the time of marketing authorisation will be the result of the assessment of quality, safety and efficacy data submitted with the marketing application. |
| Well-established use | When an active ingredient of a medicine has been used for more than 10 years and its efficacy and safety have been well established. In such cases, application for marketing authorisation may be based on results from the scientific literature. |

## 1. INTRODUCTION

The therapeutic landscape for patients in the EU has undergone major changes. Still, considerable unmet needs remain. About 30 million European Union citizens are affected by one of the over 6000 rare diseases currently recognised. The European Union considers diseases to be rare when they affect no more than 5 per 10,000 people in the EU. 80% of these diseases are of genetic origin, and they are often chronic and life-threatening; almost 90% can begin in childhood.

For these patients, and for more than 100 million European children, treatment was either limited or non-existent before the introduction of EU legislation on rare diseases and on medicines for children (in 2000 and 2006 respectively). That situation represented a huge unmet medical need and a significant public health challenge. There were often no medicines at all available for doctors treating patients with rare diseases. Children were regularly prescribed medicines indicated for adults, which had not been tested or adapted specifically for use in young patients. This 'off-label' use of adult medicines comes with the risk of inefficacy and/or adverse reactions in children, who cannot simply be regarded as 'small adults' from the developmental and physiological points of view.

When these policy challenges were identified, the EU already had a well-established legislative framework for medicinal products that had developed considerably since its inception in 1965. It covered the whole life-cycle of medicines, from clinical research to post-marketing surveillance (pharmacovigilance). Its main aim was, and still is, to ensure that all medicines in the Union are authorised by demonstrating their safety, quality and efficacy before they reach patients.

However, this framework was general in nature. It contained no incentives for development in particular areas of medical need. Decisions on product development were generally left to the market and were subject to commercial decisions driven by considerations of return on investment. Public research funding was often the only means available to support neglected fields.

Both the areas of rare diseases and medicines for children were economically unattractive. This was because the market size was generally small and the research and development of products, including the conduct of clinical trials, was more complex. From the 1990s onwards, this led to a policy discussion about how best to correct this market failure and ensure the development of more medicines to treat patients suffering from rare diseases and/or appropriate for use in children. This discussion was influenced by the apparent success of legislative intervention in the US, where orphan and paediatric legislation was introduced in 1983 and 1997 respectively, and was based on the same rationale of imbalance in risk and reward.

In 2000, Regulation (EC) No 141/2000 (hereinafter 'the Orphan Regulation') and in 2006 Regulation (EC) No 1901/2006 (hereinafter 'the Paediatric Regulation') were adopted by the European Commission.

Although the two Regulations are designed to address the same problem, the tools they use differ substantially. The purpose of the Orphan Regulation is to reward research and development through incentives and, ultimately, to place medicines for rare diseases on the market, where there was previously no commercial interest. The Paediatric Regulation, however, works mainly with obligations. It compels companies already developing products for adults to screen them for possible use in children, and only provides rewards once this obligation has been fulfilled, to compensate for the additional costs incurred. [1]

**Purpose and scope of the evaluation**

The two Regulations are subject to the ex-post evaluation presented in this document.[2] The purpose of the evaluation is twofold. Firstly, it assesses the strengths and weaknesses of the two legal instruments, both separately and in combination with each other. It focuses on how they have catered for products for unmet medical needs, taking into account how pharmaceuticals are developed, science advances, and business models change. Secondly, it provides insights into how the various incentives and rewards for which the Regulations provide have been used, along with an analysis of the related financial consequences, both in general and by stakeholder group.

There are several reasons why the two Regulations are evaluated together. Firstly, they are both designed to tackle a market failure that results in a lack of medicines for the two groups of patients concerned. Secondly, they often address the same therapeutic areas, as the great majority of orphan diseases affect children[3] and many paediatric diseases can be classified as rare. Thirdly, there are some conceptual overlaps, for instance as regards incentives provided to companies where market exclusivity for orphan medicines is extended through the Paediatric Regulation. For these reasons, the Commission Report on the Paediatric Regulation[4] published in 2017 concluded that the two Regulations would need to be assessed together before any amendments could be made.

However, undertaking a joint evaluation has its limitations. For example, as noted above, the two Regulations employ different tools to try to achieve their goals,, making it difficult to analyse and compare the results together. The evaluation also relies on two different studies and on different consultation activities.

The evaluation covers 2000-2017 (Orphan Regulation) and 2007-2017 (Paediatric Regulation) and is based on sound evidence about how the two instruments operate from both a public health and a socioeconomic perspective. It covers five evaluation criteria: the effectiveness, efficiency, relevance, coherence and EU added value of the Regulations.

The evaluation describes the impact of external factors on the Regulations' expected outputs. Those factors include scientific and technological advances, developments in

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1 The Orphan Regulation incentivises new developments while the Paediatric Regulation rewards the companies for testing the possible use of their medicines in children.

2 Ex-post evaluations are used throughout the European Commission to assess whether a specific intervention was justified and whether it worked (or is working) as expected in achieving its objectives and why.

3 Wakap at al, Eur j Hum genetics, (28) p.165, 2019

4 COM(2017) 626.

other jurisdictions, the functioning of national health systems, the commercial strategies employed by companies, and Member States' pricing and reimbursement decisions. Such factors are mostly heterogeneous by their very nature. The EU and its legislation have limited influence on them, and they were not taken fully into account when the legislation was designed. Nonetheless, they affect its performance and relevance. The legislative intervention and its outputs therefore need to be viewed and analysed in the context of these influencing factors.

The evaluation has been carried out at a time when issues of access to medicines, their availability and their affordability are very high on the EU political agenda. A roadmap for a new pharmaceutical strategy was published in June 2020.[5] The purpose of this strategy is to improve and expedite patients' access to safe and affordable medicines and to support innovation in the EU pharmaceutical industry. The orphan area is often seen as a micro-environment exemplifying many of the aspects tackled in the pharmaceutical strategy. Orphan medicines make up a growing share of new authorised products and account for an increasing proportion of Member States' spending on pharmaceuticals. In 2018, almost one third[6] of centrally-authorised medicines (excluding generics and biosimilars) were orphan medicines.

At the same time, access to these products varies widely between Member States. In 2016, the Council called on the Commission to examine the impact of pharmaceutical incentives on the availability and accessibility of orphan medicinal products.[7] The European Parliament also debated the issue of access to medicines[8], including medicines for children. In its 2016 Resolution[9], Parliament recognised that the Paediatric Regulation has been beneficial to children overall, but less effective in certain therapeutic areas (e.g. paediatric oncology and neonatology). It therefore called on the Commission to consider revising the Regulation.

The results of this evaluation will guide reflection on any future changes to the legislative framework.

## 2. BACKGROUND TO THE INTERVENTION

### Description of the intervention and its objectives

The last half-century has witnessed significant progress in the field of medicines, benefiting patients and society in general. However, substantial gaps remain in the therapies available. This is especially true both for patients suffering from a rare disease, and for children in general.

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5 https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12421-Pharmaceutical-Strategy-Timely-patient-access-to-affordable-medicines

6 Data obtained from the Agency.

7 Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States https://www.consilium.europa.eu/en/press/press-releases/2016/06/17/epsco-conclusions-balance-pharmaceutical-system/

8 'Options for improving access to medicines'; EP resolution of 2 March 2017 (2016/2057(INI)).

9 EP resolution of 15 December 2016 on the regulation on paediatric medicines (2016/2902(RSP)) http://www.europarl.europa.eu/doceo/document/TA-8-2016-12-15_EN.html#sdocta7

Although rare diseases affect a limited number of people per disease, collectively they affect one person in every 17 people within Europe. Obtaining the correct diagnosis is a long and difficult journey in itself. It takes an average of five years to diagnose a child with a rare disease. However, even if a disease has been identified, very few medicines are available, and for many rare diseases there is no pharmaceutical remedy at all. At the time of the EU's intervention via the Orphan Regulation, companies generally had limited interest in developing medicines for rare diseases. They considered it unlikely that the cost of development would be recovered by selling the product to small numbers of patients at the 'normal' prices envisaged.

Similar problems existed with medicines for children. Many products used for children were prescribed and administered on the basis of the doctor's own experience rather than on the results of clinical research. Moreover, medicines were not available in a pharmaceutical form suitable for children. Paediatricians had to use medicines authorised for adults by adapting the dosage, for example by simply crushing adult-size tablets. With some notable exemptions, such as childhood vaccines – one of the success stories of modern medicines – companies were often uninterested in investing in paediatric medicines. This often meant conducting research and development for a small number of patients, given that children are not a uniform sub-group of patients; different growth and maturation rates require multi-national trials. Furthermore, as recently as the 1980s, paediatric clinical trials were stigmatised, it being thought that children should be protected from participating in medical research.

At the end of the 1990s, the pharmaceutical market was dominated by big companies, which were often interested in developing 'blockbusters' that could be sold in large volumes to tackle common diseases. By contrast, the costs of research and development meant that industry was often disinclined to invest in developing remedies for diseases with small numbers of patients.

The 'standard' incentives provided by the general legislative framework for pharmaceuticals (8 years of data protection, 10 years of market protection and 20 years of patent protection) were failing in these areas. They were not considered enticing enough. In other words, they did not ensure a large enough return on investment to make it worthwhile for companies to develop orphan medicines or to research medicines suitable for paediatric use. It would be wrong to assume that there were no medicines in these areas before the relevant legislation was adopted, as some such products did reach the European market. However, without a specific framework, there was no certainty that such medicines would be developed for and placed on the EU market. The number of medicines available was considered insufficient, both in absolute terms and in comparison with other regions.

Member States tried to boost the development and commercialisation of orphan and paediatric medicines through various national measures, which were not coordinated, and by funding programmes of research into rare diseases. However, these activities had almost no success and raised concerns that such scattered attempts could lead to distortions of the EU internal market.

Other regions were more successful. Starting in the 1980s, the US and Japan introduced specific legislative frameworks to foster the development of medicines to treat rare diseases or for use in children.

The explanatory memorandum[10] of the orphan legislative proposal prominently refers to the success of US legislation, where, over 13 years (1983-1996), 837 products were awarded the status of orphan drug, 323 were aided by grant programmes, and 152 obtained marketing approval. Unsurprisingly, therefore, EU orphan legislation shares parts of its design with the US model. The prospect of obtaining market exclusivity for a given period, during which companies would recover their investment, seemed at the time to be the best way of copying the success of the US system.[11] It was also recognised that market exclusivity would not be the only major incentive. It would be up to the Community and the Member States, within their respective spheres of competence, to provide other incentives for developing medicines for rare diseases. It was thought that the Community would support research, while Member States would provide tax incentives.[12]

As regards remedies for common diseases, it is quite usual for products developed in another region to find their way to Europe eventually. However, the increase in orphan and paediatric products in the US did not automatically lead to a similar increase in the EU. Only some such products were placed on the EU market at the same time.

For orphan medicinal products, this might have been due to the administrative and logistic costs (authorisation fees, costs of legal representatives and staff responsible for conducting batch releases, maintenance costs) associated with a marketing authorisation for low-volume products. Another possible reason was the lack of specific measures to protect such products from generic competitors in the EU. These factors meant that the business case for placing such products on the market was not particularly strong. In a survey conducted for this evaluation, respondents referred to a combination of scientific, financial and regulatory hurdles as the biggest entry barriers facing developers.[13]

As regards medicines for children, even where companies had collected data on their use in children to obtain a marketing authorisation in the US, they had nothing specific to gain by providing such data to the EU on their own initiative. In many cases, the increase in sales volume of adult medicines achieved by extending use to children was not very sizeable, and it had to be balanced against the additional costs of maintaining more complex marketing authorisations serving different populations.

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10 Introduction of the explanatory memorandum to the Commission proposal for the Orphan Regulation (COM(1998) 450 final).

11 Alternatively, the EU would have needed to rely on 'free-riding' of US-approved medicines, which could have had a negative impact both on the number of orphan products and their timely availability to EU patients. Moreover, some Member States had considered acting independently at the time, and therefore EU action was considered necessary to avoid distortion of the internal market in an already heavily regulated field of medicines.

12 Section 'Other incentives' in explanatory memorandum (COM(1998) 450 final).

13 Section 6.1.1 of the 2019 Orphan study report.

## The objectives and main design features of the two regulations

### ***Orphan Regulation***

The specific objectives of the Orphan Regulation are to:

- Ensure research and development and the placing on the market of designated orphan medicinal products (***availability***) (specific objectives 1 and 2);
- Ensure that patients suffering from rare conditions have the same quality of treatment as any other patient (***accessibility***) (specific objective 3).

Products fall under the scope of the Orphan Regulation if they either fulfil the '*prevalence criterion'* of no more than 5 in 10,000 people affected by the disease in the EEA or the '*insufficient return upon investment criterion*', meaning that, without incentives, it is unlikely that the marketing of the medicinal product in the EU would generate sufficient return to justify the necessary investment. Furthermore, the condition in question has to be life-threatening or chronically debilitating. No satisfactory treatment should exist in the EU, or, if it exists, the product in question should provide a significant benefit[14] to patients affected by that condition in comparison with the existing treatment.[15]

The Regulation establishes a **two-step EU procedure**:

- First, a company may request that a product be granted an '**orphan designation**' by the European Commission, based on a positive opinion adopted by the European Medicines Agency (hereinafter 'the Agency') at any stage of development. An early orphan designation may allow developers (researchers, SMEs or big pharma companies) to secure R&D financing, either through the EU research framework or through a national funding mechanism, and may help attract investors more easily.[16] In addition, an orphan designation may enable a product to receive dedicated support from the Agency, such as scientific advice (known as protocol assistance for orphan medicines)[17], before the Agency grants marketing authorisation.
- Once the development is completed, the product can, as a second step, benefit from an **EU-wide marketing authorisation**.[18] If, at the time of granting the marketing authorisation, continued compliance with the designation criteria is confirmed, the product will enjoy a **monopoly period of 10 years** ('market exclusivity')[19], which can be extended to 12 years if a paediatric research and development programme is completed (see Figure X).[20] If the designation is not confirmed, the company will receive a standard marketing authorisation. (It is noteworthy that US legislation does not include a check on continued compliance with the designation criteria at the time of granting a marketing authorisation.) Once the Agency has granted market exclusivity at the request of a Member State, the monopoly period may be

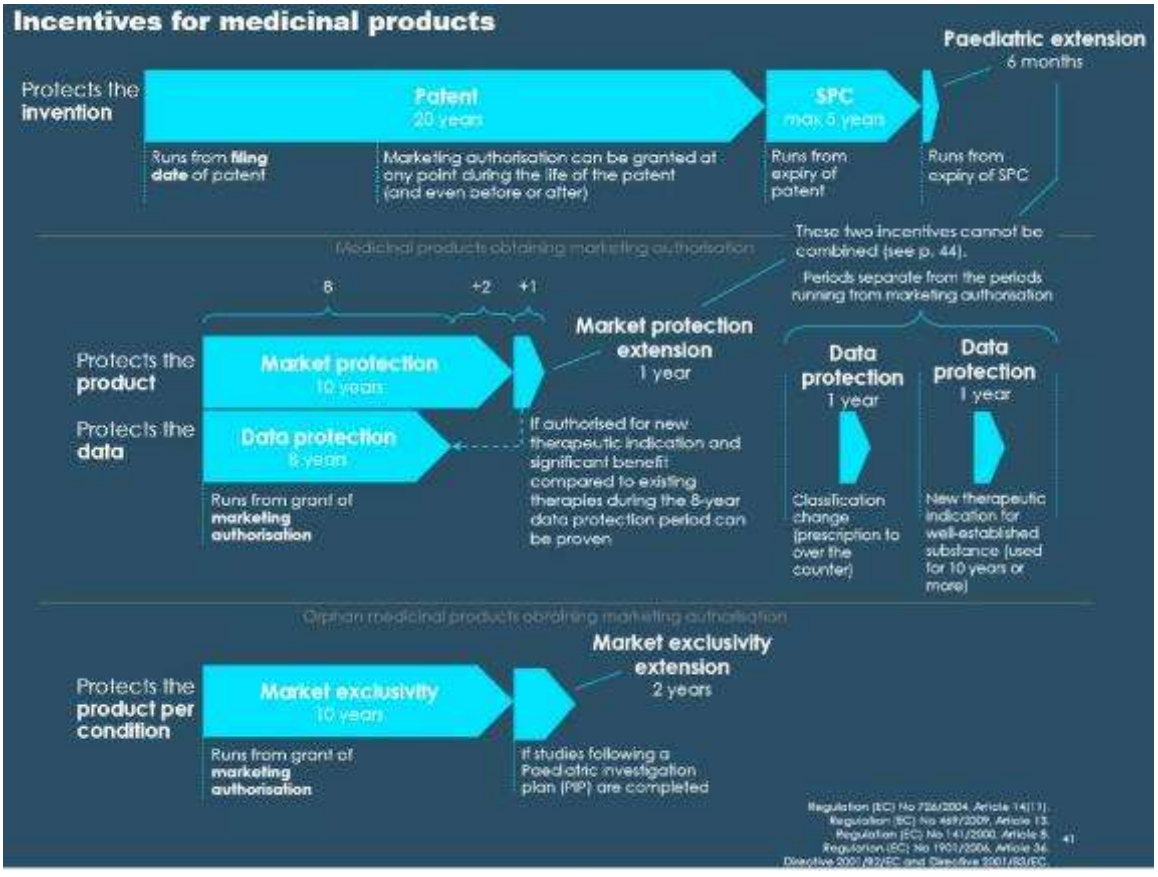
14 See Article 3(2) of (implementing) Regulation No 847/2000.
15 Article 3(1) sub b of the Orphan Regulation.
16 Article 9(1) of the Orphan Regulation.
17 Protocol assistance offers the sponsor of a designated orphan medicine the possibility of requesting advice from the Agency on the conduct of tests and trials, as it is a scientific advice for medicinal products which receives an orphan designation (Article 6 of the EU Orphan Regulation).
18 Regulation 726/2004.
19 See Article 8 of the Orphan Regulation.
20 See Article 37 of the Paediatric Regulation.

shortened to six years if it is established after five years that the product no longer meets the orphan designation criteria.[21]

It was expected that the provisions and the various incentives created by the legislation would help boost research and development and increase the number of orphan medicines available to patients in the EU. It was anticipated that between 5 and 12 applications for orphan designation and for marketing authorisation would be submitted annually between 2000 and 2002.

In the long term, the Regulation would improve the survival rates, life expectancy, therapeutic possibilities and/or the quality of life of patients with rare diseases. Given the generally long development cycles of pharmaceuticals (up to 10-15 years)[22] the legislation was not expected to have an immediate impact. Rather, the intention was to change the therapeutic landscape gradually over time.

**Figure 1**: Graphic showing the various incentives for developing pharmaceuticals[23]




21 Article 8(2) of the EU Orphan Regulation.

22 Section 1.4.2. of the Study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

23 Chapter 2.1 of the Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

***Paediatric Regulation***

The Paediatric Regulation, designed to tackle the lack of appropriate medicines for children in Europe, has three specific objectives:

- Enable high-quality clinical research in children (specific objective 1);
- Ensure, over time, that most medicines used by children are specifically authorised for such use with age-appropriate forms and formulations and are made available (specific objectives 2 and 3);
- Increase the availability of high-quality information about medicines for use in children (specific objective 4).

To achieve these objectives, the Regulation has established **a system of obligations compensated by rewards**. Companies are obliged to screen every new product they develop for its potential use in children, thereby gradually increasing the number of products with paediatric indications and paediatric information. The possibility of obtaining certain rewards compensates for the burden thus created.

In practice, at an early stage in the development of any new medicinal product, companies have to agree with the Agency on a paediatric research and development programme (a '**paediatric investigation plan'** (PIP))[24], or to obtain, under certain conditions, a derogation (waiver) from this obligation.[25] As a general rule, paediatric clinical studies must be conducted in parallel with adult studies, unless it has been agreed that some or all of the paediatric studies can be deferred**.**[26] Such 'deferrals' are granted if conducting the paediatric studies concurrently would delay the marketing authorisation for adults.

Compliance with the obligation is checked when the company files a marketing authorisation application for the (adult) product. In the event of non-compliance, the application is rejected for use on either children or adults.

If the PIP is completed and all the agreed studies have been conducted, the company may benefit from one of two mutually exclusive rewards:

- **A six-month extension of the** supplementary protection certificate (SPC, an intellectual property right that serves as an extension to a patent) (see Figure 1). The SPC[27] extension[28] covers the entire *product*, not only the *paediatric* part. Extension of the SPC is not automatic; an application must be submitted to the national patent office and filed two years before the SPC expires,[29] or
- **A two-year extension of the orphan market exclusivity** for orphan medicines.

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24 Articles 15 and 16 of the Paediatric Regulation, No 1901/2006.
25 Article 11 of the Paediatric Regulation, No 1901/2006.
26 Articles 20 and 21 of the Paediatric Regulation, No 1901/2006.
27 The SPC system is codified in Regulation (EC) No 469/2009.
28 The SPC adds up to a maximum of five years of additional patent time for innovative active ingredients for medicinal products in cases where they have lost more than five years of effective protection owing to the length of time taken by R&D.
29 Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009.

The reward is granted even if the studies show that the product is unsuitable for paediatric use.

Independently, a specific **paediatric-use marketing authorisation (PUMA)**[30] has been put in place to drive the development of paediatric indications for existing authorised products (no longer covered by a patent or an SPC), by offering the same protection. This is an **8-year period of data protection in parallel with the 10-year market protection period,** as applies to any newly authorised medicinal product. These protections are intended to make investment into existing molecules viable, as new paediatric indications would be protected from immediate competition with generic medicines already present on the market. The PUMA scheme is complemented by EU research funding provided for studies of possible paediatric use of old medicinal products no longer covered by patents or SPCs.

Finally, to make use of existing data to update product information on existing authorised medicines, companies are required to provide the Agency or the national competent authorities with any data they have from completed paediatric studies.

Both Regulations established dedicated committees within the Agency to deal with scientific assessment: the Orphan Committee (COMP) and the Paediatric Committee (PDCO).

It was expected that the obligation to agree on and conduct a PIP for any new product developed would boost clinical research in children. The rewards would compensate for the costs incurred in meeting that obligation. This would result in an increase in the number of medicines with paediatric indications. Moreover, gathering information on clinical studies involving children that have already been conducted or are ongoing, together with greater transparency of paediatric clinical trials, would give doctors a wider view of the treatments available.

The expected impacts were to have scientifically validated therapeutic options and to improve child patients' quality of life. Given the generally long development cycles for pharmaceuticals (10-15 years), the legislation was not expected to have an immediate impact. Rather, it was expected that it would change the therapeutic landscape gradually over time.

**Other important factors influencing the field of application of the legislation**

Any legislative intervention in a sector such as pharmaceuticals navigates in a complex environment, where external factors influence the performance of legislation. Figure 1 outlines the basic steps in the process of medicine development, showing the long development time from the research discovery to the clinical development of a medicine.

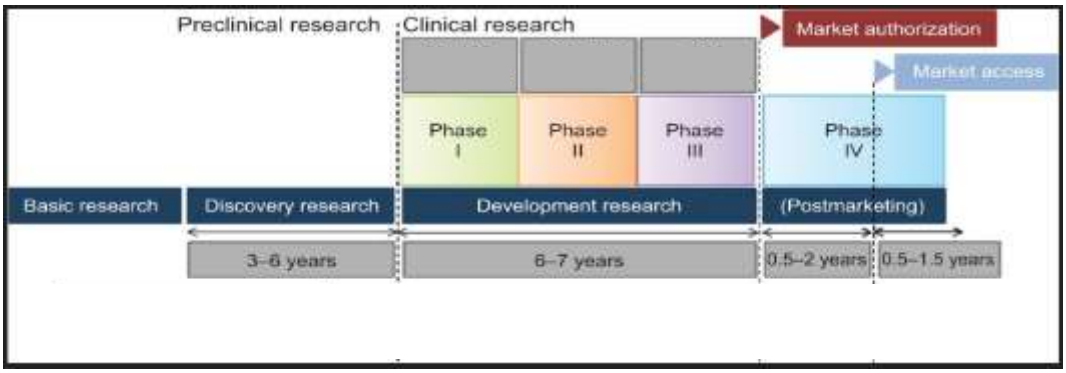
Medicine development is influenced by advances in science. Even the best designed intervention may not succeed if it is not supported by sufficient progress in basic research and solid scientific leads for product development. The complexity of clinical trials for

[30] Article 30 of the Paediatric Regulation.

paediatric and rare diseases also plays a significant role for the development of these products. Legislation may act as enabler, but cannot substitute the inherent research challenges that affect product development.

Considerable support for orphan and paediatric research, both at EU and national levels, including 'national rare disease plans', complement the Regulations. Such support helps pharmaceutical companies to secure R&D financing once the product is designated as orphan. Some Member States have also introduced reduced fees for registration and academic clinical trials, tax reductions or waivers, public funding for research, and free scientific advice. However, neither the Regulations nor research programmes provide for any specific monitoring arrangements to gather data on the relationship between research funding and developments in new orphan or paediatric medicines. This makes it difficult to estimate their impact.

**Figure 2**: Basic steps in the medicine development process (adapted from scientific literature[31], no specific references to the development timelines of orphans or paediatrics)




The availability, accessibility and affordability of medicines for patients across the EU, including orphan and paediatric medicines, are strongly influenced by factors that go *beyond* the Regulations and/or the remit of the EU.

Pharmaceutical companies' strategic decisions on whether (and where) to launch innovative medicines are often influenced by national pricing and reimbursement considerations falling outside the remit of the pharmaceutical legislation, or by the areas where they focus developments. For example, external reference pricing, used by many countries to determine the price paid for a medicinal product, is one of the reasons why companies often decide to launch their products first in the wealthiest Member States. The size of the population, as well as the organisation of health systems and national administrative procedures, are also reported as factors that influence such decisions.

Another important factor is how medical professionals decide what medicine to prescribe. For example, when a paediatric product is launched, it can take a while before doctors

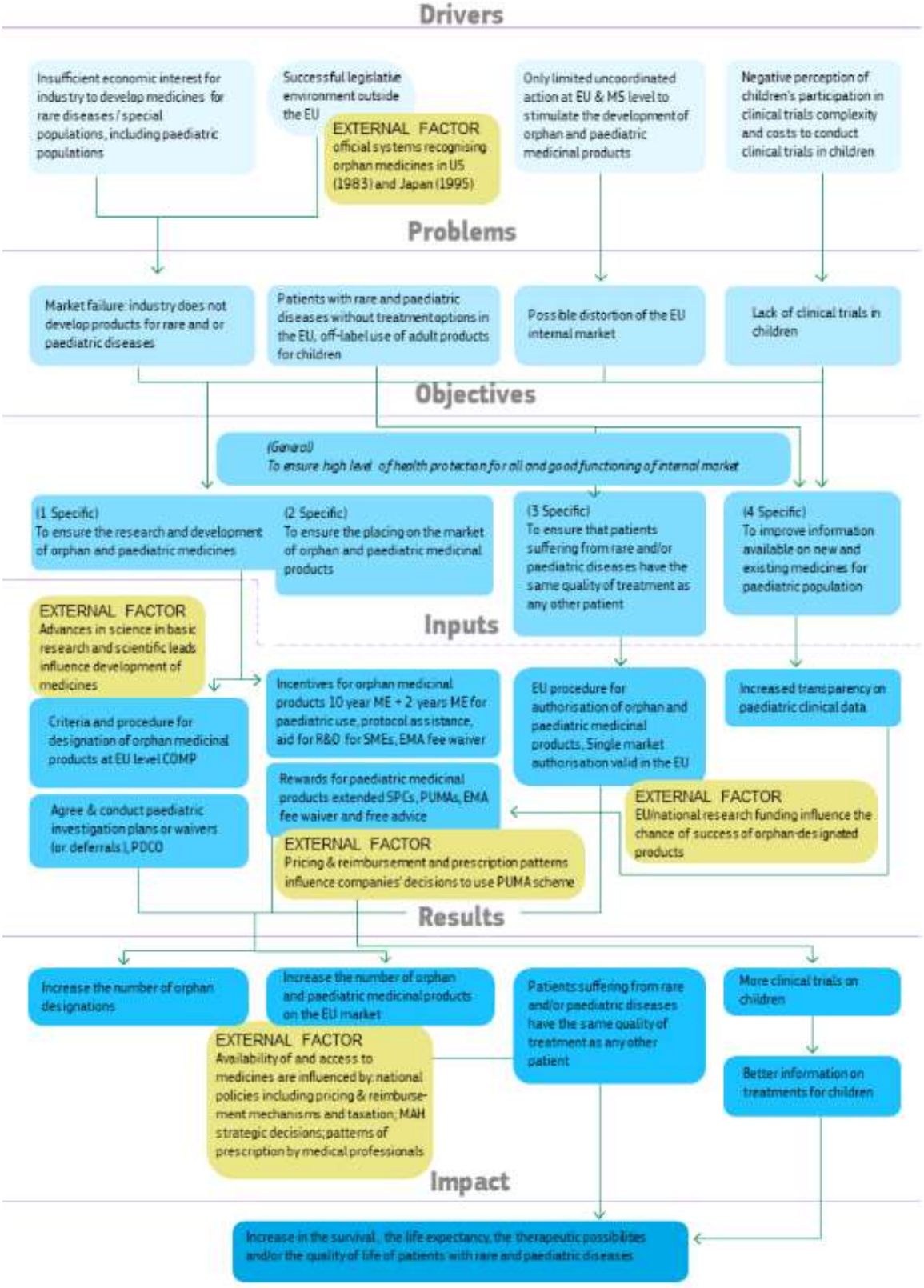
[31] Ciani O, Jommi C. The role of health technology assessment bodies in shaping drug development. DrugDes Devel Ther. 2014;8:2273-2281 https://doi.org/10.2147/DDDT.S49935

switch to prescribing it in preference to a more familiar ‘off-label’ product for adult patients.

These external factors are not new; they existed before the Regulations were adopted. However, they have increased in importance and influence over time, particularly where orphan medicines are concerned.

Chapter 5 analyses the impact of external factors in more detail.

**Figure 3:** Intervention logic underpinning legislation on orphans and paediatrics



**Baseline and points of comparison**

The baseline used for this evaluation is the situation in the EU prior to the adoption of the two Regulations.

No impact assessment was carried out for the Orphan Regulation. The baseline has therefore been reconstructed as far as possible on the basis of available data.[32]

To this end, desk research in the context of the orphan study identified the number of products which, by 2000, had been authorised by the Commission for the treatment of a rare disease. 15 medicinal products[33] were authorised at EU level for the treatment of rare diseases of the immune, blood or genito-urinary systems.[34] These products were brought to the market by 12 individual pharmaceutical companies.[35] In addition, 70 medicinal products authorised as orphans in the US were available in at least one Member State. The majority of these 70 products were substances acting on the immune system.[36] [37] These products are referred to throughout this document as 'orphan-likes', indicating that they were not formally labelled as orphan products, but were likely to serve the rare disease population in the EU.

It took up to three years after the US marketing authorisation for the medicines to become available in the first Member State. After three years, they had reached three to four Member States.[38]

However, we should stress that even without any legislative intervention between 2000 and 2017, some additional orphan medicines would have been placed on the market in the EU anyway. Accordingly, not all the products authorised during this period can necessarily be attributed to the legislation. This issue will be dealt with in further detail in Chapter 5.1.

The baseline for *paediatric* medicines is derived from the impact assessment conducted before the adoption of the Paediatrics Regulation, and it is complemented by data from a report provided by the Agency in 2012.[39]

The impact assessment analysed several options: (1) no action; (2) self-regulation by industry; (3) Member State initiatives only; (4) introducing obligations for companies decoupled from rewards and incentives without obligations; (5) data protection or (6) market exclusivity for new paediatric products; (7) market exclusivity for development of

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32 See, for instance, the Interim report on Orphan diseases and drugs (Saphir Europe), February 1995, and Section 2.1 of the Study to support the evaluation of the EU Orphan Regulation (Technopolis Group and Ecorys – August 2019).

33 5 of these 15 products belonged to the group of 'immunomodulating agents', 3 addressed diseases of the blood & blood-forming organs like leukaemia, and another 3 addressed diseases of the alimentary tract and metabolism. The rest addressed diseases of the genito-urinary system and the nervous system.

34 Orphanet Report Series, 2019.

35 See Orphan study report (2019), Section 2.3.

36 See Orphan study report (2019), Section 2.2.

37 Like endocrine therapy, immunostimulants or immunosuppressants.

38 See Orphan study report (2019), Section 2.2.

39 5-year Report to the European Commission, General report on the experience acquired as a result of the application of the Paediatric Regulation.

paediatric developments from 'old' products. It concluded that if no action were taken, the existing situation (absence of medicines tested and authorised for children) would persist. No positive changes had been observed in the EU, even after the introduction of paediatric legislation in the US. And without obligations, the pharmaceutical industry would continue to avoid developing paediatric products.

Depending on the therapeutic area concerned, between 50% and 90% (for example, cancer treatments and HIV treatments) of authorised medicines in the EU were used off-label in children, i.e. without their effects on children having been studied. In addition, information on the outcome of studies conducted on children was not systematically available. It was thus often unclear for doctors treating children whether paediatric use of a particular product was authorised, whether there were insufficient data, or whether existing data showed that the medicine had negative effects when used in children.[40] Looking, for example, at the 317 centrally authorised medicines available at the time, around 78% were relevant to children, but only 34% were authorised with a paediatric indication.[41]

The selected option in the impact assessment combined some of the individual options mentioned above in a manner that would lead to a legislative framework very similar to the one already in place in the US. It was expected that a growing proportion of the available medicines would be tested on children and that the supply of products licensed for use on children would increase. The 'best case scenario' was described as follows:

- After 10-15 years, all patent-protected medicines (unless specifically exempted) would be studied in children, but it could take up to 20 years before the majority of tested products would be authorised for use in children.
- The PUMA system, together with accompanying measures such as EU research funding, would help to foster paediatric research on off-patent products. However, it was recognised that as the associated incentives were weak, the scheme would be unlikely to result in the authorisation of a sizeable number of new products.
- The increased availability of paediatric medicines would change over time with prescription practices. While this would gradually reduce off-label use in children, such use was not expected to disappear completely.
- European R&D would be boosted directly or indirectly, improving the competitiveness of EU companies in comparison with their US competitors. However, it was noted that the way the legislation was framed, and in particular the incentives selected, might push paediatric research towards the most profitable areas, rather than towards providing for patients' unmet needs.
- The testing of medicines in children would cut costs for national health systems, as adverse effects would be reduced, for instance, as would hospitalisations associated with the off-label use of medicines not tested in children. Though this cost reduction could not be quantified, it was thought to be sufficient to offset the costs

40 The Agency's five-year report (Section 3).

41 COM(2004)599 final Commission extended impact assessment and the Agency's five-year report to the Commission (Section 3).

that health systems would incur through the delay in the marketing of generics arising from the reward of SPC extension.

To assess how the legislation has been performing, it may also be helpful to consider the baseline in terms of research funding. Before the introduction of the two Regulations, not only was the pharmaceutical industry not interested, but the research community also showed limited interest.

This meant that for the vast majority of rare diseases, understanding of the natural history of the condition and the underlying causes of a disease was limited or even non-existent. Research funding only started to pick up in the years preceding the adoption of the legislation, but still in relatively small amounts and without coordination.

The fourth EU Framework Programme for Research and Technological Development (1994-1998), for example, sought to improve knowledge of rare diseases through relatively low funding (€7.5 million).[42] At national level, some Member States[43] had adopted specific measures to increase their knowledge of rare diseases and improve detection, diagnosis, prevention or treatment. France, Italy and Spain started to introduce specific national policies to boost the development of orphan medicines. This will be described in more detail in Chapter 5.4.

As regards research on children, the major problem in Europe was the limited number of clinical trials involving children. Some paediatric therapeutic areas, such as neonatology, were particularly neglected. Conducting clinical trials on small populations, such as children affected by a specific disease, would have required multinational trials to be started in most cases, which was complex and costly. One should also bear in mind that it was common as recently as the 1980s to assume that children should be protected from clinical trials. Only later was it recognised that clinical research in children was necessary, but that it should be conducted within a framework which ensured that ethical principles were respected and minors protected from abuse. These aspects were subsequently reflected in the EU Directive on clinical trials, adopted in 2001.[44]

*Other points of comparison*

In addition to comparing the situations in the EU *before* and *after* the entry into force of the Orphan and Paediatric Regulations, this evaluation refers to other regulatory systems

[42] Allocated to 23 projects for basic research, clinical research, and to set up European registries and databases and pan-EU rare disease networks.

[43] See Orphan study report (2019), Section 2.5 (France, Italy, Spain, Denmark and Sweden).

[44] Directive 2001/20/EC.

(mainly the US for orphan and paediatric medicines and Japan for orphan medicines).[45] A benchmark with the US will complement Chapter 5.[46]

[45] Comparison of availability and access in the EU to medicines that came to the market through orphan jurisdictions in the US and Japan before 2000. See also Section 2.2. of the Orphan study report (2019).

[46] Using data from a US Government Accountability Office Report on orphan drugs (November 2018).

## 3. IMPLEMENTATION / STATE OF PLAY

### Description of the current situation

The development of a new medicine is generally a long process, taking 10 to 15 years.[47] The full effects of legislative intervention are therefore not immediately visible, emerging only gradually.

### 3.1. Orphan Regulation

The Orphan Regulation has been implemented in full, including the setting up of the Committee for Orphan Medicinal Products (COMP). The provisions of the main act were complemented by additional provisions needed to implement the criteria for designation of a medicinal product as an orphan medicine (definitions of 'similar medicinal product' and 'clinical superiority'). Several guidance documents were adopted, some of which are regularly updated:

- Guidance on Article 3 (criteria for designation), Article 5 (procedure for designation and removal) and Article 7 (Union marketing authorisation - updated in 2016);[48]
- Guidance on Article 8(1) and (3) on the assessment of similarity of medicinal products versus authorised orphan medicines benefiting from market exclusivity;[49]
- Guidance on Article 8(2) for reviewing the period of market exclusivity.[50]

In addition, to reduce the barriers to innovation in medicinal products facing SMEs, Commission Regulation (EC) No 2049/2005[51] determined in 2005 that the Agency should provide scientific advice on designated orphan medicines free of charge to SMEs. Under the Paediatric Regulation, it became possible for orphan paediatric medicines to be granted two additional years of market exclusivity. There have been several court cases concerning the correct interpretation of Articles 3, 5, 7 and 8 of the Orphan Regulation.[52]

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47 Chapter 1 of the Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

48 Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products; C/2016/7253; OJ C 424, 18.11.2016, pp. 3–9.

49 Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity.

50 Guideline on the aspects of application of Article 8(2) of Regulation (EC) No 141/2000: Review of the period of market exclusivity of orphan medicinal products.

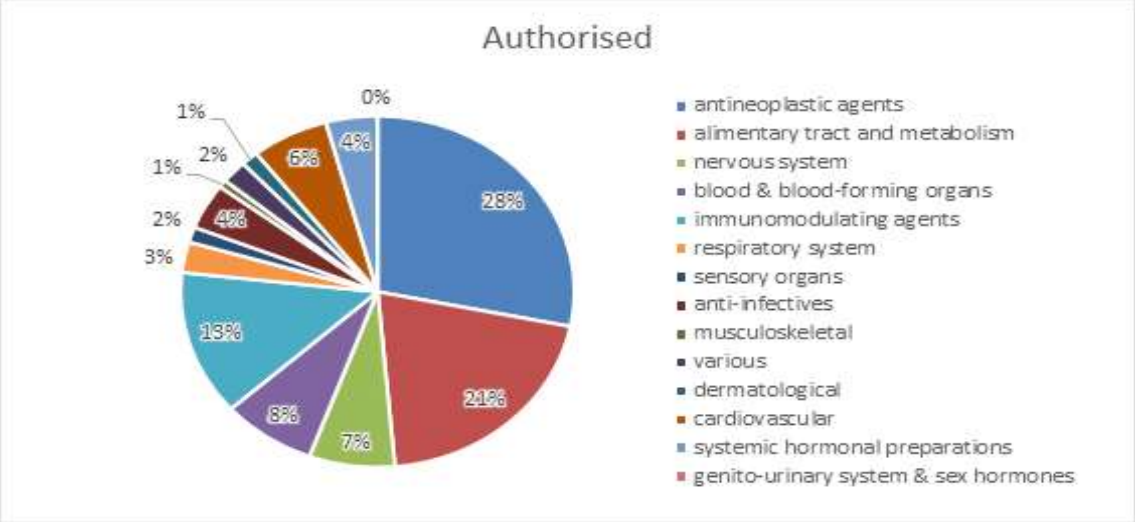
51 Commission Regulation (EC) No 2049/2005 of 15 December 2005 laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises.

52 Section 3.4 of the Orphan study report (2019).

A Commission staff working document, published in 2006,[53] stated that the EU's orphan legislation had exceeded initial expectations. In the first five years, 22 orphan medicines were authorised for the treatment of 20 different life-threatening or chronically debilitating rare diseases. It was possible that over one million patients suffering from these orphan diseases in the EU had benefited from the availability of these new treatments.

By 2017, 142 unique orphan medicines had *received* an EU marketing authorisation for 107 orphan indications. In a best case scenario, they were estimated to address the needs of 6.3 million EU patients (out of 35 million people suffering from rare diseases in the EU).[54] Of these medicines, 13 were authorised for more than one orphan disease, and a separate period of market exclusivity was granted.[55]

**Figure 4:** Therapeutic areas covered by authorised orphan medicinal products in 2017




Source: European Commission

Among both designations and authorised products, the largest share (Figure 4) is for anti-cancer treatments, followed by treatments for conditions of the alimentary tract and metabolic disorders. Overall, designations have covered a broad spectrum of therapeutic indications.

For the treatment of acute myeloid leukaemia alone there are 74 designations. Other diseases that have received attention are: glioma (56 designations), cystic fibrosis (51

53 Commission Staff Working Document on the experience acquired with the Orphan Regulation from 2000 to 2005.

54 Section 5.2. of the Orphan study report (2019).

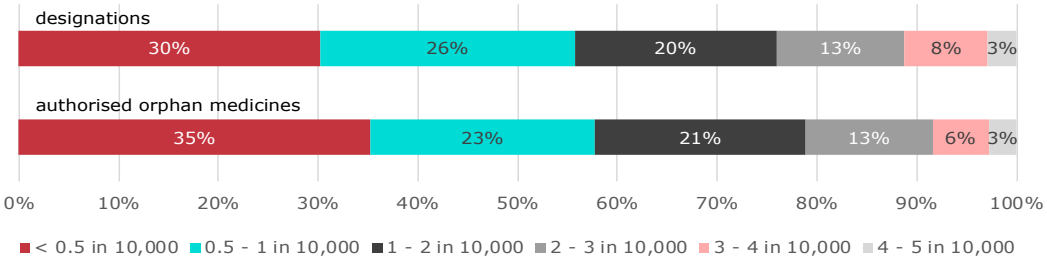
55 These numbers are further benchmarked against the performance of the Orphan Drugs Act in the United States in Chapters 5.1 (effectiveness) and 5.2 (efficiency).

designations), pancreatic cancer (47 designations), ovarian cancer (40 designations), multiple myeloma (32 designations) and Duchenne muscular dystrophy (31 designations).

The US Food and Drug Administration approved 351 orphan drugs for marketing between 2008 and 2017. 53% of these approvals were in one of two therapeutic areas that were also common for granted designations: oncology (42%) and haematology (11%).[56]

The distribution by prevalence is very similar among designated and authorised products (Figure 5). Around a third of products are for treatments with a prevalence of less than 0.5 in 10,000. These are mainly products for the treatment of diseases affecting the musculoskeletal system.

**Figure 5: Share of designations and authorised orphan medicines by prevalence**




Source: The Agency data, 2018.

Whereas in the past the vast majority of medicines were small chemical molecules, nowadays many new treatments are based on more complex biological products, such as proteins, antibodies or other large molecules, produced by means of biotechnology. They account for around one fifth of all 107 orphan designations.[57] Moreover, the share of advanced therapy medicinal products (ATMP) had shot up to around 18-20% of all new designations by 2016 (with a small decline of 14% in 2017).

Another general market development worth noting is the trend for larger pharmaceutical companies to purchase promising medicines at a late stage of R&D from smaller companies, instead of doing the research (or the basic part of it) themselves.[58]

### 3.2. Paediatric Regulation

[56] US Government Accountability Office Report on orphan drugs (November 2018), p. 23. See further elaboration of the benchmark with the US in Chapter 5.1 (effectiveness).

[57] Section 5.4.4. of the Orphan study report (2019).

[58] https://www.forbes.com/sites/nicolefisher/2015/04/22/are-ma-replacing-rd-in-pharma/#4f7c8116a21d

All but one of the provisions established by the Paediatric Regulation have been implemented, including the setting up of the Paediatric Committee (PDCO).[59]

The provisions of the main act were complemented by the specific guidance document:

- Guidance on format and content (updated in 2014)[60]

The provision mandating the creation of a distinctive symbol to be placed on products authorised specifically for paediatric indications was not implemented, as it was found that it could have been confusing for parents.[61]

*More clinical trials for children*

The number of agreed paediatric investigation plans (PIPs) exceeded 1000 in 2018, of which 450 were completed by June 2018.[62] The agreed PIPs covered a wide range of therapeutic areas, with infectious diseases (12%), oncology (10%) and endocrinology/metabolic diseases (9%) at the forefront. However, no particular area was dominant (Table 1).

There has been a clear upward trend in the number of completed PIPs, with over 60% finalised in the last three years. Currently, the conditions with most completed PIPs are immunology/rheumatology (14%), infectious diseases (14%), cardiovascular diseases and vaccines (10% each), with oncology and endocrinology/metabolic diseases accounting for only 7% of the completed PIPs.

In parallel, until 2018, EMA waived the obligation to conduct paediatric studies for over 600 products.[63] [64]

**Table 1. Agreed, completed PIPs, authorised paediatric medicines by area**

| Therapeutic area | Number of agreed PIPs | Number of completed PIPs | Completed/ agreed PIPs | Number of authorisations of paediatric indications |
|---|---|---|---|---|
| Anaesthesiology | 3 | 0 | 0% | 0 |
| Cardiovascular diseases | 48 | 9 | 19% | 6 |
| Dermatology | 33 | 5 | 15% | 5 |
| Diagnostics | 13 | 2 | 15.4% | 1 |
| Gynaecology | 12 | 3 | 25% | 1 |

59 https://www.ema.europa.eu/en/committees/paediatric-committee-pdco
60 Communication from the Commission (2014C 338/01).
61 Section 3 of the Commission five-year report.
62 Agency's 10 years report, section 3.1, 10 years of the EU paediatric regulation (COM(2017)626) and annual reports from the Agency.
63 Ibid.
64 Under Article 11 of the Paediatric Regulation, a waiver can be agreed if the products may be inefficient or unsafe in children, if the disease they intend to treat does not exist in children, or if the product would not bring a significant therapeutic benefit compared with an existing treatment.

| | | | | |
|---|---|---|---|---|
| Endocrinology/metabolic diseases | 70 | 7 | 10% | 6 |
| Gastroenterology/hepatology | 33 | 5 | 15% | 4 |
| Haematology | 46 | 3 | 6.5% | 1 |
| Transplantation | 10 | 2 | 20% | 1 |
| Immunology/rheumatology | 46 | 14 | 30.4% | 8 |
| Ophthalmology | 17 | 2 | 12% | 2 |
| Vaccines | 37 | 9 | 24.3% | 9 |
| Psychiatry | 17 | 2 | 12% | 2 |
| Neurology | 45 | 3 | 7% | 2 |
| Infectious diseases | 96 | 14 | 15% | 14 |
| Neonatology/paediatric intensive care | 16 | 1 | 6% | 1 |
| Oncology | 83 | 7 | 10% | 2 |
| Pain | 9 | 11 | 1% | 0 |
| Pneumonology/allergy | 35* | 7 | 20% | 6 |
| Uro-nephrology | 16 | 1 | 6% | 0 |
| Orthopaedic diseases | 9 | 1 | 11% | 0 |
| Allergens* | 114 | 0 | 0% | 0 |
| **Total** | **808** | **98** | **12%** | **71** |

Note: *Allergens PIPs assessed in 2010-2011 due to a change in regulation in Germany are listed separately here.
Source: EMA database (PedRA)

Nearly all PIPs for new medicines that are linked to an adult development include a delay in the implementation of one or more measures of the PIP (deferrals) until sufficient data on safety and efficacy are available in adults or in older age-groups. To verify companies' compliance with the agreed deferrals, marketing authorisation holders are required to submit annual reports to the Agency.[65] The list of companies that have not submitted one or more annual report(s) is published annually by the Commission on the basis of an EMA report (3 in 2018 and 2017, 8 in 2016, 11 in 2015).[66]

The agreed PIPs have had a direct effect on clinical research in the EU. They have resulted in more clinical trials in Europe. For instance, 12.4% of all clinical trials included children in 2016.

The Agency provides scientific advice (SA) on paediatric matters free of charge[67], and in 2018 it reached 25% of the total of 634 pieces of advice provided by EMA.[68]

*More medicines for children*

By 2018 there were over 200 new centrally authorised medicines authorised for use in children[69], and 6 PUMA authorisations had been granted by that time.[70] In addition, before

65 Article 34.4 of the Paediatric Regulation.
66 https://ec.europa.eu/health/human-use/paediatric-medicines_en
67 Article 26 of the Paediatric Regulation.
68 Report from the Agency to the European Commission 2018
69 Including new paediatric pharmaceutical formulations and indications.
70 EMA, 10-year report, section 1.1 and annual reports from the Agency.

the Regulation was introduced, the competent authorities completed assessments of more than 19 000 reports on paediatric studies (concerning 1000 active substances).[71] This resulted in 45 central and 2219 national reassessments, leading to about 140 updates of the product information and 16 new paediatric indications.

In response to a survey that provided input into the Commission's 10-year report, the majority of respondents estimated that the increase in the number of medicines available was in the 5-10% range. As regards prescription habits, 58% of respondents said that as a result of the Regulation practitioners were increasingly prescribing approved medicines according to their licensed indication for children.

*Rewards*

By 2016, more than 40 medicinal products had been granted an SPC extension by the national patent offices in one or more Member States, resulting in over 500 national extensions;[72] eight products had obtained the orphan reward of two additional years of market exclusivity until the end of 2018.[73]

**Monitoring obligations**

*Reports under the Orphan Regulation*

Article 10 of the Orphan Regulation required the Commission to publish a general report on the experience acquired from applying this Regulation, to include an account of the public health benefits.[74]

Article 9 of the Orphan Regulation obliges the Commission to publish a regular detailed inventory of all incentives provided by the EU and its Member States to support research, development and availability of orphan medicines. Since 2000, the Commission has published three such reports.[75] They have highlighted the steady increase in the number of requests for orphan designations over the years, showing the growing interest in this field. The orphan designation has been a requirement for Framework Programme funding since 2009. Both the number of orphan medicines applications submitted and the number of designations granted by the Commission rose by over 50% over 2009-2015, in comparison with 2000-2008.

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71 Articles 45 and 46 of the Paediatric Regulation.

72 Commission 10-year report.

73 EMA annual reports to the European Commission, https://ec.europa.eu/health/human-use/paediatric-medicines_en.

74 Commission Staff Working Document on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained

75 Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products: 2015, 2005, 2002.

In line with Article 5(10), the sponsors of orphan designations are obliged to submit to the Agency an annual report on the state of development of the designated medicinal products. However, despite receiving this information, the Agency's Committee for Orphan Medicinal Products is not formally obliged to evaluate these reports.

*Reports under the Paediatric Regulation*

Article 50 of the Paediatric Regulation states that the Commission must report to the European Parliament and to the Council, 5 and 10 years respectively after the application of the legislation, on the experience acquired with that legislation.[76] These reports have been accompanied by extensive reports from the Agency to the Commission.[77]

The same article also requires the Commission, on the basis of information received from the Agency, to make public a list of the companies and products that have benefited from any of the rewards and incentives set out in this Regulation. This list includes the companies that have failed to comply with any of the obligations laid down in this Regulation. Companies discontinuing the placing on the market of a paediatric product/a paediatric indication must inform the Agency, which then makes this information public (Article 35). Further reporting obligations in the event of infringement of the Regulations' provisions are set out in Article 49 of the Paediatric Regulation.

## 4. METHOD

For the purpose of this evaluation, a Roadmap[78] was published on 11 December 2017 for a four-week period. Feedback was received from 23 stakeholders from business associations, companies, public authorities, NGOs, academic/research institutions, 5 from EU citizens and 2 from non-EU citizens.

### 4.1 Data gathering, methodology and analysis

A wide range of data sources have been used to collect evidence to answer the evaluation questions. Stakeholders' views were gathered through open public consultations and targeted consultation activities, including several workshops.[79] [80] All stakeholder groups were reached, and the risk of receiving incomplete or biased information was mitigated by

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76 Better Medicines for Children From Concept to Reality.
State of Paediatric Medicines in the EU, 10 years of the EU Paediatric Regulation.

77 General report on the experience acquired as a result of the application of the Paediatric Regulation (5-year Report to the European Commission, July 2012);
General report on the experience acquired as a result of the application of the Paediatric Regulation (10-year Report to the European Commission, August 2017).

78 Roadmap for the evaluation of the legislation on medicines for children and rare diseases (medicines for special populations)

79 Multi-stakeholder workshop held at the Agency on 20 March 2018.

80 Conference organised by the Commission, 'Medicines for Rare Diseases and Children: Learning from the Past, Looking to the Future'. 17 June 2019.

triangulating different sources of information, including multiple stakeholders, juxtaposing divergent viewpoints, and by providing the relevant factual information where possible.

Two independent studies were commissioned to support this evaluation, referred to in what follows as the 'orphan study'[81] and the 'paediatric study'.[82] In addition, the outcomes of an independent study on the impact of the pharmaceutical incentives were also used.[83]

The methodologies used in the orphan study included a **systematic review** of the peer-reviewed and grey literature, a **portfolio analysis** of the data on all designated and authorised orphan medicines (provided by **the Agency**[84]**),** as well as sales data (provided by **IQVIA and MPA Business Services**[85]**)** and a high-level **cost-benefit analysis**. The study included targeted consultations, conducted by means of surveys and interviews, involving five distinct groups of stakeholders:

1) national public authorities in EU Member States,

2) developers of innovative medicinal products,

3) developers of generic medicines,

4) patient and consumer organisations, and

5) Academic researchers and experts.[86]

The paediatric study focused on the Regulation's economic impact. An **analysis** of the **regulatory costs** and the indirect and direct **economic and social benefits** was performed. It included a **systematic review** of peer-reviewed and grey literature, a consultation of interested parties and a Delphi analysis.

A study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe provided additional findings which fed into the evaluation.[87]

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81 Study to support the evaluation of the EU Orphan Regulation, final report, July 2019).

82 Study on the economic impact of the Paediatric Regulation, including its rewards and incentives (2016).

83 Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (Copenhagen Economics, 2018).

84 Aggregated data on uptake and costs of incentives relating to the EU Orphan Regulation were provided.

85 IQVIA is a contract research and analytical services organisation that collects data including global pharmaceutical sales data (https://www.iqvia.com/). MPA Business Services is a business intelligence and market research company for the pharmaceutical and healthcare industry. It provides services including patent analytics services (http://mpasearch.co.uk/).

86 See the abstract of the Orphan study (2019).

87 Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe ( 2018).

A synopsis report summarising all activities carried out as part of stakeholder consultations, and their results, is provided in Annex 2.

Overall, the Commission agreed with the conclusions of these studies, despite the methodological limitations described below. The only exception was the result of the cost-benefit analysis for the pharmaceutical industry.[88] The Commission did not agree with the calculations performed by the contractor, and refined the cost-benefit analysis further by adding a competitive profit margin of 10% of the 'net' turnover (i.e. turnover minus the orphan exclusivity share).[89] For more details of the methodological aspects of the studies, please refer to Annex 3 of this report.

In addition to the above-mentioned studies, use was made of:

- the reports from the Commission to the European Parliament and the Council on the 5 and 10 years of implementation of the Paediatric Regulation[90],
- technical reports from the Agency to the Commission on the experience acquired as a result of the application of the Paediatric Regulation after 5 and 10 years of its application[91], and
- yearly reports from the Agency[92] on how the legislation's various provisions had performed.

### 4.2. Limitations and robustness of the findings

*As regards the orphan study*, the shortcomings and challenges listed below should be taken into account.

- Since there was no impact assessment for the Orphan Regulation, the baseline for the intervention had to be constructed retroactively.

- For this baseline, the concept of 'orphan-likes' was established, referring to products authorised before the Orphan Regulation for the treatment of rare diseases took effect. The concept is based on the following process. A list of US orphan medicinal products was obtained from the FDA's website. Their trade names were then matched with product names listed in the IQVIA database. If the trade name was a single word, an exact match with the first word of the product name was

88 Section 8.2.2. of the Orphan study report (2019).

89 The contractor had referred to 'normal profit margins' without quantifying them (and *de facto* counting profits as costs). See, for further explanation, Chapter 5.2.1. of this SWD.

90 Better Medicines for Children, From Concept to Reality;
State of Paediatric Medicines in the EU 10 years of the EU Paediatric Regulation.

91 General report on the experience acquired as a result of the application of the Paediatric Regulation (5-year Report to the European Commission, July 2012);
General report on the experience acquired as a result of the application of the Paediatric Regulation (10-year Report to the European Commission, August 2017)

92 https://ec.europa.eu/health/human-use/paediatric-medicines_en

counted. If the trade name consisted of two words, a match with the first two words of the product name was counted, and so on, depending on the number of words in the trade name of a US orphan medicinal product. All identified products are assumed to be 'orphan-like products'. Branded products were identified on the basis of a trade name, but they may also have been marketed under different trade names in different countries. This means that the volumes of such products may have been underestimated, which would have affected sales data.

- Overall, the assessment has probably:
    - overestimated costs (per quality-adjusted life year, QALY), as some orphans can be assumed to see generic/biosimilar entry in the longer run;
    - underestimated the increased availability, as more mature markets will see products available in more national jurisdictions, associated with product launch sequencing and possible generic/biosimilar entry over time;
    - failed to analyse generic competition in its entirety. This is because the estimate of the orphan reward (calculated based on price drops following generic/biosimilar entry) is tentative, given the timing of the evaluation; so far, only a limited set of orphans have lost market exclusivity.

- R&D costs of orphan medicines for developers had to be estimated on the basis of information in relevant literature, as sponsors of orphan medicines were unwilling or unable to provide these costs. Most R&D *funding* through EU programmes in basic and translational research, including research to develop orphan medicines, came from the sixth and seventh EU Framework Programmes for Research, Technological Development and Innovation (2002–2006 and 2007–2013), and Horizon 2020 (2014-2020). In addition to these EU programmes and initiatives, it is worth noting that over 90% of EU public funding for health research comes from the Member States. Although the available data provide some insight into the level of activity and funding, it has not been possible to produce accurate estimates of overall research funding for rare diseases in the EU; in this respect, the situation of rare diseases is similar to that of almost all other types of diseases. This is partly because, while some research programmes or projects are very clearly designed to improve understanding of rare diseases or develop treatments for them, others may be much more fundamental in nature. The CORDIS database contains information on EU-funded research projects, but there is no single database containing information from national funders. Rare diseases differ in this respect from several other research areas.

As regards the use of the IQVIA database to assess the Regulation's effectiveness and efficiency, the following limitations applied:

- The research team only had access to revenue and volume data for 2008 (first quarter) to 2017 (third quarter) for EEA countries, excluding Cyprus, Malta, Denmark, Iceland and Liechtenstein. The dataset provides only partial information (retail turnover) for the Netherlands, Latvia, Greece, Luxembourg and Estonia. Finally, the dataset presents combined data (no distinction between hospital and retail data) in the case of Slovenia.
- Revenues are based on list prices. In reality, the actual prices may be different, owing to price negotiations between companies and payers, which are usually confidential.
- The supply of orphan medicines may have been underestimated, given the specific sampling issues applicable to low-volume products (e.g. when a sample of pharmacies is used to estimate retail sales) or the possible use of direct import schemes ('named patient basis'), which are not captured through nationally operating wholesalers.

These limitations affected the calculations to establish availability and companies' sales revenues and thus the findings presented in the effectiveness and efficiency sections of the staff working document (SWD).

The *paediatric study* had the following limitations:

- Since it often takes over 10 years to develop a medicine, some of the provisions introduced by the legislation are only just starting to yield the expected results (such as the number of finalised paediatric investigation plans, PIPs). This means it was not possible to collect representative data for all provisions.
- For effectiveness in particular, it has not always been possible to provide data before 2017 because publically available data were not up to date. Data were updated when made available from a publicly accessible source, such as the yearly Agency reports to the Commission.
- For efficiency, the costs incurred in drawing up a PIP were estimated, as they are based on voluntary self-reporting by organisations. Furthermore, as many clinical trials are mixed trials, respondents may have had difficulties in correctly reporting the costs of the paediatric part only. The data provided may therefore have been over- or underestimated, affecting the representativeness of the sample.
- For efficiency, several assumptions were made in determining the value of the basket of medicinal products. These are linked to:
  (1) the variability of the year in which the rewards for the products selected were granted;
  (2) the variability of the Member States in which the rewards were granted;
  (3) the impossibility of determining the impact of generic entry in some Member States; and
  (4) the different dosages and presentations of the same product available in

various Member States.
Triangulations of information and extrapolations were used in the analysis to ensure the robustness of the findings.

- For efficiency, the costs incurred by regulatory authorities could not be estimated in detail.

## 5. ANALYSIS AND ANSWERS TO THE EVALUATION QUESTIONS

### 5.1 EFFECTIVENESS

**Main findings**

*Orphan Regulation*

The various incentives provided by the *Orphan* Regulation have spurred on the development of new treatments for rare diseases. However, not all orphan products authorised under the Regulation are the direct results of such incentives. Of the 131 orphan medicines authorised in the EU since 2000, the Orphan Regulation is estimated to be responsible for at least 8-24 new ones. The remaining 107-113 products were made available more quickly, and reached more people across the EU, than before the Regulation took effect. SMEs, in particular, benefited from protocol assistance and fee reduction. However, in many cases charitable foundations and academic institutions are not eligible for fee reduction because of difficulties in meeting the 'SME criteria'.

The development of new orphan medicines addressed some of the rarest diseases. However, the tools provided by the Orphan Regulation have not done enough to direct the development in areas of greatest 'unmet medical need'. The Regulation has not been sufficiently effective to catalyse the clinical development to areas where there are no treatments yet. At the same time, the number of treatment options is expanding in specific areas, such as oncology. Here, the market is starting to look more and more like that of the non-orphans.

Stakeholders have questioned whether the currently used prevalence threshold of 5 in 10,000 is an appropriate criterion. The criterion of 'insufficient return on investment' has only been used once, as companies seem to fear the possible shortening of the market exclusivity period to six years for economically successful products, when reassessed after five years.

Marketing authorisation of orphan medicines at EU level (availability) has not translated into accessibility of the authorised medicines for patients in *all* Member States. Access to orphan medicines varies considerably across Member States, mainly owing to factors beyond the Regulation's ambit, such as different national pricing and reimbursement

systems, companies' strategic decisions on market launch, and the role of healthcare providers.

*Paediatric Regulation*

The Paediatric Regulation has led to an increase in clinical research involving children and in medicinal products specifically authorised for them, as well as to improvements in the level of information available on such products. However, these advances have been more substantial in cases where a parallel adult medicine development was ongoing.

The Regulation has no effective instruments to direct research and development toward specific therapeutic areas and it works better in areas where the needs of adult and paediatric patients overlap. The SPC extension is of particular relevance, economically speaking, to products with high sales in adults (blockbusters). Accordingly, it may not be successful in incentivising the development of medicines in line with children's most pressing needs. Neither regulation has proven effective in boosting the development of innovative medicines for children with rare diseases.

Little use has been made of the other rewards provided by the Paediatric Regulation, the orphan reward, or the PUMA (paediatric use marketing authorisation) scheme.

The analysis showed that the Regulation has had a positive effect overall in gradually helping to reduce off-label use of adult medicines in children. This result is however impacted by external factors, such as companies' launch decisions, the reimbursement and pricing decisions taken by national competent authorities, and doctors' patterns of prescription.

How effective the two Regulations have been can be assessed from the relation between the effects observed and the stated objectives. To this end, this chapter assesses the extent to which the two Regulations have helped boost research, development and authorisation of remedies for rare diseases and medicines for children. It also examines whether the products developed under the Regulations serve patients' needs effectively, in terms both of addressing unmet needs and of timely availability across the EU. Finally, it examines the Regulations' impact on R&D and competitiveness.

### *5.1.1 – The impact on research and development for orphan medicines*

The Regulation has had a substantial impact on R&D in the field of orphan medicines in the EU. Between 2000 and 2017, 1956 designations were granted and 142 orphan medicines were authorised (11 were subsequently withdrawn, thus leaving 131 on the market). The increasing number of orphan designations reflect the industry's growing interest in developing orphan medicines. In the first three years following the adoption of the Orphan Regulation, between 72 and 80 applications for designations were submitted

annually (see Figure 6), instead of 5-12, as was initially estimated for that period. In recent years, the number has exceeded 200 applications per year.

The 1956 designations covered 698 different indications. They included 637 treatments (91%), 53 products used for prevention (8%), and 8 products used for diagnosis (1%).

However, only about 5% of orphan products under development (designations) went on to be authorised as orphan medicinal products.

By the end of the first five years, 22 orphan medicines had been authorised for the treatment of 20 different life-threatening or chronically debilitating rare diseases. An upward trend can be seen from the average numbers of orphan marketing authorisations in three six-year periods: 3.7 per year in 2000-2005, 7.8 per year in 2006-2011 and 12.2 per year in 2012-2017. At the same time, the US saw an even more impressive increase (from 17 in 2008 to 77 in 2017).[93]

**Figure 6: Number of applications submitted, designations granted and authorised orphan medicines (2000 – 2017)**


Source: Agency (2018)

93 US Government Accountability Office Report on orphan drugs (November 2018), p. 23.

To estimate what proportion of the orphan medicines authorised in the EU can be attributed to the EU Orphan Regulation, the trend in marketing authorisations for orphan medicines from 2000 to 2017 was compared with the general market trend in pharmaceutical product development. This analysis[94] shows that since 2011, the number of marketing authorisations for orphan medicines has not only grown over time, but has grown substantially faster than those for non-orphan medicines. Using these data, it was estimated that of the 131 orphan medicines authorised in the EU, between 18 and 24 (almost 20%) were developed as a result of the legislation. If orphan medicines had followed the same market trend as non-orphan medicines, then only about 107 to 113 would have been authorised.[95] Having said that, we have to acknowledge that there is no best available statistical methodology to assess how the legislations impact directly the development of medicines due to the lack of sufficient data. Therefore, the above mentioned figures are indicative and may be under representative.

**Table 2 Average number of new marketing authorisations per year**

| Year | Orphan medical products | Increase (%) | Non-orphan medical products | Increase (%) |
|---|---|---|---|---|
| 2000-2005 | 3.7 | | 28.8 | |
| 2006-2011 | 7.8 | 111 | 63.8 | 122 |
| 2012-2017 | 12.2 | 56 | 68.3 | 7 |

Source: Orphan Study Report

Compared to the EU, the US has higher annual figures for both designations and marketing authorisations for orphan medicines. Differences in the eligibility criteria for obtaining an orphan designation in the EU, US and Japan also result in different percentages of designated orphans finally authorised in these regions (8% of successful marketing authorisations from orphan designations were identified in the EU, compared to 15% in the US, and 65% in Japan).[96] [97]

In the EU, rare diseases are defined as affecting smaller numbers of people than in the US. Some medicines not eligible for orphan designation in the EU are thus considered orphan medicines in the US.

Under Japanese legislation, only medicines with a strong chance of approval are designated as orphan drugs. This may account for Japan's high approval to designation ratio.

94 For all calculations, see Section 1.4.2. of Annex 3.
95 Idem.
96 Murakami M and Narukawa M, Drug Discovery Today, (2016), 21(4):544-549.
97 See also Annex 7 (International context).

In 2017, the FDA took several steps to improve the consistency and efficiency of its evaluations to verify the accuracy of manufacturers' claims in their orphan designation applications. These steps included introducing a standard review template and providing guidance on completing it.[98] No comparable analysis of the consistency of the EMA assessments was performed in connection with this report.

**Role of incentives under the Orphan Regulation**

The average additional protection offered by the **market exclusivity reward** was calculated at 3.4 years. The economic value of this reward, calculated for a limited sample of products, averaged 30% of total turnover. For around half of the analysed sample, market exclusivity was the last protection to expiry.[99]

Developers pointed out that companies' decisions to launch new products in the EU were influenced by the possibility of market exclusivity laid down by the Regulation and the legal certainty it provides.[100] They considered market exclusivity to be the main incentive[101], which, together with orphan designation, would enable fledgling companies to attract venture capital.

A comparison with the US nuanced these statements. In this context, developers underlined 'non-incentive' drivers of growth in orphan medicines, such as the ability to demand high prices. The same report noted that marketing exclusivity was having a declining impact on protecting orphan medicinal products from competition in the US.[102]

Market exclusivity is not the only major incentive. The EU and its Member States, within their respective spheres of competence, provide *other* incentives for developing medicines for rare diseases. While the EU supports research, some Member States provide tax incentives, for instance.[103]

Although developers considered the two-year **paediatric extension** to the market exclusivity to be very important,[104] only a few medicinal products had actually benefited from this reward.[105]

The specific form of scientific advice offered by the Agency under the Regulation, known as **protocol assistance,** has significantly increased over time: from 4 in 2000 to over 125

98 US Government Accountability Office Report on orphan drugs (November 2018), p. 7.
99 See Chapter 5.2 and Annex 3 of this SWD.
100 Section 10.2 of Orphan study report (2019).
101 A natural monopoly that could give pharmaceutical companies a very strong bargaining position in price negotiations with payers. (Section 1.1 of the Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018)).
102 US Government Accountability Office Report on orphan drugs (November 2018), pp. 31-32.
103 Inventory of EU and national incentives to support research and development.
104 Section 7.1.1. of the Orphan study report (2019).
105 An analysis of this reward will be provided in Chapter 5.1.3. of this SWD.

requests per year in 2017. While the information available does not allow any firm conclusions to be drawn[106] as regards the role of protocol assistance, several studies show a strong association between compliance with protocol assistance recommendations and marketing authorisation success for orphan medicines. Targeted surveys have indicated that protocol assistance is very important for industry, especially for relatively inexperienced developers. The growing share of small and medium-sized enterprises (SMEs) among applications for protocol assistance (50% in 2017) tallies with the observation that SMEs now account for around half of all designations annually.[107]

The **fee reduction** is considered important by developers, especially SMEs, as fees are waived completely for this group. It was noted, though, that for some sponsors, such as charitable foundations and academic institutions, it can be difficult to meet the requirements for SME status[108] and for them the Agency fees can still be significant. There were no data to determine whether these fee reductions, compared to the overall costs of R&D, have made an appreciable impact on the number of products under development. It is not known either how often these fees do represent a real barrier to potential sponsors.

The effectiveness of the incentives also depends on many other contextual factors that influence the outcomes of clinical development of orphan medicines, such as the experience of the developer, market and product characteristics, and the stage of development of the product. Even the best designed intervention may not succeed if it is not supported by progress in basic research or new scientific leads for product development. It was clear from the beginning that market exclusivity would not be the only main incentive, and that it would be up to the EU and the Member States to provide other incentives for developing orphan medicines, such as support for research.

Moreover, the effects of individual incentives cannot be isolated from each other, nor can the effectiveness of incentives offered by the EU Orphan Regulation be seen as separate from that of incentives offered by similar regulations in other jurisdictions such as the US.[109]

In the international comparison of incentives, the duration of market exclusivity (10 years in the EU 10, vs. 7 years in the US) is the most striking difference. However, other jurisdictions (US, Japan) also provide tax incentives, whereas the EU does not.[110] In this

106 Section 7.1.1. of the Orphan study report (2019).

107 Section 7.5.2. of the Orphan Study report (2019).

108 SMEs are micro, small and medium-sized enterprises (companies employing fewer than 250 people, with an annual turnover not exceeding EUR 50 million, and/or an annual balance sheet total not exceeding EUR 42 million.

109 Although in a recent US report developers downplayed the significance of US incentives for developing orphan drugs (US Government Accountability Office Report on orphan drugs, November 2018, p. 31).

110 See also Annex 7 for a comparison of incentives offered by the EU, US and Japanese regulatory frameworks.

respect, the US market may be regarded as quite attractive; most of the revenues from orphan medicines are earned in the US alone.[111]

*5.1.2 – The impact on unmet needs and timely availability for orphan medicines*

The Orphan and the Paediatric Regulation were designed to address the unmet medical needs of patients suffering from rare diseases and of children. However, the concept of unmet medical need has not so far been standardised among patients, industry, regulators, HTA bodies and payers.[112] [113] For the purpose of this analysis, the concept of unmet medical need was therefore operationalised. It was assessed whether, and to what extent, the Regulations have contributed to the development and availability of orphan drugs and paediatric medicines, and what therapeutic areas are covered by these medicines.

The extent to which new orphan medicines target conditions for which no alternative treatments exist and the rarity of conditions for which designations were granted were also considered. Finally, it was assessed whether EU patients have access to such medicines. After all, there is no point in developing treatments if patients have no access to them.

**Product development in different therapeutic areas and indications**

Since 2000, almost all therapeutic areas have been covered by authorised orphan medicines. Only in the categories of genito-urinary tract conditions and sex hormones and anti-parasitic products have no medicines yet been authorised.[114] Despite this development, 95% of rare diseases still have no treatment option; the situation in the US is very similar.[115] [116] Furthermore, of the 142 authorised orphan medicines, only 28% target diseases for which there were no alternative treatments.

To compare this to the situation *before* the Orphan Regulation came into force, 70 medicinal products already authorised as orphans in the US were available in at least one

[111] 70% of global revenues from orphan medicines come from the US (Orphan Drug Report 2019, EvaluatePharma). See also Chapter 5.2. of this SWD.

[112] The concept was important for decision making. Value in Health, Volume 22, Issue 11, November 2019, pp. 1275-1282;

[113] See, *inter alia*, the outcomes of the European Commission Conference on 'Medicines for Rare Diseases and Children: Learning from the Past, Looking to the Future' (June 2019) – details in Annex 2 (Synopsis report).

[114] See Section 5.4.1 of the Orphan study report (2019).

[115] Orphan products, like any medicinal product, must be clinically tested before attaining marketing authorisation. While the legislation may act as enabler, it cannot substitute inherent research challenges that affect product development.

[116] US Government Accountability Office Report on orphan drugs, November 2018.

Member State in 2000.[117] Most of these 70 products were substances acting on the immune system.[118]

In the years immediately after the Regulation's introduction, the annual number of new orphan indications declined rapidly. While in 2001 78% of orphan designations were for new indications (i.e. indications for which no products had been authorised), in recent years the figure fell to less than one in five (<20%) designations.

For those indications where products have already been authorised, a product needs to demonstrate significant benefit over existing treatment options to be maintained as an orphan product and to receive market exclusivity. Owing to the increasing number of orphan medicines authorised, more and more products need to demonstrate significant benefit. An analysis performed in 2018 on products authorised between 2000 and 2015 showed that demonstration of significant benefit was required in 64% of designations and for 73% of products at the time of marketing authorisation. This indicates that the EU Orphan Regulation is becoming less effective in directing research to areas where there are no treatments yet, and product development tends to cluster around certain (more profitable) therapeutic areas. Consequently, the number of treatment options is expanding for some conditions, and the market is starting to look more like the one for 'standard' medicines.

An area which has attracted considerable attention, for instance, is anti-cancer treatments, accounting for around a third of all designations and authorised products so far. As treatments for rare cancers often have broader applicability across a range of other cancers - some of which may not be considered rare - these products may have a higher profit potential. A similar degree of concentration has been observed in the US, where a large share of orphan drug marketing approvals (42%) were in oncology between 2008 and 2017.[119]

Stakeholder consultations indicate that the accelerated development of new treatments in oncology can be explained by a better understanding of the natural history of disease and of the molecular pathways it involves.

The lack of development in certain therapeutic areas, according to the developers surveyed, may be attributable to the fact that companies tend to focus on certain areas of disease, on a lack of scientific expertise, and on a lack of basic research in certain fields. Other possible reasons are insufficient knowledge of disease mechanisms and poor understanding of the

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117 See Chapter 2 (Baseline and points of comparison) of this SWD. These 'orphan-likes' were not formally labelled as orphan products in the EU, but have likely also served the rare disease population in the EU.

118 Such as endocrine therapy, immunostimulants or immunosuppressants.
See Section 2.2. of the Orphan study report (2019).

119 US Government Accountability Office Report on orphan drugs, November 2018, p. 23.

underlying biology. On top of this, for ultra-rare diseases (affecting less than one patient in 10,000) the study of patients' clinical symptoms and the conduct of effective clinical trials is constrained by the small number of patients available for robust statistical analyses. The same barriers to developing orphan medicines have also been identified in the US.[120]

The Regulation has therefore not met its aim of addressing unmet medical needs in all therapeutic areas.

**Development of follow-on products**

Granting orphan market exclusivity to a given product could potentially constitute a barrier to developing follow-on products of an orphan indication covered by the first authorised product. If that were the case, patients unable to benefit sufficiently from the first medicine could potentially be deprived of additional treatment options.

In theory, the EU Orphan Regulation contains provisions to mitigate the impact of market exclusivity on the development of follow-on products. First, the market exclusivity for orphan medicines only extends market protection against competition by 'similar medicines with similar indications'. A similar medicine is understood to contain 'an identical active substance, or an active substance with the same principal molecular structural features and which acts via the same mechanism'.[121]

A product that contains a different active substance, or that acts on a different molecular pathway is therefore not prevented from entering the market alongside the original product, even if the latter is still under market exclusivity. In the case of biological medicines including advanced therapy medicinal products (ATMPs), whose principle molecular structural features cannot be identified, the similarity between two active substances is assessed on the basis of their biological and functional characteristics.[122] However, to be eligible for an orphan designation itself, that product would need to demonstrate significant benefit over the treatment already authorised.

It could therefore be argued that the fact that a competing product has obtained a marketing authorisation influences decisions on whether to continue the development of a product. For 82% of orphan indications where there is at least one authorised orphan medicine, there is no other authorised orphan medicine (yet). Also, in a market that is inherently small, developers may question whether there is sufficient willingness among patients and

120 Idem, p. 30.

121 Article 3C of Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority'. Available at https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2000_847/reg_2000_847_en.pdf. Accessed 13 January 2019.

122 Owing to major developments in the field of ATMPs, the definition of 'similar medicinal product' was amended in 2018 by Commission Regulation (EC) 2018/781.

prescribers to switch to another product. However, most developers surveyed reported that competition with another organisation, whether likely or already existing, does not lead to the suspension, termination, refocusing or delay of new or ongoing R&D.

Another study[123] showed that the likelihood of a rare disorder with an approved orphan medicine obtaining at least one follow-on orphan medicine was strongly associated with the number of people affected by this disease, turnover of the first orphan product, specific disease class, the extent of scientific knowledge about the disease, and whether it starts during childhood or later on. In areas where there are no follow-on orphan medicines, the main reasons seemed to be the time needed to develop follow-on products and market size, rather than any 'monopolies' created by market exclusivity.

**Rarity of conditions and 'insufficient return on investment'**

Around a third of authorised orphan products are for treatments with a prevalence of less than 0.5 in 10,000. These are mainly products for the treatment of diseases affecting the musculoskeletal system, but also some rare forms of cancer. A recent study shows that 84.5% of analysed rare diseases have a very low prevalence (less than 1 in 1,000,000). However, most of the *population* burden of rare diseases is attributable to the 4.2% diseases in the most common prevalence range (1–5 per 10,000).[124]

Although the Orphan Regulation helped promote the development of products tackling some of the rarest diseases, where the market potential is limited, according to some stakeholders (patients' organisations, national authorities, and researchers), it also stimulated development in areas where sufficient market stimuli already exist. Stakeholders questioned whether the prevalence threshold currently used of 5 in 10,000 is appropriate as a criterion. In this regard, it was argued that the expected use of a product in an underlying condition (once, repeated, life-long) has a decisive role and may also need to be taken into account during the assessment if the development of truly financially-unattractive areas is to be fostered (such as paediatric oncology). Hence, the question is raised whether a different method for calculating prevalence is needed or even a different criterion (the US and Japan, for instance, also use criteria based on absolute numbers of patients in these countries).

Moreover, a graduation/differentiation of the incentives to the magnitude of rarity or the scale of investment needed may enable incentives to be focused better on therapeutic areas that are neglected or where a bigger investment is necessary. It has been also suggested that using the rare disease registries project supported by the European Reference

[123] Brabers, Moors, Van Weely, & La De Vrueh, (2011) 'Does market exclusivity hinder the development of follow-on orphan medicinal products in Europe?' Orphanet J Rare Dis, 6: 59.

[124] Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2019. 10.1038/s41431-019-0508-0.

Networks could help the Committee for Orphan Medicinal Products (COMP) access the best available data.

By the end of 2017, only one application had been received under the 'insufficient return on investment criterion', and that was subsequently withdrawn. According to the industry, the criterion's lack of success is due to the difficulty of estimating future investments and returns on that investment *a priori*, before the therapeutic indications for which the product may be used or the price at which it will be sold are clear. However, other stakeholders suggested that applications on the grounds of expectation of insufficient return on investment are absent for another reason, too; such an application could make sponsors of economically successful products vulnerable to reassessment. Reassessment could lead to the market exclusivity period being reduced to six years if the product were found to be sufficiently profitable. Antimicrobials, on the other hand, could have benefited from the incentives of the Orphan Regulation under the provision of 'insufficient return on investment'. The development of new medicines to replace ineffective antimicrobials seems to be inadequate to meet patients' needs.

Yet no novel antimicrobials have been developed to date. Arguably, the insufficient return on investment criterion in the Orphan Regulation could have been used, but developers have not had recourse to it. This lack of development was also recognised in a recent special report by the Court of Auditors in November 2019.[125] The question of how to address market failures affecting the provision of new antimicrobials should be further examined, in consultation with the Member States and other stakeholders.

In the US, a legal act[126] in 2012 created incentives for sponsors to bring to market antibacterial and antifungal drugs intended to treat serious or life-threatening infections. It allows the FDA to designate certain antimicrobial drugs as qualified infectious disease products. Through this designation, sponsors can profit from incentives to bring antibacterial and antifungal drugs for serious or life-threatening infections to market more rapidly and be granted a five-year extension of any exclusivity that the application qualifies for upon approval.

**Availability of and access to orphan medicines**

An analysis of IQVIA data indicated[127] that the Orphan Regulation has not only stimulated new development of orphan medicines, but has also helped **make them available faster in the EU**. It was estimated that orphan medicines became available on average nine months earlier than would have been the case without the Regulation.

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125 Special Report No 21/2019, 'Addressing antimicrobial resistance: progress in the animal sector, but this health threat remains a challenge for the EU' (European Court of Auditors, November 2019).

126 Generating Antibiotic Incentives Now (GAIN), part of the Food and Drug Administration Safety and Innovation Act (FDASIA).

127 For detailed calculations, see Section 1.4.2. of Annex 3.

In addition, the Orphan Regulation has also helped to made orphan medicines **more widely available**. The 142 orphan medicines authorised between 2000 and 2017 have helped up to 6.3 million patients in the EU, out of roughly 35 million European patients suffering from rare diseases. Before these medicines were authorised, there were no satisfactory treatment options authorised in the EU for 8 out of 20 rare conditions (40%). More than one million patients suffering from these orphan diseases in the EU were already benefiting from the availability of these new treatments by 2005.[128]

Since 2005, all orphan medicines have had to be authorised through the centralised marketing authorisation procedure. However, this has not ensured that *all* EU patients suffering from the same orphan disease automatically have the same choice of treatment. Not all centrally-authorised medicines are launched in all Member States: in some, access to orphan drugs is very limited.[129]

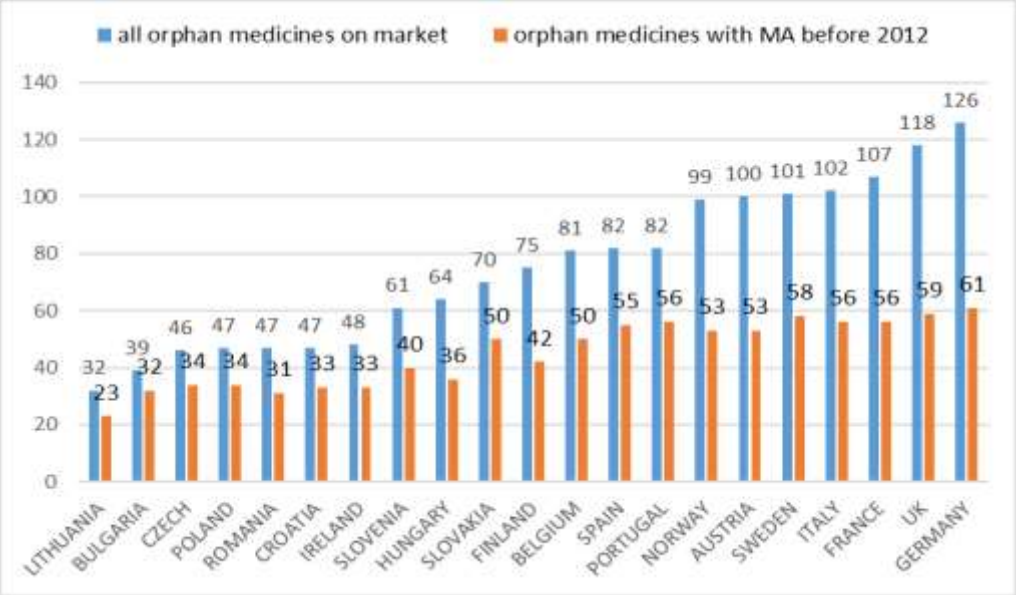
Countries such as Germany, the UK, France, Austria, Sweden and Italy have a high market uptake of orphan medicines, with more than 100 orphan drugs available (Figure 7).[130] This suggests that the market conditions in these countries may be favourable. In particular, measures taken by Member States in areas of national competence, such as reimbursement and pricing, corporate taxation, and healthcare provision, significantly affect the current availability of orphan medicines on the market.

[128] Commission Staff Working Document on the experience acquired with the Orphan Regulation from 2000 to 2005.

[129] Stakeholders suggested that, to improve overall availability and access, measures are needed that focus on greater alignment of pricing and reimbursement policies and procedures and on joint procurement and negotiation. Sections 6.2.3. and 9.5.2. of the Orphan study report (2019)).

[130] This was measured through IQVIA sales data (2008–2016), where any sales figure larger than zero is considered indicative of availability of a medicine on the market.

**Figure 7:[131] Number of orphan medicines for which sales were observed in 2016 (IQVIA) by Member State**




Several *external* factors influence availability and access to orphan medicines. Although these factors already existed in 2000, their role seems to be more prominent now in influencing availability and access to orphan medicines. The Orphan Regulation does not impose any obligation on marketing authorisation holders to market an authorised orphan medicine in all EU Member States. Indeed, a marketing authorisation holder may decide not to place a product on a particular market ('launch decision'), because it does not see it as commercially attractive; possible reasons are a small treatment population, existing competition, or treatment alternatives. Stakeholders have also pointed to concerns of parallel export.[132]

National pricing and reimbursement practices and policies also influence patients' access to orphan medicines. An example is the system of 'external reference pricing' by which a country determines the official 'price list' based on the prices averaged over a set of fixed reference countries. This system causes marketing authorisation holders to engage in strategic decision-making to maximise overall prices and results in 'cascaded' market entry, whereby some countries are more likely to see a rapid placement on the market than

[131] Source: analysis of IQVIA data in Section 6.2.1. of the Orphan study report (2019). This included withdrawn and expired orphan medicines.

[132] Parallel imports and exports of medicinal products are a lawful form of trade within the EU Single Market. However, in certain cases Member States may restrict parallel trade, as long as the measures are justified, reasonable and proportionate, to ensure a legitimate public interest. (https://europa.eu/rapid/press-release_IP-18-3459_en.htm).

others.[133] This is also linked to how much a country can pay, or is willing to pay, for a medicinal product.

Findings show[134] that companies tend to launch more medicinal products faster in wealthier countries with a higher GDP than in countries with lower GDP. The trend is stronger in countries with a larger population of potential patients.[135] This suggests that launch decisions are guided to some extent by market attractiveness.

Moreover, the frequently high prices of many orphan medicines, in particular, often mean that whether a patient can access a treatment also depends largely on whether it is fully reimbursed by the health system, or whether personal payments or co-payments are required.

'Payers'[136] also decide which products will be provided and paid for by the public healthcare system or health insurance funds, on the basis of national pricing and reimbursement policies often supported by health technology assessment[137] (HTA). A survey of NCAs indicated[138] that in most Member States there are no major differences in reimbursements between orphans and other medicines. In addition to or apart from the special regulations or policies on orphans, there are separate budgets, more relaxed assumptions or accepted levels of uncertainty in the HTA process, or managed entry agreements in some Member States.[139] [140] However, even once a decision has been taken to reimburse an orphan medicine, entirely or partially, differences in financing and reimbursement systems between Member States can influence whether and when patients are able to access a treatment.

Indeed, in many countries decision-making on reimbursement is often informed by the work of HTA agencies to establish cost-effectiveness.[141] Moreover, several countries have brought in 'managed entry agreements'. These agreements are used in the context of

133 See also Section 2.2 of the Study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

134 Section 2.2 of the Study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

135 Gross domestic product, measuring the overall size of an economy with derived indicators such as GDP per inhabitant (per capita). See also: https://ec.europa.eu/eurostat/statistics-explained/index.php/National_accounts_and_GDP

136 Health ministries are typically involved in laying down the policies and criteria that determine how public funds can be directed for pharmaceutical products.

137 A health technology assessment measures the added value of a new health technology compared to existing ones. Examples of health technologies include medicinal products, medical equipment, diagnostic and treatment methods, rehabilitation, and prevention methods (see also: https://ec.europa.eu/health/technology_assessment/overview_en).

138 See Section 6.2.2. of the Orphan study report (2019).

139 Sarnola, K. et al. Eur J Clin Pharmacol 74, 895–902 (2018).

140 Malinowski KP et al. Front. Pharmacol. 9:1263 (2018).

141 Section 9.5 of the Orphan study report (2019).

reimbursement for medicines whose evidence base is immature. They are designed to balance the need for speedy access to the health system for treatments addressing an important unmet medical need with the principle of maximising value for money and affordability.[142]

The methods used for HTA may vary and outcomes are dependent on national factors, such as the characteristics of the healthcare system and how the product is to be used in treatment. The draft Commission proposal on HTA[143] may provide a higher level of convergence in HTA methodologies and greater coherence between EU procedures for marketing authorisation and national procedures for the reimbursement of medicines.

Finally, access to orphan medicines can be influenced by health professionals' prescribing practices and habits. In fact, even when products are placed on a market by a marketing authorisation holder and the medicine is largely reimbursed, there is no guarantee that all patients will receive it. Reasons may include unfamiliarity with the disease/product and/or a lack of diagnostic capacity.[144] [145]

Unequal access to medicines, and particularly to orphan drugs, remains an issue today. The Regulation has only succeeded in part in providing the right tools to ensure that patients suffering from rare conditions have the same quality of treatment as any other patient, thanks to the development of more orphan medicines and their increased availability.

*5.1.3 – The impact on research and development of paediatric medicines*

**More clinical research, more products and more information on paediatric medicines**

The Paediatric Regulation has helped boost paediatric clinical research, increase availability of products with paediatric indications in the EU market and improve the information available about these medicines. The vast majority of stakeholders who responded to a public consultation[146] thought the Paediatric Regulation had had a positive impact in addressing the lack of medicines studied and developed appropriately for children.

142 Section 9.5.2 of the Orphan study report (2019).

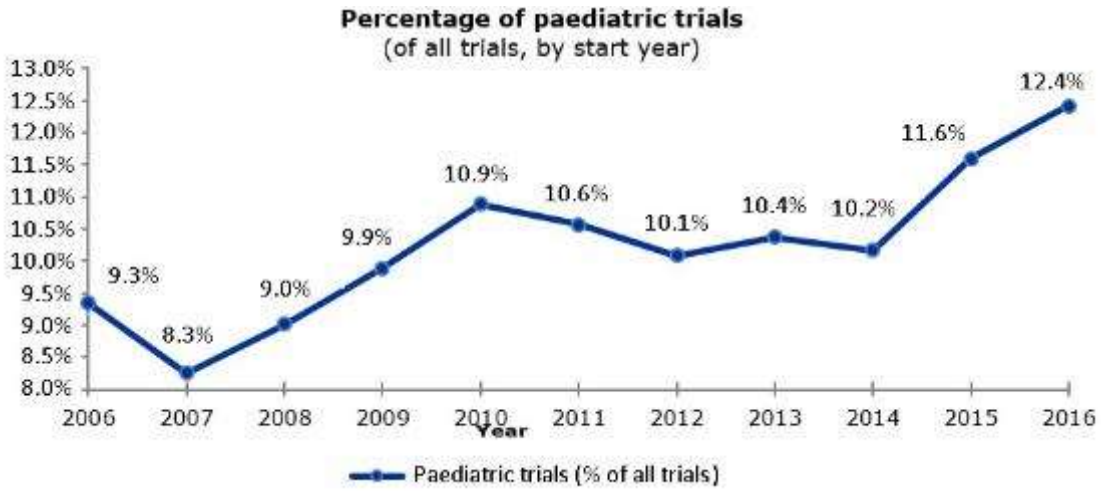
143 https://ec.europa.eu/health/technology_assessment/eu_cooperation_en

144 A doctor needs to be aware of the availability and potential benefits of a treatment before they can allow a prescription. Usually, this involves a form of codification in prescription guidelines developed by medical professional associations. Additionally, adequate capacity needs to be available to correctly diagnose a rare disease. These factors influence doctors' decisions when prescribing medicines for patients.

145 Section 6.2.2. of the Orphan study report (2019).

146 Replies to the public consultation on the Commission report on the Paediatric Regulation.

**Figure 7: Proportion of clinical trials that include children**




Source: 10 years of the EU Paediatric Regulation report, European Commission

Over 1000 PIPs had been agreed on by the end of 2018.[147] An agreement on a paediatric investigation plan means that companies need to invest in additional paediatric research. On average, every PIP includes around three clinical studies. These studies have led to an increase in paediatric trials as a percentage of all trials conducted in the EU, from around 8.3% (188 exclusively paediatric trials) in 2007 to 12.4% (473 exclusively paediatric trials) in 2016 (Figure 7).[148] They have also led to an increased use of scientific advice from 7.6% of the total items of advice provided by the Agency in 2007 to 24.4% of the total in 2016.[149] Importantly, clinical trials involving neonates (a particularly neglected paediatric subpopulation) were included in over a quarter of all the PIPs agreed on, often at the Agency's request.

By June 2018, about 18% of the PIPs agreed on had been completed, with a clear upward trend in recent years.[150] Over 60% were completed in 2013-2016.[151]

By 2016, 101 paediatric medicines and 99 new paediatric indications had been authorised centrally. For nationally-authorised products in the same period, 10 new paediatric medicines were authorised and 57 new paediatric indications approved.[152] The contribution made by the Regulation to these results can be estimated by comparing data collected from the three years preceding its application (2004-2006) with later periods when the

147 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council (COM(2017) 626, Section 3 and annual reports from the Agency.

148 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council (COM(2017) 626, Section 8 – source: EudraCT.

149 Section 3.5 of the Agency's 10 years report.

150 Idem.

151 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council (COM(2017) 626, Section 3.

152 Section 1.1 of the Agency 10 years report.

Regulation was fully operational and authorisation of all paediatric medicines was preceded by a PIP. From 2004 to 2006, 30 new medicines and indications were authorised for paediatric use. In 2012-2014 and 2014-2016, the figure rose to 63 and 74 respectively; in other words, the output had more than doubled.

Furthermore, the Agency and the national competent authorities had received around 19,000 reports on paediatric studies involving 1000 active substances that had been completed before the entry into force of the Paediatric Regulation.[153] These reports resulted in 45 central and 2219 national reassessments, leading to about 140 updates of product information and 16 new paediatric indications for products already authorised.[154]

The figures above concerning both clinical research in children and the authorisation of medicines for children match expectations and the best-case scenario described in the impact assessment, which predicted that within 10-15 years all patent-protected medicines would be studied in children (unless exempted from this obligation). However, given the long development time for medicines, particularly with complex and rare diseases, as is often the case with paediatric diseases, it could take up to 20 years before most products could be authorised for use in children.

While the main aim of the Paediatric Regulation is to ensure that every new adult medicine has been researched for its potential paediatric use, it should be borne in mind that by the end of 2017 the Agency had approved almost 500 waivers from the obligation to conduct a PIP (against the 1000 PIPs it had agreed on).[155] [156]

It is generally appropriate to waive paediatric studies if the target disease does not exist in children.[157] However, one cannot rule out the possibility that a compound, given its mechanism of action, may in some cases be beneficial to children, albeit for a different medical condition. This is particularly relevant in the field of oncology. While many paediatric cancers share biological similarities with adult cancers, they occur in different organs and are therefore usually classed as different conditions. The way the legislation is designed thus means that certain compounds which might be useful for children are not tested on them. The US, which had a similar problem, has recently introduced changes to its legislation.[158]

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153 Articles 45 and 46 of the Paediatric Regulation.

154 Chapter 2 of the Agency 10 years report.

155 Product-specific and class waivers 10 years report from the Agency (Section 3) and Commission 10-year report (Section 4).

156 In 2016, 486 were product-specific waivers. By 2018, the figure had risen to over 600 product-specific waivers.

157 Article 11 of the Paediatric Regulation.

158 The new US legislation, set to become fully applicable in 2020, will incorporate the concept of mechanism of action and observed changes in oncology drug development towards histology-independent indication. See: https://www.congress.gov/115/plaws/publ52/PLAW-115publ52.pdf

The Agency has tried to mitigate this issue through a review of its class waiver decision in 2015, revoking some automatic waivers for carcinomas.[159] Some advances have been observed since then. However, the progress made is not solely attributable to the review of the class waiver list. As paediatric development is global, the revision of the legislation in the US[160] may also have played a role. Moreover, the change in the class waiver list does not seem to have encouraged companies to submit voluntary PIPs for all the medicines concerned.[161]

The Regulation also delivers slowly because nearly all paediatric studies for new medicines that are linked to an adult development are deferred in some aspects.[162] While deferrals are, in principle, an appropriate instrument, they could in practice imply delaying patients' access to a potentially promising paediatric medicine. In particular, neonatal studies are very often deferred until experience has been gained with other age groups and this may lead to continuing off-label use for this vulnerable group of patients. The Agency is reviewing internal practices to ensure consistency in its decisions and to avoid lengthy deferrals.

It is also relevant to mention that the Regulation has made it compulsory to publish protocols[163] (which provide details of how a clinical trial is conducted) and the results of paediatric clinical trials.[164] As a result, searchable information is now available about ongoing and completed trials registered in the EU and interventional clinical trials which are included in an agreed PIP. This tool provides crucial information for patients, parents and clinicians on research data and experimental therapies.

**The role of rewards**

The quantitative impact described above is directly linked to the obligation laid down in the Paediatric Regulation for companies to invest in paediatric research. The reward in this case does not drive paediatric research directly; it is designed as compensation for that obligation, not as an incentive. It is worth noting that the US system does not compensate companies for mandatory paediatric research under the Paediatric Research Equity Act. Financial incentives are provided for voluntary research only on the basis of a priority list which represents a balanced portfolio of therapeutic areas and paediatric needs, without replicating research funded elsewhere.

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159 Section 3.14 of the Agency 10 years report.

160 Idem 199.

161 According to preliminary data received by the Agency.

162 Article 20 of the Paediatric Regulation states that deferrals are to be granted when it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population or when studies in the paediatric population will take longer to conduct than studies in adults.

163 Article 41 of the Paediatric Regulation.

164 https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-clinical-trials ( https://www.clinicaltrialsregister.eu/)

The Regulation specifies that rewards can be claimed only once a PIP has been completed. By 2016, over 40 medicinal products had been granted an SPC extension by national patent offices in one or more Member States. This indicates that the reward system is working. However, the SPC extension is a valuable reward only if it is the last protection to expire, which is very often not the case.[165] Not all companies complying with the obligation introduced by the Paediatric Regulation have been able to receive the reward. In the first 10 years, only about 55% of the products for which a PIP was completed were granted an SPC extension.[166] There are several reasons for this. Not all products covered by the obligation are eligible for an SPC. Moreover, the SPC extension must be requested two years before the certificate expires. Given the length and complexity of the clinical studies to be conducted (most PIPs have a duration of 10 years or more), some companies fail to complete the PIP on time.

However, this deadline is an incentive for companies to speed up the completion of paediatric research, and it ensures that generic competition learns sufficiently in advance about any extension of the protection period that may affect the market launch of generics.

Since the economic value of this reward is directly coupled with the volume of sales within the adult population, however, (the extension of the SPC applies to the whole product, not just to the paediatric indication), the SPC extension is more attractive to pharmaceutical companies with a larger share of the patient group overall. This may encourage companies to prioritise PIPs for products which bring the highest return on investment, not for those with greatest paediatric need. The analysis conducted[167] has shown that the SPC paediatric extension was obtained for all the blockbuster products[168] analysed but one.

While it is not a specific driver, the particular character of the reward system thus affects the Regulation's effectiveness.

The other main reward provided by the Paediatric Regulation, the two-year extension of the market exclusivity period[169] for paediatric orphan products, has been granted in only a few cases. By the end of 2018, eight medicinal products had obtained the two-year additional extension of market exclusivity.

This low number can be explained by the fact that when the paediatric legislation was developed, about 60% of orphan-designated products were off-patent (2003-2004) and

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165 Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018), Chapter 4.1.3.

166 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council (COM/2017/0626, Section 6).

167 Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018), Chapter 5.

168 Products with annual revenues exceeding USD 1 billion.

169 See chapter 3.2.2. of this evaluation.

were thus ineligible for an SPC extension. However, over time this has changed substantially, and in 2013-2016, 95% of the orphan-designated products which had obtained a marketing authorisation were covered by a patent.[170]

It should also be borne in mind that the orphan market exclusivity reward is incompatible with the six-month paediatric extension of the SPC.[171] When an orphan product is still covered by a patent and there is a possibility of requesting an extension of its SPC, this reward may be more financially worthwhile to developers, as it extends protection for all the indications of a product, while the orphan rewards are valid only for indications covered by the orphan designation. This is probably why some companies waived the orphan designation in order to make the product eligible for the SPC extension (there is an example in Chapter 5.2.3. of this SWD).[172]

The Regulation included one instrument to encourage paediatric-specific research for existing products, the PUMA scheme. The impact assessment recognised that the incentives the scheme provides would be weak, despite being considered the best and the most practical. It was considered that only the combination of the PUMA with support for off-label research and an inventory of paediatric needs could make the scheme attractive.

However, despite paediatric research on non-patent-protected substances being financed via the various EU research framework programmes and the inventory of paediatric needs being established, experience with this scheme has been disappointing. By 2018, only six medicines had been authorised. Although the Agency approved more than 20 PIPs with a view to submitting a PUMA, it remains uncertain how many will ever be completed and result in a new product appearing on the market.

Several reasons have influenced the relatively low success of the PUMA scheme. First, trials linked to a PUMA are more difficult to perform: the medicinal products concerned are already available on the market and are often widely used off-label. Consequently, health professionals and patients may not be motivated to engage in studies with older medicines.[173] According to industry representatives,[174] another reason for the limited success may be found in the price agreed by Member States for medicines authorised under the PUMA scheme. Member States seem to recognise little added value in older medicines, even if they include a new age-appropriate formulation or new paediatric indications. This

170 Section 6.2.1. of the Agency's 10 years report.
171 Articles 36 and 37 of the Paediatric Regulation.
172 Chapter 5 (case study Glivec) of the Study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).
173 Mukattash TL, Millership JS, Collier PS, McElnay JC. Healthcare professional experiences and attitudes on unlicensed/off-label paediatric prescribing and paediatric clinical trials. Eur J Clin Pharmacol. 67(5):449-461, 2011.
174 Public consultation conducted by the Commission with a view to drawing up the report to the European Parliament and the Council on the 10 years of the Paediatric Regulation (see Annex 2, Synopsis report, for details of the consultation.

means they may not agree on the higher prices – compared with the price of the existing product – necessary to cover the costs incurred through the novel clinical research.

This shows that the commercial success of a PUMA is influenced by complex factors beyond the scope of EU law, which can be hardly addressed at EU level. To some extent, the output is consistent with the impact assessment, which indicated that the scheme might be unlikely to result in sizeable numbers of authorised products.

Nevertheless, surveyed stakeholders (in particular from industry, public authorities and academia) suggest that this tool should be maintained anyway, as it has proven successful in bringing certain products onto the market.[175]

*5.1.4 – Impact on unmet needs and the timely availability of products for paediatric medicines*

**Unmet needs**

Thanks to the Regulation, the last 10 years have seen considerable progress in the development of medicines for children in certain therapeutic fields. Rheumatic or infectious diseases are often referred to as prime examples. The significant surge of new treatments for children with rheumatic disorders following the completion of PIPs has transformed a sector that was previously neglected.

At the same time, those positive developments do not follow a strategic plan, but are often linked to developments in adult markets. The starting point for most PIPs is a research and development programme for adults. Progress in a paediatric field is dependent on companies' adult product pipeline. Where the adult needs or market expectations overlap with paediatric needs, children will benefit directly. In contrast, there are many diseases that are biologically different in adults and children, where the disease burden differs, or that only exist in children. With these diseases, the mechanism introduced by the Regulation sometimes struggles to produce results.[176]

This is confirmed by the fact that the therapeutic areas covered by the agreed PIPs do not necessarily correspond to the actual paediatric disease burden, although they cover a wide range of therapeutic areas.[177] WHO data indicate that the disease burden for children from birth to less than 15 years of age is highest for mental and behavioural disorders, neonatal conditions, congenital anomalies, and respiratory diseases. Together, these account for almost 60% of the total disease burden. If we compare the disease burden affecting this group of children in the EU with agreed PIPs/paediatric indications, however, we find that only 3% of PIPs were agreed for mental and behavioural disorders, while the figure for

175 Public consultation on the functioning of the Paediatric regulation conducted by the Commission in 2016
176 This also emerged at the conference held by the Commission in June 2019.
177 Section 3.1 of the Agency 10 years report.

neonatal conditions is just 2%. Instead, the highest proportion of PIPs were agreed for infectious diseases (21%) and malignant diseases (13%), which rank 9th and 10th respectively in the disease burden index (DALYs).[178]

This may result in most developments taking place in areas with limited paediatric unmet needs. For example, many companies have concentrated their research activities on type II diabetes, leading to several new products for adults. This has also resulted in an increase in the number of paediatric products of this type in the pipeline, although type II diabetes is relatively rare in children.[179]

As the legislation was designed to increase the number of medicines studied for children in general, it contained no provisions specifically designed to boost development in particular therapeutic areas. Consequently, the Paediatric Regulation, taken on its own, has limited potential for steering activities towards particular therapeutic areas.[180] Its positive impact and the change in culture it has encouraged are thus most visible in the integration of paediatric development into the overall development of new medicines. It has been less successful with projects aiming to develop remedies for diseases found only in children. The impact assessment had already anticipated the possibility that the Regulation might push development toward the most profitable areas, not towards those with greater unmet needs as far as children are concerned.

A particular area of unmet needs is that of rare diseases in children, bearing in mind that 90% of all rare diseases manifest in childhood.[181]

Looking at the impact of the Orphan Regulation, only about half the 111 orphan products authorised for diseases that start in childhood (56 products) have actually been authorised for use in children. As regards the various therapeutic areas covered by these products, oncological orphan products are somewhat less likely overall to have a paediatric use indication than non-oncological products (34% vs 48% respectively) (Figure 8).[182]

One would expect paediatric indications to be added later, after the completion of a PIP under the Paediatric Regulation. However, by the end of 2016, although 150 PIPs had been agreed for medicinal products which had also received an orphan designation, this resulted in only nine paediatric indications being authorised as orphan medicinal products.[183]

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178 Section 3.2 of the Agency 10 years report.

179 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council (COM(2017) 626, Section 4 (period of reference: 2007-2015).

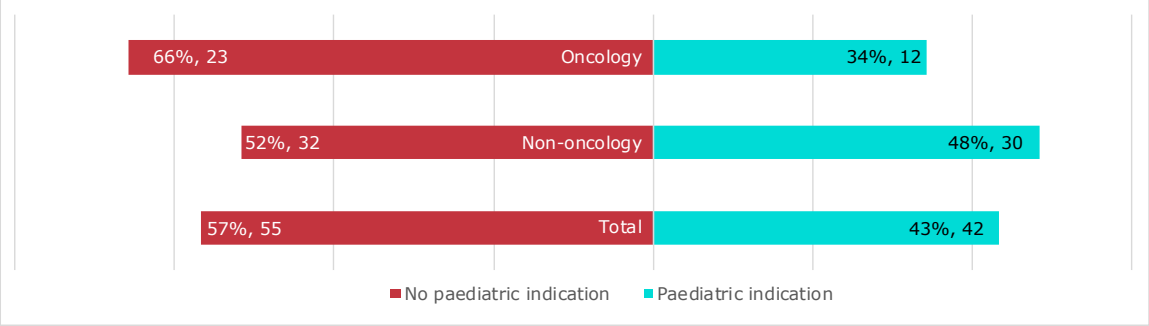
180 For example, the inventory of therapeutic needs developed by the Agency in accordance with Article 43 of the Paediatric Regulation was designed to help developers of medicinal products identify opportunities; this activity is ongoing in the joint Agency-Commission paediatric action plan (action 1).

181 Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database, *European Journal of Human Genetics*, 2019.

182 Section 5.4.5 of the Orphan study report (2019).

183 Section 3.17 of the Agency 10 years report.

**Figure 8: Authorised orphan medicines with a paediatric use indication for conditions affecting adults and children, by therapeutic area**




Source: Orphan study report (2019).

These figures show that while both the Paediatric and the Orphan Regulations have had a positive impact, they have not been able to solve the problem of the shortage of treatments available for children with rare diseases. This is also confirmed by the concerns raised by 'non-industry' stakeholders.[184]

Furthermore, the SPC extension is incompatible with the orphan market exclusivity. The SPC extension is more attractive to pharmaceutical companies, as it covers a larger patient group overall. This may encourage companies to prioritise products offering the highest potential return on investment, not children suffering from rare diseases.

The focus on conditions that affect adults only, or that affect adults as well as children (as opposed to primarily paediatric conditions), seems to indicate that the two Regulations lack sufficient capacity to incentivise development of specific paediatric medicines. Neither the Orphan Regulation nor the Paediatric Regulation offers specific incentives to promote the successful development of innovative medicines for use exclusively in children.

### Availability of and access to paediatric medicines

Issuing a marketing authorisation or adding paediatric information to existing marketing authorisations does not automatically translate into making a product immediately available to paediatric patients in the EU. This may be because of pending reimbursement decisions at national level or doctors' prescription habits. Sometimes, even when a paediatric product is available, off-label use continues for a while, which shows there is some inertia in the system. The majority of respondents taking part in a survey conducted by the Commission in 2017 said the Regulation had led to an increase in the paediatric medicines available at the bedside, and that practitioners were increasingly prescribing approved medicines in accordance with the licensed indication for children. In line with the expectations set out in the impact assessment, while off-label use in children is

[184] Section 9.1.2 of the Orphan study.

decreasing, it is likely to continue to some extent. This is determined by factors independent of the Regulation, such as health professionals' prescription and the reimbursement decisions taken by national health systems.

The launch of a paediatric indication or product on a national market is often linked to the launch of the corresponding adult product. It has been observed that companies often rely on a staggered roll-out of any new products, resulting in delays until the product is finally available throughout the EU. This also indirectly affects the availability of paediatric medicines[185] on the various markets.

This cannot be prevented altogether, even though the Regulation includes some instruments tailored specifically to ensure that paediatric medicines are placed on the market once a PIP is completed and the product has been authorised. First, the reward of a supplementary protection certificate will only be granted once the product has been authorised in all Member States. [186] Second, when a new paediatric indication is authorised for an existing product, the new indication must be placed on the market within two years of the moment of authorisation[187]; and third, if an authorisation holder intends to discontinue the marketing of a paediatric product, they have an obligation to transfer the authorisation to another company or provide access to the relevant data.[188] However, the legal obligations are not sufficiently stringent enough to force companies to place the product on all Member State markets.

*5.1.5 – Impact on competitiveness and the research landscape*

Neither Regulation was specifically designed to improve the competitiveness of European industry. However, at the time of the proposal for the Orphan Regulation it was thought that companies, especially SMEs, would benefit in terms of job creation and highly qualified jobs.[189] Generally speaking, this would have been a positive secondary effect that could have gone hand in hand with increased research. The impact assessment of the Paediatric Regulation[190] also predicted that it would boost European R&D either directly or indirectly, thereby improving the competitiveness of EU companies vis-à-vis their US competitors.

Although it is not possible to assess the direct impact of the Orphan Regulation on the research environment, or vice versa, it is feasible to assess how the research environment

185 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council (COM(2017) 626, section 3.
186 Article 36(3) of the Paediatric Regulation.
187 Article 33 of the Paediatric Regulation.
188 Article 35 of the Paediatric Regulation.
189 Communication to the Commission about a Draft Proposal for a European Parliament and Council Regulation (EC) on orphan medicinal products and Explanatory Memorandum (p. 6 - impact on firms).
190 https://ec.europa.eu/smart-regulation/impact/ia_carried_out/docs/ia_2004/sec_2004_1144_en.pdf

has changed since 2000. Before the Regulation's introduction, research into orphan drugs was limited, very little expertise was available, and what little there was did not lead to significant progress in research. Since 2000, over €1.4 billion has been made available[191] through the EU's framework programmes for research, technological development and innovation. EU support has improved understanding of the underlying causes of rare diseases, enabled more accurate diagnostics and helped develop new therapies and integrate patient registries and research data.

This ecosystem supports the competiveness of EU industry. In addition, extension of the SPC under the Paediatric Regulation indirectly boosts the competiveness of pharmaceutical companies and provides some guarantee that profits will be redistributed, thus enabling the development of sound R&D infrastructure.[192]

However, it is important to note that decisions on the location of pharmaceutical research and development are driven primarily by factors *other* than a period of protection (such as those granted to incentivise the development of pharmaceuticals) provided in a particular country. Possible relevant factors are the quality of the labour force, tax levels, infrastructure, and research and development subsidies.[193]

### 5.2 EFFICIENCY

**Main findings**

The Orphan Regulation has added 210,000-440,000 quality-adjusted life years to the lives of EU patients. This represents a substantial improvement in the quality of life of patients with rare diseases. At the same time, the costs to health systems, mostly paid for by governments, rose by €23 billion between 2000 and 2017. This comes in addition to EU and national public funding invested in research.

The average additional protection offered by the market exclusivity reward was calculated at 3.4 years; 30% of revenues from sales of orphan medicines can be regarded as the value of this reward. The cost-benefit analysis for the pharmaceutical industry associated with the Regulation has been positive.

For the 73% of orphan medicines with an annual turnover below €50 million in the EEA, the market exclusivity reward has helped to increase profitability, without giving the sponsor an unbalanced compensation. However, for the 14% of orphan medicines with an

191 Directorate-General for Research and Innovation (European Commission): 'Rare diseases: A major unmet medical need', November 2017; https://ec.europa.eu/info/publications/rare-diseases_en

192 Study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe ( 2018).

193 Idem; Section 2.1, Impact on innovation.

annual turnover above €100 million in the EEA, the 10-year market exclusivity may have led to overcompensation, and the incentives may not have been indispensable. The tool to limit market exclusivity in highly profitable cases has proven ineffective.

The Regulation is not entirely efficient. Findings have shown that there are currently 22 orphan medicines on the EU market and that they are authorised for two or more orphan indications. Limited generic competition was shown after expiry of the market exclusivity and/or the protection provided by other pharmaceutical incentives, with a slower price fall for orphans compared to other medicines. Medicines in well-established use and repurposed medicines account for only a small share of the orphan drugs that have reached the EU market.

Taking into account both the direct and the indirect induced effects, the cost-efficiency of the *Paediatric* Regulation has had a positive cost-benefit ratio for both pharmaceuticals companies and society in general. However, not all companies have reaped direct rewards from their investment in research, and costs to society have been created that are linked to monopoly rents.

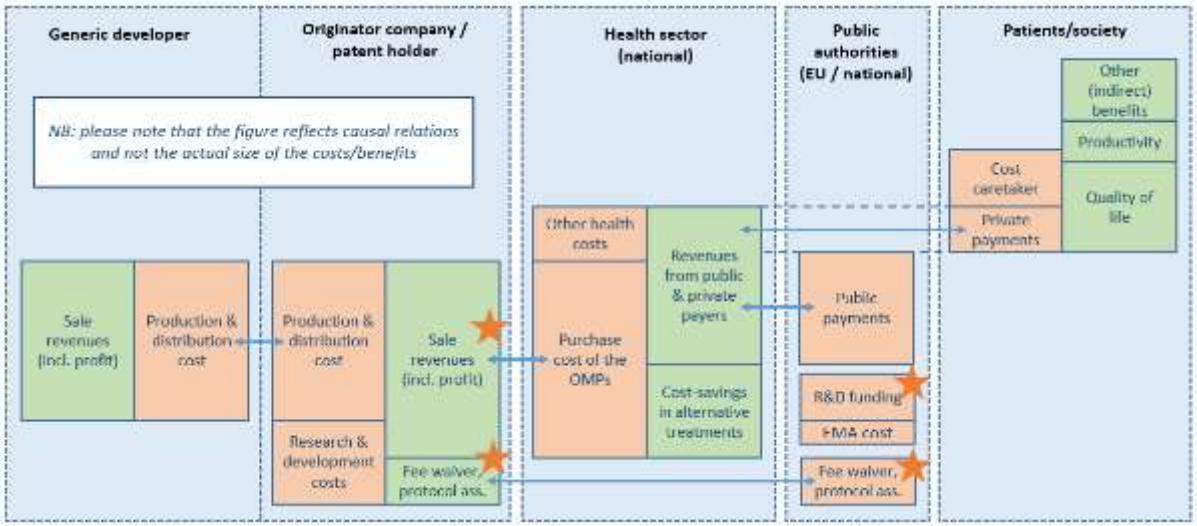
Nevertheless, developers still perceive this legislation as burdensome and the main reward provided and the extension of the SPC is reported to be inefficient and complex.

### *5.2.1 How costs and benefits of the Orphan Regulation have been distributed*

The changes brought about by the Orphan Regulation (in terms of the development of new orphan medicines, a faster introduction to the EU market and a wider accessibility to such products[194]) have resulted in both extra costs and benefits for the following stakeholder groups: the pharmaceutical industry, the health sector, public authorities and patients, and society in general.

**Figure 9: Overview cost (red) and benefits (green) for various stakeholders**

[194] For more details, see Section 1.4.2. of Annex 3.




Source: Orphan study report (2019) (Note: the schematic reflects only causal relations but not the actual size of the costs/benefits; the orange stars refer to the four 'rewards' the Orphan Regulation introduced (i.e. market exclusivity, protocol assistance, fee waivers and aid for research).

- *Pharmaceutical industry*[195]

With few exceptions, companies were unwilling to share an estimate of the average total R&D costs per product.[196] The costs of developing an orphan medicinal product have been estimated to range from €479 million to €725 million, the average being €602 million. This estimate does not take account of well-established use and repurposed medicines (for which R&D costs are much lower). The estimated R&D costs for an orphan medicine appear to be lower than those for a non-orphan (around 27%).[197]

The analysis took account of the fact that R&D costs can potentially be spread over worldwide sales; not all of the R&D investments made by the companies concerned can be assigned to the EU market. In the absence of clear data on the share of sales in the EU compared to worldwide sales of medicines for rare diseases, several assumptions were made. They led to the conclusion that the Orphan Regulation has resulted in an increase of €11 billion in R&D expenditure on orphan medicines over 2000-2017.[198]

195 There are two types of sponsors in the pharmaceutical industry: developers of innovative medicines ('originators') and developers of generic medicines. While both originators and developers of generic medicines need to cover the costs of manufacturing, marketing and distribution of orphan medicines in the EU, it is the originators that cover R&D costs. These costs are limited for developers of generic medicines.

196 Section 8.2.2. of the Orphan study report (2019).

197 Section 8.2.2. of the Orphan study report (2019).

198 The sum of €11 billion corresponds to the rounded extra R&D costs of 21 extra products attributed to the EU Regulation. See also Section 2.1. of Annex 3.

To assess the costs of manufacturing, marketing and distribution of orphan medicines, the results of the analysis of the economic value of the market protections were taken into account. Analysis based on a sample of four orphan medicines where generic entry was observed[199] shows that 30% of revenues from sales of orphan medicines can be regarded as the value of the market exclusivity reward, while, on average, 70% of revenues[200] reflect the turnover level that would apply under competitive market conditions (i.e. following generic entry or in cases where generics could potentially enter the market).

Based on the extra sales of €19.1 billion, the extra cost of selling medicines in 2000-2017 was calculated at €12.04 billion (after correction for a 'competitive profit margin'). This margin was assumed to be 10%[201] (and added to the cost-benefit as a benefit) of the 'net' turnover (i.e. turnover minus the orphan exclusivity share).[202]

The most obvious 'benefit' from the Orphan Regulation to developers of orphan medicines is that, should they successfully bring a product to market, they will be able to generate additional sales in the EU/EEA. Thanks to the Orphan Regulation, orphan medicines enter the EU/EEA market faster and are more widely available (higher volumes) within the EU/EEA. All effects taken together have resulted in increased sales of orphan medicines in the EU market of an estimated value of €19.11 billion[203] between 2000 and 2017.

The additional 3.4 years of protection period resulting from the market exclusivity are estimated to bring an extra R&D compensation (margin of 30% for an additional number of years) of €4.59 billion. In addition, the fee waiver and protocol assistance rewards under the Orphan Regulation during 2000-2017 are estimated to have a value of €0.16 billion.

**Table 3: Industry costs and benefits (originators) that can be ascribed to the Orphan Regulation, 2000-2017 (discounted value 2018, prices 2018, in billions of euros)[204]**

| Effect | Costs | Benefits |
|---|---|---|
| R&D costs associated with the additional orphan medicines developed (EU part)[a] | -/- €11.0b | |
| Sales revenues of additional orphan medicines in EU | | €19.11b |
| Costs of manufacturing, marketing, distribution and applicable taxes relating to additional sales of orphan medicines in EU | -/- €12,04b | |
| Extra R&D compensation due to market exclusivity reward | | €4.59b |

199 Section 8.3.2. of the Orphan study report (2019).

200 This 70% is derived from the assumption of a 30% 'market rent' due to the orphan exclusivity.

201 See, for instance, Hill et al., 2018, that aimed to 'estimate the generic price that can be achieved if profit margins are competitive'. Although more specific profit margins are likely applicable to this specific market setting (low volume and low number of competitors), these were not readily retrievable from the literature.

202 A margin of 7% (10% of 70%) is the amount remaining (after subtracting the 30% exclusivity reward) as a 'competitive profit margin' (a margin that would apply, for instance, where there is generic market competition). 37% x 19.11b = 7.07 billion as a net benefit of additional orphan medicines in the EU. This implies that the cost of selling these extra orphans is 12.04b (19.11b - 7.07 b).

203 Almost 45% of this is attributable to sales from newly developed orphan medicines, another 44% is due to faster access to the EU/EEA market for the other 110 orphan medicines, and 11% can be attributed to the wider spread of medicines.

204 Section 8.2.2. of the Orphan study report (2019).

| | | |
|---|---|---|
| **Cost saving due to protocol assistance and fee waivers** | | €0.16b |
| **Total** | -/- €23,04b | €23.86b |
| **NET BENEFIT** | +€0,82b | |
| **Range Net Benefits (minimum – maximum)** | -/- €11b to +€11b | |

Source: DG SANTE, on the basis of the Orphan Study (2019)

It is hard to assess the total net benefit to industry in the overall calculation of costs and benefits, given a lack of data on R&D costs, the costs of manufacturing, marketing and distribution, and profit margins. Applying some assumptions enables us to establish the net benefit at about €0.82 billion (over 2000-2017). However, there is a margin of uncertainty around this estimate of net benefit.

First, the costs of research and development are based on figures found in the literature. They may thus be underestimates or overestimates. The full costs of developing the 21 orphan medicines in this analysis have only been compared to revenues generated in the reference period (2000-2017). Many of these products have only been on the market for a relatively short time, and they can reasonably be expected to continue generating revenues and profits for the industry long after 2017. Moreover, revenues from other jurisdictions (such as the US and Japan) were not taken into account when attributing R&D costs to the Regulation, although the global market for orphan medicines is very much dependent on the US.[205] It may thus be assumed that the balance for industry is more positive than a benefit of €0.82 billion over 2000-2017.

- *Health sector*

The health sector, comprising all medical services needed to treat patients suffering from rare diseases[206], bears the costs of treatment with orphan medicines. These costs consist of the extra use of orphan medicines resulting from the Orphan Regulation and the additional healthcare costs (additional costs of treatment with orphan medicines, minus savings on costs of alternative treatments). As it was not possible to assess the additional healthcare costs, given the limited information provided in the available HTA reports, the extra costs to the healthcare system have been assumed to be equal to the extra revenues realised by industry (sales revenues of €19.1 billion and additional R&D compensation due to the market exclusivity reward of €4.6 billion), making a total of €23.7 billion.

These costs are financed from a combination of public sources (taxation or compulsory health insurance premiums) and private ones (patients' own contributions in the form of out-of-pocket expenses and voluntary health insurance premiums). For the purpose of this

[205] 70% of global revenues from orphan medicines come from the US alone (Orphan Drug Report 2019, EvaluatePharma).

[206] Section 8.2.1. of the Orphan study report (2019).

cost-benefit analysis, it has been assumed that 97% (€23.0 billion) of healthcare costs were covered by public funding, while 3% (€0.7 billion) were privately financed.[207]

**Table 4: Costs and benefits due to the EU Orphan Regulation for the health sector, 2000-2017 (discounted value 2018, prices 2018, billions of euros)[208]**

| Effect | Costs | Benefits |
|---|---|---|
| **Extra costs due to treatment with orphan medicines** | -/- €23.7b | |
| **Additional extra costs due to new treatments (e.g. clinical costs)** | NDA[209] | |
| **Savings in costs of alternative treatment** | | NDA |
| **Public and private financing** | | €23.7b |
| **TOTAL** | -/-€23.7b | €23.7b |
| **NET BENEFIT** | | €0.0b |

Source: Orphan Study (2019)

- *Public authorities*

In addition to financing public healthcare, public authorities incur *additional* administrative costs associated with implementing the Orphan Regulation. These additional costs are related to:

- the functioning of the Agency and committees, such as COMP (estimated at €0.02 billion);
- research subsidies provided by the EU and various national governments (estimated at €1.1 billion);
- fee waiver and protocol assistance[210] (estimated at €0.2 billion) as an integral part of the support provided by the Agency.[211]

A large proportion of the additional healthcare costs is reimbursed from collective sources (government budgets, collective health insurance systems, or other sources).

Although healthcare systems across the Member States are organised and funded in different ways, orphan medicines are generally financed from public sources. Survey respondents from national public authorities indicated that, in most Member States (17 out of 20, 85%), the reimbursement mechanism for orphan medicines is the same as for non-orphan products. Orphan medicines are financed by a national health service in the majority of cases (15 out of 20, 75%). In a minority of cases (6 out of 20, 30%), orphan

207 See Section 2.4. in Annex 3 for assumptions.
208 Section 8.2.3. of the Orphan study report (2019).
209 No data available.
210 The Agency's fee system was evaluated in 2019. The outcome of this evaluation shows that the current fee system is generally efficient and effective, including in funding some non-fee-generating and uncompensated activities, as well as reductions and fee waivers. See: https://ec.europa.eu/health/human-use/legal-framework/ema_fees_en
211 The costs of this assistance, incurred by the Agency, are fully financed by the EU.

medicines are also partly financed by a health insurance system. For six reporting Member States (30%), out-of-pocket payments are reported.[212]

**Table 5: Costs (attributable to the Orphan Regulation) to national governments and the EU, 2000-2017 (discounted value 2018, prices 2018, billions of euros)[213]**

| Effect | Costs | Benefits |
|---|---|---|
| **Administrative costs to the EMA and national authorities** | -/- €0.02b | |
| **Aid for research** | -/- €1.1b | |
| **Fee waivers, protocol assistance** | -/- €0.2b | |
| **Healthcare financing** | -/- €23.0b | |
| **TOTAL** | -/- €24.3b | €0.0b |

Source: Orphan Study (2019)

Costs to public authorities attributable to the Orphan Regulation have been estimated at €24.3 billion. They included the estimated costs to healthcare financing of orphan medicines and the additional administrative costs set out in Table 4 (putative benefits to public authorities have not been identified and included).[214]

- *Patients and society*

This stakeholder group is affected by rare diseases either directly, as patients, or indirectly (e.g. as carers or relatives).

It was assumed in the analysis that in the EU, 97% of all healthcare *costs* arising from orphan medicines and associated treatments are financed from public sources. At €0.7 billion, the private contribution to healthcare costs was limited.[215]

The societal costs of a disease are considered to be wider than those borne by healthcare systems. The non-healthcare costs of a disease are the use of social services; the costs of involvement of carers, whether professional or informal, outside the healthcare system; and productivity losses resulting from unplanned absences from work or early retirement by patients (or carers). However, any wider *societal* impact could not be established at the level of the Orphan Regulation.[216]

In fact, the societal cost perspective adopted in the present analysis does not take account of productivity losses in society avoided thanks to the Orphan Regulation. Moreover, the costs and benefits are based on an assessment of the 2000-2017 period, which was the Regulation's start-up phase. In the longer run, it is to be expected that more generics and biosimilars will enter the market as products' orphan status expires, resulting in lower costs

[212] See Section 1.4.2. of Annex 3 for detailed calculations.
[213] See Section 2 of Annex 3 for detailed calculations.
[214] See Section 2.3. of Annex 3 for detailed calculations.
[215] See Section 2.4. of Annex 3 for detailed calculations.
[216] The calculated societal cost-effectiveness (outcome-efficiency expressed in terms of euros per health effect gained) of the Orphan Regulation is not out of line with the upper cost-effectiveness values commonly observed in health economic evaluations of new technologies for EU healthcare systems.

and/or greater availability of treatment for patients. All this means that the calculated societal cost-effectiveness of the Orphan Regulation presented here is based on a comparatively *conservative* assessment; it takes account of extra costs, but not of the long-term savings that may be expected in future.

Health *benefits* reflect the improvement in patients' quality of life attributable to treatment with orphan medicines. They can be expressed and measured in the number of QALYs[217] that patients gain per incremental cost.[218] The level of health benefits was assessed using information on the incremental cost-effectiveness ratio (ICER)[219] from HTA reports.[220] The Orphan Regulation's cost-effectiveness for society can be considered acceptable when compared to ICER thresholds in use internationally.[221]

Based on a multiplication of the calculated ICERs (range €54,000 to €110,000) and the estimated extra healthcare costs presented in Table 4 (Costs and benefits due to the EU Orphan Regulation for the healthcare sector, 2000-2017), an estimated 210,000 to 440,000 QALYs were gained thanks to the Regulation (2000-2017).[222] The wider *economic* benefits could not be established at the level of the EU Orphan Regulation. However, they are likely to be a positive value, given that rare diseases are often very disabling and represent a heavy burden on society.

**Table 6: Costs and benefits to patients arising from the Orphan Regulation, 2000-2017 (discounted value in 2018; prices 2018, billions of euros)[223]**

| Effect | Costs | Benefits |
|---|---|---|
| Private contribution to healthcare costs | -/- €0.7b | |
| Change in non-health costs of disease | NDA | |
| Health benefits | | 210,000 – 440,000 QALYs |
| TOTAL | -/- €0.7b | |

Source: Orphan Study (2019)

217 QALYs (quality-adjusted life years) are a measure of the state of health of a person or group, in which the benefits, in terms of length of life, are adjusted to reflect quality of life.

218 Direct impacts on healthcare costs are typically taken into account in health technology assessments (HTAs). The extra costs to the healthcare system had to be assumed to be equal to the extra revenues accruing to industry because only a few HTA reports contain all the relevant elements around cost of treatment with orphan medicine and cost savings for alternative (comparator) treatment, QALYs and ICERs.

219 ICER is a measure of the 'value for money' a medicine offers in comparison to other treatments. ICERs were available for 32 orphan medicines. 24 ICERs relate to orphan medicines that have not been withdrawn from the market and for which sales were recorded in the EU.

220 ICERs were available for 32 orphan medicines, 24 of which were orphan medicines that have not been withdrawn from the market and for which sales were recorded in the EU.

221 See, for instance, the threshold of €80,000 per QALY in the Netherlands. (https://kce.fgov.be/sites/default/files/atoms/files/d20081027396.pdf).

222 See Section 2.4 of Annex 3 for detailed calculations.

223 Section 8.2.5. of the Orphan study report (2019).

To conclude, while the above estimates of costs and benefits to different groups of stakeholders are informative, they cannot directly answer the question of whether the balance of costs and benefits is proportionate or 'fair'. Most costs 'trickled down' to national governments, which has caused frictions, political and otherwise, in recent years. Although no firm conclusions can be drawn as to whether the extra revenues resulting from the Orphan Regulation outweigh the additional R&D investments, it is likely that a more positive value for industry would have been obtained if revenues from non-EU jurisdictions and post-2017 profits had been taken into account in the analysis.[224]

*Affordability*

The Regulation's efficiency is certainly influenced by pricing and reimbursement considerations, which are linked to affordability. However, these lie beyond the EU's remit.[225]

The final judgement on the fairness of the balance of costs and benefits is a qualitative assessment based on the value placed on health gains and a reasonable profit margin. Member states applying cost-effectiveness analysis to inform reimbursement decisions for new medicinal products often will do so using QALY. For orphan products specifically an average cost of €54,000 per QALY can be observed based on available cost-effectiveness analyses and market shares (weights for the average).

Nonetheless, even medicines that are assessed as exceeding such threshold values are sometimes reimbursed under pressure by advocacy groups and public opinion. This indicates that within societies there is substantial willingness to pay for medicines to treat rare diseases, sometimes at a very high cost. At the same time, public debate is increasingly focused on medicine prices. Although the discussion is not restricted to orphan medicines, such products have received particular scrutiny, given the market exclusivity offered.

The important question, then, is whether the prices charged for medicines to which additional exclusivity rights are granted are reasonable in relation to the developer's investments, especially in cases where development was supported by public research funding.

### *5.2.2. Level of compensation for orphan medicinal products*

The main purpose of market exclusivity was to extend the time during which the marketing authorisation holder could charge a 'monopoly rent' to recover the investment made.[226] The analysis evaluated whether market exclusivity offers sufficient compensation to

[224] See limitations in Chapter 4.2. of this SWD.

[225] As already described in Chapter 2 (Background to the intervention) of this SWD.

[226] A monopoly rent refers to a situation in which a monopoly producer lacks competition and can thus sell its goods and services at a price above (and sometimes far above) the otherwise competitive market price (at the expense of consumers and payers).

encourage investment in developing orphan medicines. This assessment includes a comparison of the market characteristics of orphan and non-orphan medicines, a calculation of the economic value of market exclusivity, and the impact of competition on the compensation provided.

The analysis of turnover of non-orphan, orphan and 'orphan-like' medicines in the EU/EEA[227] showed that in 86% of cases turnover levels for orphan medicines were below €100 million per year, with most having a turnover below €50 million. Similar turnover levels could be observed for orphan medicines introduced before the legislation came in (the 'orphan-likes'). Only for a subset of orphan products (14%) or orphan-likes (17%) was the annual turnover estimated to exceed €100 million. By contrast, the average turnover of non-orphan products introduced after 2000 was estimated to be almost 50% higher than that of orphans.[228]

**Table 7: Distribution of average annual turnover (2008-2016) for various types of products in the EU, by turnover class (millions of euros per year)**

| | <€10 m | €10-50 m | €50-100 m | >€100 m | Average turnover |
|---|---|---|---|---|---|
| **Orphan-likes (N=82)** | 60% | 18% | 4% | 17% | € 79 m |
| **Orphan medicines (N=105)** | 48% | 25% | 13% | 14% | € 56 m |
| **Newly introduced non-orphan medicines (branded products) (N=1,071)** | 50% | 20% | 10% | 20% | € 83 m |

Source: Orphan Study (2019)

On average, evidence suggested that market exclusivity extends by 3.4 years the period for which authorised orphan medicines are protected from generic competition. Furthermore, with a sample of 16 orphan medicines it was possible to determine a new equilibrium price for four products,[229] based on the price realised by generic competitors. The economic value of market exclusivity reward for this limited sample of products averaged 30% of total turnover.[230]

For most orphan products, in particular those with an annual turnover below €50 million and average R&D costs, it was estimated that the market exclusivity reward helped to increase profitability, without giving the sponsor an unbalanced or unfair compensation. However, 14% of orphans had high sales turnovers in the EU (above €100 million) and

227 See Section 6.1.1. of the Orphan study report (2019).

228 As already stated in Chapter 4.2, the following limitations to the IQVIA database applied: data on revenues and volume data only covered 2008–2017 for most EEA countries (excluding Cyprus, Malta, Denmark, Iceland and Liechtenstein); the IQVIA data did not include revenue and volume data in non-EU jurisdictions (like the US); revenues were based on list prices (and not on net prices).

229 For more details, see Section 1.4. of Annex 3.

230 For detailed calculations, see Section 2.1. of Annex 3.

would not need a 10-year market exclusivity reward to be commercially viable, unless R&D costs were much higher than the average estimates (see Chapter 5.2.1).

However, low turnovers do not necessarily mean that the return on investment in orphan medicines is 'insufficient', as this depends on the specific situation. It is important to take into account development costs (which are mostly unknown) and the issue of whether there is generic competition after expiry of any protection for a given product.[231]

*5.2.3. Cost reduction and inefficiencies associated with the Orphan Regulation*

The following possibilities for cost reduction have been identified.

First, cost savings could be made if the market was able to switch rapidly to generic medicinal products after the expiry of market exclusivity and/or protection of other pharmaceutical incentives. In the analysis of 16 orphan medicines[232], generic competition was observed only for three orphan products; the price decrease at individual level was not known.

Possible reasons could be that other protections are still in effect, either in the EU (patents, SPCs, data exclusivity and market protection) or in the US. Another reason could be the prospect of too small a return on investment.

Also, a substantial share of authorised orphan medicines are biological molecules, so competition depends on developing biosimilars. All surveyed developers of biosimilars indicated[233] that the complexity of development and/or manufacturing influences decisions on whether and when to develop a biosimilar version of an orphan medicine. In addition, matching the quality of the reference orphan medicine can be challenging, as manufacturers control the release of commercial supplies.

As market exclusivity and/or the protection of other pharmaceutical incentives of more authorised orphan medicinal products are set to expire in the next few years, we are likely to see increased generic entry in the near future. Recent data shows that the overall price fall after generic uptake is 50% for medicinal products in general.[234] For orphan medicines, the literature suggests that prices have so far tended to fall more slowly on generic entry.[235] Potential cost reductions could also be achieved by reconsidering those of the Orphan Regulation's provisions that are designed to limit excessive profits and allow faster entry of similar medicines onto the market, by reducing market exclusivity after five years.

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231 While the expectation of low returns on investment can indeed drive market failure, it is by no means the sole reason. Insufficient basic research, lack of scientific leads for product development, and the complexity of the clinical trials of medicines for rare diseases all play an important part as well.

232 See Section 1.4. of Annex 3.

233 Section 8.4.3. of the Orphan study report (2019).

234 Section 2.3 of the Study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

235 Section 8.3.4. of the Orphan study report (2019).

Under the existing rules, orphan status cannot be challenged on the grounds of product profitability if such status was not sought on the basis of the 'insufficient return on investment' criterion. As applications for orphan designations have so far, in all cases but one, been based on the 'prevalence' criterion, it has been practically impossible to trigger a reduction of the market exclusivity period for any orphan product.

Potential inefficiencies and undesirable consequences may also arise from 'indication stacking', well-established use, and repurposing, as further explained below.

*'Indication stacking'*

There are currently 22 orphan products authorised for two or more orphan indications on the EU market. These indications refer to distinct orphan conditions, and each entitles the product in question to a period of market exclusivity. These periods may run in parallel, with their own start and finish dates. Similar trends can be observed in the US: of 251 orphan medicinal products authorised between 2008 and 2017, 15.9% had two orphan indications, while 7% were approved to treat *three or more* orphan indications.[236]

While these products have served patients in need and public health, thanks to the extension of the areas in which they can be used, there are also *negative* aspects. If a product receives an authorisation for an additional indication or indications, it is assigned a *new* period of exclusivity for that specific indication. However, it is often unclear whether such a period is really necessary to recover the additional costs of R&D.

While overlapping or consecutive periods of market exclusivity can delay generic entry and may block the development of generic orphan medicines, they cannot prevent generic entry altogether, as each exclusivity period is tied to a specific orphan indication. A manufacturer willing to produce and market a generic version of an orphan medicine once the first market exclusivity period has expired is entitled to do so.

The discussion on *whether* and *how* to reward the development of these 'follow-on' products, after the orphan medicine is authorised for the first indication, often goes hand-in-hand with concerns about a practice known as 'salami slicing'. This phenomenon refers to splitting certain common diseases into many 'artificial' subsets. Each of these subsets could then be considered a rare disease (such as certain forms of cancer).[237] Under the EU Regulation it is possible to obtain orphan designations for subsets of common diseases (although only subject to stringent conditions). At the same time, advances in personalised medicine, may add another layer of complexity to the current regulatory framework. Such developments may hold great potential for optimal tailoring of treatments to diseases and

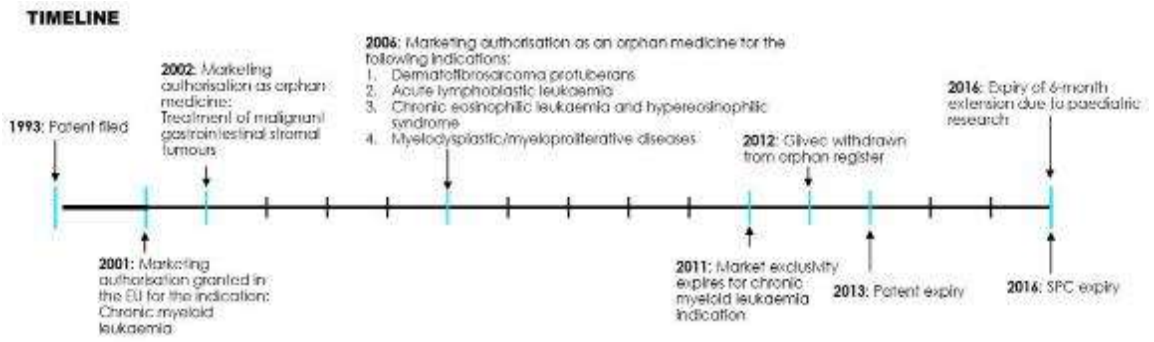
[236] US Government Accountability Office Report on orphan drugs, November 2018, p. 23.

[237] The prevalence of a condition would consequently be based on the sub-type and sub-population. The aim of this is to obtain the incentives associated with the Regulation through these new subgroups.

patients. However they should not lead to unnecessary multiplications of rare diseases out of common diseases, to gain market exclusivity periods.

The number of products authorised for multiple orphan indications in the EU is relatively small, and, in most of those cases the periods of market exclusivity for each indication overlap to a very significant extent. Various stakeholders[238] suggest that reducing the 10-year market exclusivity period for each subsequent indication is a possible way to limit inefficiencies and potential overcompensation. When considering eligibility for orphan designation, it might thus be preferable to consider cumulative prevalence for all the indications covered by the product, rather than the prevalence of each individual indication.

**Figure 10: Example of a product with multiple therapeutic indications benefiting from a number of pharmaceutical incentives (including orphan and paediatric incentives)**




This figure illustrates how different pharmaceutical incentives are granted at different stages of a pharmaceutical product's life cycle. The case study of Glivec,[239] an anti-cancer medicine authorised for a range of orphan indications, may be instructive here.

A PIP was also conducted, and the company subsequently *deregistered* Glivec as an orphan medicinal product, which provided the opening to file for an SPC extension and thus to benefit from six months of additional protection under the SPC system. At the same time, the same company still had a similar product (Tasigna) with therapeutic applications that overlapped with those of Glivec. (The company had maintained orphan market exclusivity for this product, which enabled it to benefit from both the orphan and the paediatric system.)[240]

238 Section 8.4.1. of the Orphan study report (2019).

239 Data taken from Chapter 5.3 of the Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

240 Chapters 5.4 and 7 of the Study on the effects of supplementary protection mechanisms for pharmaceutical products (Technopolis, 2018).

There are currently four *generic* versions of Glivec on the market. All were granted a marketing authorisation in 2013.

**Well-established use and repurposing**

19% of orphan medicinal products[241] have reached the EU market under these criteria. By way of a comparison, about 38% of orphan medicinal products newly authorised in the US between 2008 and 2017 were authorised for a new indication of a medicinal product previously approved to treat a rare or non-rare disease.[242]

Products authorised through this 'route' have attracted substantial scrutiny because of recent cases in which producers substantially increased the price of a newly-authorised medicine that was already available to patients, at a far lower price, as a magistral formula or in the form of hospital preparations.

**Chenodeoxycholic acid (CDCA)** for the treatment of a rare genetic disease, Cerebrotendinous Xanthomatosis (CTX). CDCA was originally developed in 1976 as a treatment for gallstones. However, it had already been used since the late 1970s as an off-label treatment for CTX, most recently as Xenbilox, marketed by Sigma Tau. Since the medicine had not previously been authorised for the treatment of CTX, and as it met the designation criteria, an orphan designation was granted to Leadiant (Sigma Tau's new name). Not long after this, the company raised the price of the medicine around 500-fold, causing a public outcry, since the investment the company had to make to 'develop' the product as an orphan medicine had been minimal: CDCA had already been shown to be safe and effective and it was registered on the basis of a literature review and two retrospective cohort studies.

These price increases often bear no relation to actual R&D costs. Market exclusivity is the main factor enabling them to engage in monopolistic price setting.

The fact that the current regulatory framework for the Orphan Regulation contains no provisions to safeguard the affordability and accessibility of orphan medicines, even when no significant R&D investments have been made, may be regarded as a significant inefficiency. However, the absence of data on the costs of development for such products makes it difficult to objectively estimate what would constitute an appropriate reward.

In 2016, a Commission notice[243] was issued with the aim of limiting inappropriate use of the Orphan Regulation, such as may occur when sponsors apply for orphan designations on products that have long been in use in the medical community. However, it has proven problematic to apply, as the information available in scientific literature on the use of

[241] Data up to 2018 (Section 5.5 of the Orphan study report (2019)).
[242] US Government Accountability Office Report on orphan drugs, November 2018, p. 24.
[243] Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products, C/2016/7253; OJ C 424, 18.11.2016, pp. 3–9.

hospital preparations is often very limited. Although sponsors are expected to do due diligence and provide all available evidence from their own studies and literature, the COMP has limited means at its disposal to verify whether the information is complete. A similar trend was observed in the US, where it was noted that the FDA does not always ensure that all information is consistently recorded in its review templates and evaluated when making designation determinations.[244]

### *5.2.4. How the costs and benefits of the Paediatric Regulation have been distributed*

The costs and benefits of the Paediatric Regulation have been quantified for the relevant stakeholder groups and a cost-benefit analysis has been undertaken.

- *Pharmaceutical industry*

The 2016 economic study estimated the total annual costs incurred by industry in connection with the Paediatric Regulation at €2,106 million, of which €82 million are administrative costs, while the rest is associated with paediatric R&D (mostly concerning clinical trials agreed in PIPs).[245]

Average costs incurred per PIP are estimated at €19.6 million. Of these, 4% (€728,000) are administrative costs arising from the application for a PIP and possible modifications, while 96% (€18.9 million) are R&D costs.[246] These estimated costs are normally incurred over several years, as the average duration of a PIP is between 5 and 10 years (though some are expected to last over 20 years).[247] However, the costs incurred for an individual PIP vary significantly. They depend on such matters as the number of clinical studies included in the PIP, the number of subjects involved in the trials, the duration of a PIP, the therapeutic area, the scale of cooperation with clinical and research networks, and the number of modifications of the PIP that are required. Table 7 shows the estimated average costs of each stage of a PIP, as well as the percentage of PIPs that incur such costs.[248] Details of the calculations concerning the cost of compliance with the Paediatric Regulation are given in Annex 3, in section 1 of the paediatric part.

**Table 7: Estimated costs of a PIP, broken down into stages, and the percentage of PIPs that incur such costs (based on data for completed phases only, 2008-2015), in millions of euros)**

244 US Government Accountability Office Report on orphan drugs, November 2018, p. 34.

245 Final Report of the Study on the economic impact of the Paediatric Regulation, including its rewards and incentives (December 2016); Section 2.2.

246 R&D costs include the costs of in-vitro studies and animal studies conducted during the development of a paediatric formulation, clinical trials, and other R&D costs.

247 Final Report of the Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – December 2016, Section 2.2.4.4.

248 Final Report of the Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – December 2016, Section 2.2.

| Stage | Average | % of PIPs incurring costs | % of PIPs incurring costs if PIP is discontinued |
|---|---|---|---|
| Preparation of the initial PIP application | €0.4 | 100 | 100 |
| Annual reporting and further PIP modifications | €0.1 | 55 | 29 |
| Other administrative costs | €0.2 | 42 | 21 |
| In-vitro studies and animal studies | €0.8 | 40 | 36 |
| Development of a paediatric formulation | €1.6 | 47 | 29 |
| Phase II paediatric clinical trials | €7.3 | 48 | 21 |
| Phase III paediatric clinical trials | €15.7 | 72 | 36 |
| Other R&D costs[249] | €14.4 | 44 | 21 |

Source: Study on the economic impact of the Paediatric Regulation (2016)

The system underpinning the Regulation is built on the assumption that products covered by the PIP requirement should be eligible for a reward, once paediatric development is completed, to balance the investments made by industry. However, this is not always the case. In fact, when an adult development programme stops, the PIP is often discontinued as well. The administrative and R&D costs of discontinued PIPs are estimated at €144 million per year.

To calculate the economic value of the SPC reward, the analysis focused on eight products which (1) received an SPC extension between 2007 and 2012, and (2) lost their exclusivity before the third quarter of 2014. The results were then extrapolated to four further products. The sample size was quite small, as only a fraction of products with completed PIPs have lost protection so far, so the data on how this affects revenues are limited. Moreover, the figures for those products may need to be interpreted with some caution, as companies may, in the early years, have prioritised products predicted to earn the highest return on investment through the SPC extension.

There are significant differences between products and countries, most likely linked to the competitiveness of the particular therapeutic market and/or national policies to encourage generic substitution. Consequently the economic value of the SPC extension varies considerably as a percentage of total revenue (between 10% and 93%, averaging 56.6%). Overall, the adjusted economic value of the SPC reward for the eight products concerned amounts to €926 million, with revenues especially geared towards some blockbuster products included in the sample size.[250] Details of the calculations underpinning the analysis of the economic value of rewards and/or incentives are provided in Annex 3 (section 2 of the paediatric part).

[249] Other R&D costs are incurred through activities ranging from, for example, preparing study outlines; medical writing for a clinical plan, including data and database management; coordination activities and transaction costs; and conducting non –interventional studies.

[250] Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016; Section 3.2.6.

The impact assessment conducted on the proposal for a Paediatric Regulation estimated that the value of a six-month extension of the SPC would offset the costs incurred by companies through mandatory paediatric testing. In certain cases, companies would make profits as a result. If an SPC extension is granted, it usually covers the costs incurred through the PIP (€926 million in revenue for 12 products, against average costs of €19.6 million per PIP).

However, it is important to note that up to 2016 only 55% of completed PIPs benefited from a reward. While it is expected that over time the proportion of products that benefit from this reward will increase, as companies start to plan their paediatric research better and earlier, it is unlikely that the success rate will ever reach 100%. This eventuality was not considered in the impact assessment.

In turn, it was not possible to estimate the economic value of the orphan reward and the PUMA. As regards the orphan reward, this was because only a limited number of products have benefited from it, most of which are still under protection. As for the PUMA, the 2016 economic study concluded that, in line with one of the possible scenarios laid down in the impact assessment, this reward does not seem to offer meaningful market exclusivity because the product can, in any case, be subject to off-label use of generics.[251] Furthermore, the fact that the new indication needs to be developed exclusively for children in order to be eligible for the PUMA often makes it too costly and complex, especially for SMEs. All of these points make projections of the commercial value of the product and the possible return on investment less predictable for companies.

Nevertheless, the risk-benefit analysis, detailed in Annex 3 (paediatric part, section 4.7), shows how the economic spill-over effects resulting from private R&D investments, which would not have happened without the Regulation, lead to the creation of more jobs and the promotion of innovation across sectors. A €2 billion investment in R&D associated with PIPs produces a €3.2 billion return in both the pharmaceuticals sector and in other sectors of the economy over 10 years.[252]

- *Regulatory authorities*

The Paediatric Regulation says that the EU budget's contribution to the Agency covers the work of the Agency and its PDCO committee. It is also intended to support the Agency's

[251] In many cases, healthcare professionals prescribe cheaper generic products off-label, in preference to the newly-authorised paediatric indication. In addition, national healthcare systems may be reluctant to reimburse the PUMA-rewarded product when cheaper alternatives are available.

[252] Administrative costs are not included in this calculation. They can be estimated at €78 million/year for all PIPs. Even if such figures were included, the cost-benefit calculation for industry would thus remain positive.

activities associated with the publication of paediatric clinical trials and the European network.[253]

It should be noted that part of the costs associated with PIP procedures conducted by the Agency are borne by national competent authorities contributing to the Agency's scientific work, which are not remunerated. On the basis of unpublished data on the costs of paediatric-related activities collected for the Commission report on the evaluation of the European Medicines Agency's fee system[254], the annual costs of NCAs for PIP assessment were estimated at €0.6 million, those of waiver assessments at €90,000 and those of compliance checks at about €50,000 per year.[255]

The impact assessment for the Paediatric Regulation estimated increased annual costs to regulators at €5 million, and in particular for EMA. This estimate seems to be correct, as the calculated average cost-base fee for industry for paediatrics was estimated at €4.8 million/year in the fee study.[256]

- *Society and patients*

The cost-benefit analysis under the Paediatric Regulation takes account of the benefits to society and children's health resulting from the Regulation's application. These benefits are: the switch from off-label to more on-label use of medicines, better treatment for children, fewer adverse drug reactions, shorter periods in hospital, better quality of life for children, increased school attendance, and less time spent by carers. The spill-over effects of industry's research investments are also taken into account. Details of the cost-benefit model and related calculations are given in Annex 3, sections 3 and 4 of the paediatric part.

The costs to society arise from the extra monopoly rent accruing to the company through the reward system (in particular the six-month SPC extension), which delays the market entry of cheaper generics and pushes up total healthcare expenditure. These extra costs are borne by the healthcare system and individual patients (directly or through their contribution to healthcare-related taxes and health insurance).

The cost-benefit analysis[257] looks at the benefit-cost ratio over 10 years for the eight medicinal products that received a PIP-related SPC extension and which were considered

253 Article 48 of the Paediatric Regulation.

254 Commission Staff Working Document on the evaluation of the European Medicines Agency's fee system.

255 The costs of PUMA-related fee incentives are fully borne by the EMA.

256 Section 2.1 of the EMA fee system study.

257 Details can be found in Annex 3. Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016: Chapter 6.

previously.[258] Five of these are used on-label in children, while for the other three data indicate continued off-label use in children after negative PIP studies.

The cash and non-cash benefits for society and child health can be estimated at €199 million. The extra costs to society arising from companies' monopoly rent, to which revenue received by other beneficiaries, like wholesalers, and taxes must be added, can be estimated at €590 million.[259] Of these, €551 million are estimated to be costs incurred by national health services. This gives a negative ratio overall. Only two of the eight products considered had a strongly favourable benefit-cost ratio. The negative benefit-cost ratio was highest for products with negative PIP studies, as they do not provide any alternative treatment options for children.[260]

A broader basket of products was also assessed by estimating the future benefits and costs of products that had passed the Agency compliance check and been authorised. This basket also included products which, though required to comply with the PIP obligation, would not receive a SPC extension. These PIPs would result in paediatric products that did not involve costs to society associated with additional monopoly rent.[261] In such a simulation, the benefit-cost ratio for society remains negative, though less so (€500 million versus €590 million).

The impact assessment expected that direct benefits from the Regulation, such as the reduction of adverse effects or shorter hospitalisations, would offset costs incurred through delayed generic entry. However, indirect effects were not taken into account.

The economic spill-over effects resulting from the private R&D investments generated by the Paediatric Regulation are dealt with in the risk-benefit analysis detailed in Annex 3, section 4.7 of the paediatric part. On the basis of companies' annual investments in PIP-linked R&D of about €2 billion, the total return on investment to society after 10 years was estimated at €6 billion. This figure is significantly higher than the estimated monopoly costs linked to the SPC extension (€590 million).[262]

### *5.2.5. Inefficiencies of the Paediatric Regulation*

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258 Sufficient data were available for only eight medicinal products to conduct the CBA. See Section 6.2.1 of the Paediatric study report (December 2016).

259 Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016: Chapter 6.3.5

260 Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016: Chapter 6.2.

261 Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016: Chapter 6.3.5.

262 Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016: Chapter 6.4, Table 28 in particular. For simplicity, it was assumed that the rate of return over the years would be linear, with a maximum cumulative return on investment 10 years after the initial R&D investment. However, in practice the spill-over effects are expected to be highest in the earlier years and to follow a decay curve.

The analysis above identifies several inefficiencies that could be addressed.

First, the SPC extension is awarded even if the outcome of the PIP is negative. This means that during the 'protection period' society cannot benefit from new paediatric treatments and the entry onto the market of cheaper generics for the adult medicine is delayed. This approach seems to have led to additional costs to society and patients, without any direct additional benefits. However, it is important to remember that a negative PIP still provides relevant data on the potential danger of the use of the product in children.

The reason for the second inefficiency is that paediatric medicines are developed worldwide, so companies often submit parallel requests for marketing authorisation in several countries. Lack of coordination between the requests made by various regulatory agencies in different parts of the world for the specific characteristics of studies to be conducted in children may lead to duplications of research.

To address this issue, the Agency created a 'paediatric cluster' in 2007, a monthly exchange between global regulators to discuss the coordination of their actions, first with the FDA and later joined by Japan, Canada and Australia. The objective is to enhance the science of paediatric trials and to avoid undue exposure of children to them. The benefits of this data sharing are a reduction in regulatory costs for companies and increased efficiency. The Agency-Commission joint paediatric action plan provides for further improvements in international cooperation.

Third, the Paediatric Regulation obliges companies to conduct paediatric research for each marketing authorisation application, unless a waiver is deemed appropriate. The small population size may often lead to competition between companies, if several target the same patient group for their respective research programme. This may lead to delays in completion and push up costs.

The 2016 economic study compared the costs of paediatric clinical trials in the EU and the US, both as enrolled study subjects, and as individual paediatric investigations (associated with developing a medicine) and clinical trials.[263] For the EU, cost estimates were based on information on individual PIPs and data on both completed and incomplete R&D phases. US cost estimates were based on data from two prominent studies published in the US. The cost of a paediatric investigation averages €21 million in the US and €18 million in the EU. As regards individual paediatric studies, the estimated amounts were €7 million in the US and €6 million in the EU. The study acknowledged that there were large

[263] Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016. Chapter 2.3.

variations in the sample dataset underlying the cost estimates, so significant uncertainties remained in these estimates. However, it noted that the cost estimates match.[264] [265]

The new Regulation on clinical trials,[266] which has not yet entered into force, is intended to streamline procedures for getting a clinical trial approved in Europe, particularly for multinational trials. It may help boost efficiency in conducting paediatric clinical trials.

### *5.2.6. Administrative burden*

The administrative burden for developers associated with the Orphan Regulation has not been further substantiated, given the assumption that application of the Orphan Regulation is voluntary.[267]

The Regulation is responsible for some administrative burden at Agency level. These costs are relatively small but are likely to increase as the number of applications continues to grow. The issue of increasing workload also affects the national competent authorities contributing to the work of the COMP. The burden associated with the work performed by COMP members falls largely on their home institutions, which currently receive no financial compensation for that work in the absence of fee revenues.[268]

Lastly, some of the Agency's procedures create additional administrative burden, the necessity and proportionality of which should be examined (e.g. the obligation for sponsors to submit an annual report on the orphan designation to EMA).

As regards the *Paediatric Regulation*, stakeholders say the PIP application and related administrative procedures consume significant resources,[269] especially the frequent modification of an agreed PIP. Streamlining the PIP process is one of the measures considered in the joint Agency-Commission paediatric action plan.[270]

The inefficiencies associated with the functioning of the SPC reward procedure are another aspect. The SPCs are granted at national level, meaning that paediatric SPC extensions must be requested independently from the national patent office in each Member State.

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264 Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016. Section 2.3.

265 Li, J.S. et al., 2007. Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program. JAMA, 297(5), pp. 480–488; Baker-Smith, C.M. et al., 2008. The economic returns of pediatric clinical trials of antihypertensive drugs. American Heart Journal, 156(4), pp. 682–688.

266 Regulation (EC) 536/2014 on clinical trials on medicinal products for human use.

267 Unlike the obligations under the Paediatric Regulation.

268 How this affects the fees system and the Agency's long-term sustainability was assessed in the 2019 evaluation of the Agency's fee system. See: https://ec.europa.eu/health/human-use/legal-framework/ema_fees_en

269 Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016: Chapter 4.3).

270 https://www.ema.europa.eu/en/documents/report/european-medicines-agency-european-commission-dg-health-food-safety-action-plan-paediatrics_en.pdf

Each patent office handles applications independently, which may result in divergent decisions.

Some patent offices receive specific training on the SPC procedure under the national regulatory system (e.g. in the Netherlands). This has improved the way these offices deal with SPC submissions.[271] A separate evaluation of the SPC system is currently under way.

From the perspective of public authorities, one particular area that merits attention is the growing administrative burden imposed on the national competent authorities of PDCO members (absences, workload). Since the Regulation took effect, the number of procedures (especially PIPs, modifications, waivers, deferral) has increased, pushing up PDCO's workload as a result. While there is no evidence that this has adversely affected the quality of assessments, the long-term impact on the proper functioning of the system is unknown.[272] In the short term, the ongoing Agency-Commission paediatric action plan seeks to find ways to streamline some of these procedures, to reduce the burden on the committee.

[271] Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016: Chapters 4.3 and 4.5.

[272] 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council, (COM(2017) 626, Section 9.

### 5.3 RELEVANCE

**Main findings**

The specific objectives of the Orphan and Paediatric Regulations have proven relevant to addressing the problems that existed when the legislation was adopted, and still exist today.

The narrow problem definition on which the orphan legislation is based was not well thought out and was thus inappropriate for addressing wider and more recent needs, such as treatments for infectious diseases. As a result, the current legislation is less relevant than it might be.

The objectives of both the Orphan Regulation and, to some extent, the Paediatric Regulation, have evolved over time. When the Orphan Regulation was designed, the priority was to bring products for patients with rare diseases to the EU market. Today, any legislative intervention in this policy area would also need to guarantee equal access to medicines across the EU. Moreover, the market for orphan medicines has become more financially attractive, as evidenced by the number of companies with orphan medicines in their portfolio. This changing context calls into question whether the system of rewards and incentives instituted by the Regulations remains relevant to current needs.

Finally, ongoing and future developments, both scientific and non-scientific, in the pharmaceutical sector, especially in the field of advanced therapies, personalised medicine and innovative trials design, will have significant implications for the Regulations' relevance in the future. These new products, which challenge the system of orphan designation, call for policy changes in defining orphan condition and deciding which subset(s) to take into consideration when applying for orphan designation.

To assess the relevance of these two Regulations, we need to analyse whether the objectives and tools they set out were and are appropriate to tackle the problems that *existed*, the issues that are being faced *now*, and challenges in the near *future*.[273]

At the time of the intervention, the problems were identified as a lack of treatment for patients with rare diseases and of medicines specifically studied and developed for children. The legislation therefore focused on these two groups.

Looking at the objectives of each of the instruments, they can be seen as adequate responses to the problems identified at the time. Making medicines for rare diseases available by fostering research and development, and providing the same quality of treatment for patients with rare diseases, certainly addressed the needs of the patients concerned. Research on and testing of medicines for children and providing information about those medicines addressed the lack of targeted medicines for children.

[273] See also the description of the intervention and its objectives in Chapter 2 of this SWD.

Looking at the problem today, it becomes obvious that the lack of treatment is broader. Lack of treatment affects not only rare diseases, but also infectious diseases. On the one hand there are known diseases for which existing antibiotics no longer work, owing to the development of antimicrobial resistance. On the other hand, there are new diseases, in particular viral diseases, for which adequate medicines have yet to be developed. Since the 1970s, newly-emerging diseases have been identified at an unprecedented rate of one or more a year. There are now nearly 40 diseases that were unknown a generation ago.[274] More research is needed to develop new medicinal products and alternative treatments, as well as innovative anti-infective approaches to tackle this emerging threat.[275] The narrow problem definition used as the basis of the orphan legislation has proven inadequate to address those needs.

The tools of both legal instruments were designed to address the root cause identified at the time: market failure (in particular, the fact that the target group of patients was too small to generate a profit). They were designed to create financial incentives for industry to invest in research, development and clinical trials on medicines in both target groups.

The results in the effectiveness section have shown that the root cause, low expected return on investment, still exists. The comparative analysis shows that turnover levels for orphan medicines can be lower than those of non-orphans, sometimes significantly so. However, this does not necessarily apply to the whole target group as defined in the legislation. The orphan medicine market has become more financially attractive, as proven by the number of companies with orphan medicines in their portfolio and the interest that venture capitalists show in investing in this field.[276] This has resulted in the development of medicines in some therapeutic areas where treatments already exist, while other areas have none. Rare diseases can thus no longer be viewed as a homogeneous group for which no treatments are available, and may need more differentiated tools to direct investments to the areas where they are most needed.

Although antibiotics were not included in the initial consideration of needs and problems, the root cause of low return of investment applies here as well. Pharmaceutical companies are unwilling to invest in developing new antimicrobials because of concerns about non-profitability. In fact, new antimicrobials would need to be developed and kept on the shelf for reasons of antimicrobial resistance.[277] This means there is no market in practice, so companies have no interest in developing new antimicrobials which would bring them no return on investment. Based on this analysis, antibiotics could be assigned an orphan designation under the 'low return on investment' criterion in the legislation. However, that tool has not so far boosted investment in this field. This shows that the tools currently

[274] https://www.who.int/whr/2007/overview/en/index1.html
[275] A European One Health Action Plan against Antimicrobial Resistance (AMR): https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf
[276] Section 6.4 of the Orphan study report (2019).
[277] https://ec.europa.eu/health/amr/antimicrobial-resistance_en

available are not fit for purpose. A more in-depth assessment of root causes, along with appropriate tools to tackle the lack of investment, is needed in the area of antimicrobials.

In paediatrics, findings on effectiveness show that rewarding companies for testing medicines for use in children boosted the development of paediatric medicines linked to medicines for adults. However, therapeutic areas involving diseases that affect only children have been left behind. More differentiated tools may thus be needed for paediatrics as well, to direct investments where they are needed most.

The objectives of the orphan and paediatric legislation also implied that an EU authorisation would translate into medicines being accessible to patients in all Member States. However, the tools for progressing beyond the authorisation stage were limited. The legislation relied on industry decisions to make medicines available in each Member State. The main influences on such decisions are companies' strategic decisions on the one hand, and national pricing and reimbursement policies on the other. However, the legislation contains no provisions that could influence those stages. Although the legislation achieved the objective of making medicines available, it fell short of achieving affordable medicines that are accessible to patients in all Member States.

**Progress in science and the changing context**

Science has also moved on over the last 20 years, and the tools provided by the two Regulations may no longer be appropriate in the light of these advances.

*New types of products and production techniques*

While science evolves, the opportunities it provides also increase. The tools laid down in the legislation were designed in line with the approaches to developing and authorising medicines that prevailed at the time. For new types of medicines that do not follow conventional approaches, this may pose challenges.

**Advanced therapy medicinal products (ATMPs)** and biological medicines account for a growing proportion of all EU orphan designations.[278] They offer many therapeutic advantages in the treatment of rare diseases, particularly those which have the potential to cure such disorders, but also pose challenges as regards applying the Orphan Regulation framework. This framework relies on criteria which must be met if a product is to receive an orphan designation. This designation should ensure that only products addressing a rare disease fall under the scheme. It should also reward development by granting exclusivity, unless a significant benefit can be demonstrated by the new product (or clinical superiority in the case of a similar medicine).

[278] See Chapter 2.1. of this SWD.

ATMPs may reach the market with limited clinical data via conditional marketing authorisations. The conditional marketing authorisation makes it difficult for COMP to assess at the time of initial authorisation whether the product offers any significant benefit over and above existing treatment options, and hence whether the orphan designation can be confirmed and the company can profit from market exclusivity. In addition, this form of authorisation also challenges the step after the conditional authorisation when Member States need to decide how to price the medicine and provide reimbursement. In targeted surveys, representatives of HTA institutions and Member States have indicated that the limited evidence at the time of granting the conditional marketing authorisations represents a real challenge for assessors who need to determine whether a product is cost-effective and should be admitted into reimbursement systems.[279]

Over the last 20 years there have been numerous advances in genomic research, making it possible to better define diseases and understand the molecular causes of complex diseases. This change is not new per se but is in constant evolution. The fact that subtypes of new diseases are being identified that were previously thought to be part of a broader disease is beneficial to patients and researchers. In the context of rare diseases, **personalised genomic approaches** are particularly relevant, as an estimated 80% of rare diseases have a genetic component. With personalised medicine becoming increasingly developed, it could be at the forefront of clinical applications within the next 20 years.

The personalised medicine approach has already shown to be highly cost-effective, with new medicines now available that target, among others, rare diseases such as rare melanoma and cystic fibrosis in patients carrying specific mutations. As mentioned in the Council conclusions of 7 December 2015 on personalised medicine for patients[280], personalised medicine is not only about medicines (pharmaceuticals/medicinal products) but rather about putting the person at the centre of healthcare by better understanding the genetics, the detailed biological mechanisms and interactions with the environment, therefore facilitating the discovery and development of effective treatments for rare and common diseases alike.

Personalised medicine does not change the definition of the disease, but targets better the patient population responding to a certain medicine. Therefore developments in personalised medicine should not lead to unnecessary multiplication of rare diseases out of common diseases and hence to multiplication of exclusivity periods.

The EU's experience with applications **for orphans defined by biomarkers**[281] shows that although they can define a valid sub-set of a condition acceptable for orphan designation,

279 Section 7.2.4. of the Orphan study report (2019)

280 http://data.consilium.europa.eu/doc/document/ST-15054-2015-INIT/en/pdf

281 The Agency defines a biomarker as 'a biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals.' https://www.ema.europa.eu/en/glossary/biomarker.

there is still a need to demonstrate medical plausibility and significant benefit in the defined condition. The fact that the medicine concerned does not work outside the sub-set it is being developed for must also be demonstrated. However, establishing the absence of efficacy is generally challenging and not a primary goal in the development of medicines (which focuses primarily on establishing safety and efficacy). It is therefore challenging for applicants to provide robust evidence that a product is not efficacious outside a specific sub-set.

In addition, biomarkers are increasingly used in what is known as tissue-agnostic development in oncology, where the product development is not focused on patients with a particular type of cancer, but rather on any patient expressing particular biomarkers, independent of the tissue or origin of the cancer. Treatments developed this way may display activity against multiple types of cancer or subsets thereof, which would require changes to the policy on defining the orphan condition and on which subset(s) should be taken into consideration when applying for orphan designation.

In the US, the use of sub-setting orphan designations through biomarkers is becoming more widespread, particularly in the field of oncology. Between 2009 and 2015, 28% of oncological orphan medicines there were based on biomarker-defined subsets. This represented 12% of all new oncology medicines authorised in that time period. However, as reflected above, opening the EU system to more sub-setting may not bring more developments in areas where there is no treatment available, but could put further strain on national reimbursement systems.

*New ways of conducting clinical trials*

There have also been major developments in how clinical trials are designed and conducted since the introduction of the Orphan and Paediatric Regulations. These developments can benefit both pharmaceutical companies and patients by improving research productivity and accelerating the rate at which new treatments are brought to market, while also reducing the burden on patients. However, some of these developments affect the way both Regulations can be applied, including the work of the Agency Committees.

For example, basket trial designs are designed around a mechanism of action, providing evidence on the mechanism of action rather than efficacy as such. As the sample sizes within each basket are small, COMP may find it challenging to estimate significant benefit. Furthermore, in cases where basket trials address a novel mechanism of action that presents itself differently from the description in the existing definition of the condition, this can pose challenges in the EMA authorisation procedure similar to the one described above.

As regards the Paediatric Regulation, these novel ways to conduct clinical trials may have a direct effect on the PIP, which requires applicants to submit paediatric investigation plans very early in the development phase. An early design of a PIP creates opportunities for

discussion of paediatric matters early on in the development of a product. However, in some cases it may be challenging to consider and design all aspects of medicine development for children in the very early phases of development. This is especially true in the case of innovative and adaptive clinical trials design. This may lead to a subsequent need to amend the agreed paediatric investigation plan several times, which increases the administrative burden and may even delay authorisation. Some of the measures set out in the joint Agency-Commission paediatric action plan[282] are designed to further explore whether there is a non-legislative way of addressing this issue.

To conclude, scientific developments will mostly have a clear positive effect on the potential for developing new treatments for patients with rare diseases. At the same time, they may challenge the framework and application of the Orphan Regulation and, to a lesser extent, that of the Paediatric Regulation. It is therefore important for the regulatory framework to be kept sufficiently up to date with such developments and their potential consequences, so that the framework can capitalise on opportunities while limiting potentially unwanted effects. A main area of tension where the Regulation is being challenged as a result of scientific advances is the definition of an orphan condition.

### 5.4 COHERENCE

**Main findings**

The Orphan Regulation offers a set of incentives that work well together and it is relevant to both smaller and larger developers. The fee waivers, protocol assistance, market exclusivity and support for research complement one another. However, better alignment of timing and information needs between the four Agency Committees dealing with orphan and paediatric medicines could reduce the risk of inefficiencies.

The Orphan Regulation and national research programmes and policies complement and support each other to a large extent. However, there is no monitoring to enable the interplay between EU research funding and the Orphan Regulation to be assessed. More specifically, there are no indicators to demonstrate how public research investments contribute to successful authorisations of orphan medicines. Furthermore, the Orphan Regulation does not interact in a coherent fashion with the Directive on Medicinal Products for Human Use (2001/83/EC) as regards generic entry. The Orphan Regulation only allows developers of generic medicines to initiate an application for a marketing authorisation once the market exclusivity period has expired.

The Paediatric Regulation mostly interacts in a coherent manner with related EU and national legislations and measures. However, national rules on the conduct of trials with children may still delay the completion of a paediatric investigation plan (PIP). Moreover,

[282] https://www.ema.europa.eu/en/documents/report/european-medicines-agency-european-commission-dg-health-food-safety-action-plan-paediatrics_en.pdf

as regards the SPC extension reward, the fact that this incentive is granted by national patent offices that act independently makes it difficult for companies to forecast whether this can be done successfully. An improvement in the situation for multinational paediatric trials can be expected with the application of the new Regulation on clinical trials and the implementation of the joint Agency-Commission paediatric action plan.

The combined application of the Orphan and Paediatric Regulations has not provided sufficient incentives to foster the development of new innovative medicines for use in children with rare diseases.

In evaluating how the two Regulations fit within a broader over-arching architecture, the degree of consistency between the provisions of each Regulation was analysed (*internal* coherence). How they relate to other EU (legislative and non-legislative) and national actions (*external* coherence) was also assessed.

**Internal coherence**

*Orphan Regulation*

The various tools provided by the Orphan Regulation work well together to support the development of new orphan medicines. No barriers, overlaps or contradictions were identified. Responses to targeted consultations suggest that the various tools of the Orphan Regulation work together in a coherent manner. The sponsors interviewed said that each tool or incentive served a specific purpose, addressing different aspects and pressure points across the innovation lifecycle. The fee waivers, protocol assistance, market exclusivity and support for research (or for encouraging research) have created a stronger policy response to unmet medical needs than any one of those incentives would have done in isolation. They seem to function in synergy and are not disconnected or confused, according to the interviewees.

*Paediatric Regulation*

The overall system of obligations and rewards put in place by the Paediatric Regulation is perceived by all the stakeholders interviewed as working in a coherent way.[283] [284] This was also confirmed by the data, as analysed in the effectiveness section.[285]

[283] Public consultation on the Paediatric regulation conducted in 2016).
[284] Section 4.2 of the Orphan study report (2019).
[285] Chapter 5.1 of this SWD.

However, the fact that the SPC extension is granted by national patent offices that act independently and the timelines for applying for such a reward make it difficult for companies to predict whether the outcome of their request will be successful. Furthermore, the SPC extension leads to higher rewards if paediatric development is linked to adult development (a detailed analysis is provided in the effectiveness section).[286]

*Agency committees*[287]

A product may be assessed by up to four[288] Agency committees: COMP for the orphan designation, PDCO for approval of the PIP, CHMP for the benefit-risk assessment required for marketing authorisation, and in the case of ATMPs, CAT has the primary responsibility for the assessment of the application (but the final opinion is adopted by CHMP). CHMP can also grant conditional marketing authorisations on the basis of less comprehensive data.[289]

The overall opinion[290] of members of the committees was that the committees work reasonably well together and that there are no major issues.

However, a few areas were identified where there had been occasional challenges,[291] which may also lead to inefficiencies:

- CHMP, PDCO, CAT and COMP use different timelines for their assessments and sponsors submit different data to each committee. This can make scientific discussions difficult as they lack common ground, which can adversely affect the outcome or the timing.[292]
- The timelines associated with decision-making are different for CHMP/CAT and COMP. As a result, the COMP process is not well integrated in the CHMP/CAT process, which may lead to delays in some cases.
- In addition, while it is PDCO that decides on the PIPs, the decision on the orphan designation is taken by the Commission, based on a scientific opinion from COMP. This adds more time to the process.

The majority of developers of orphan medicinal products were broadly positive in the targeted consultation about the coherence of the various committees' activities. The clarity of communication and on time assessments were widely rated as being coherent. However,

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286 Section 5.2 (Effectiveness) of this SWD.
287 Section 9.3 of the Orphan study report (2019).
288 Depending on the type of product and orphan indication.
289 Commission Regulation (EC) No 507/2006. This Regulation stipulates that to meet patients' unmet medical needs and in the interests of public health, it may be necessary to grant conditional marketing authorisations ('CMAs') on the basis of less comprehensive data than is normally the case.
290 Section 9.3 of the Orphan study report (2019).
291 Idem.
292 For example, PDCO and COMP may look at the same product development without any formal interaction.

the respondents were less positive about the consistency of outcomes, especially the alignment and coherence of procedures among committees.

**External coherence**

*Orphan Regulation*

- *Other legal instruments*

The *Orphan* Regulation interacts with other EU legislative acts, mainly Directive 2001/83/EC on Human Medicinal Products, the SPC Regulation and the ATMP Regulation.[293] Developers of orphan medicines can benefit from incentives and rewards offered by each of these legal instruments, depending on the product characteristics of the new medicine. However, while the data and market protection periods applicable to all human medicines[294] would allow generic competitors to *place* generics on the market at the end of the 10-year protection period, for orphan medicinal products[295] generic competitors can only submit an *application* for marketing authorisation at that point in time. This may delay generic entry.

Developers of orphan medicinal products say that the protections offered by the SPC and the Orphan Regulation have benefited pharmaceutical innovation and the development of orphan medicines in particular. They did not report any specific tensions between the operations of the two Regulations.[296]

- *EU and national research initiatives and programmes*

The Orphan Regulation states that medicinal products designated as orphan medicinal products are eligible for incentives made available by the Community and Member States.[297]

**EU research incentives**

A variety of EU initiatives and programmes exist that support the development of treatments for rare diseases. The EU has made major investments during the last two decades to support cross-border and interdisciplinary research in almost all medical fields including rare diseases, which has contributed to the understanding of the underlying causes of these diseases and to the development of diagnostics and treatments. Since 2000, more than €1.7 billion has been made available, via the EU Framework Programmes for

293 See also Section 2.1 of this SWD.
294 Article 10 of Directive 2001/83/EC).
295 Article 8(1) of the Orphan Regulation.
296 Section 9.1.1. of the Orphan study report (2019).
297 Aid for research into the development and availability of orphan medicinal products (Article 9(1) of the Orphan Regulation).

Research, Technological Development and Innovation (FP5, FP6, FP7 and Horizon 2020), to over 340 collaborative research and innovation consortia (projects) in the area of rare diseases.[298] Such research projects bring together multidisciplinary teams representing universities, research organisations, SMEs, industry and patient organisations from across Europe and beyond.

**Table 8: EU budget allocated to collaborative research & innovation projects on rare diseases**

| Framework Programme | Timeframe | EU contribution, millions of euros | Number of projects addressing rare disease(s) |
|---|---|---|---|
| FP5 | 1998-2002 | 64 | 47 |
| FP6 | 2002-2006 | 233 | 59 |
| FP7 | 2007-2013 | >624 | >118 |
| H2020 | 2014-2019 | >808 | >137 |

Source: DG RTD (data available up to January 2020)

The field of research into rare diseases has been a good example of success, showing how further investments and resources from across Europe can be brought together to a degree that would not reasonably be possible within an individual Member State, or even a sub-set of Member States acting in isolation. These activities have increased the scale of investment by the public sector in rare disease research.[299]

EU-financed private-public partnerships under the 'Innovative Medicines Initiative'[300] have also supported projects, thereby speeding up R&D of medicines for rare diseases. The ULTRA-DD project,[301] for instance, was designed to produce new tools and resources to speed up the development of orphan medicines, especially in the areas of autoimmune and inflammatory diseases.

In addition, European Reference Networks (ERNs)[302] play an increasingly important role, not only in research, but also in sharing information to improve diagnosis and the quality of care, as well as in providing clinical practice guidelines in medical fields where expertise is rare.[303] [304] ERNs are expected to have a major structuring effect on research and care by

298 On the basis of DG RTD data.

299 Section 10.5 of the Orphan study report (2019).

300 IMI is a joint undertaking between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The focus of research under the IMI umbrella has been partly led by industry (https://www.imi.europa.eu/).

301 https://www.imi.europa.eu/projects-results/project-factsheets/ultra-dd

302 Virtual networks involving healthcare providers across Europe that were established in 2017 and are financed under the EU health programme (https://ec.europa.eu/health/ern_en).

303 Most ERNs cover adult and paediatric conditions, but some of the thematic networks included in the project focus on rare paediatric diseases.

304 See also the introductory chapter of the Special Report of the European Court of Auditors ('EU actions for cross-border healthcare: significant ambitions but improved management required', 2019).

linking thematic expert centres across the EU and providing sustainable clinical networks to pool medical expertise and patient registries' data on rare diseases.

However, an important question is whether all this public funding spent on research has led to available and accessible new orphan medicines covering an unmet medical need. The information available did not provide sufficient data to answer this question, as there is no legal obligation to follow the development of the product after the first research is conducted. The EU has limited influence over the direction of the research it supports through these programmes. Interplay between these research funding programmes and the EU Orphan Regulation is not monitored or reported in any formal sense. Moreover, research funding agencies (in both Europe and the US)[305] lack quantitative performance indicators to demonstrate the direct correlation of public research investments with the impact of research on society, in terms of benefit to patients (e.g. new treatments, diagnostic tools, rare diseases identified, and orphan medicinal products developed). Often, research does not produce results until several years after the end of the funding period.

At the moment, the funding itself can only be linked to the obligation to have obtained an orphan designation, a prerequisite that has existed since 2009 for receiving Framework Programme funding.[306] There was been a rise of over 50% (see Figure 5 in Chapter 5.1 of this SWD) in both the number of orphan applications submitted and the number of designations granted by the Commission over 2009-2015 (against 2000–2008). In particular, a Horizon 2020 call for Phase I/II clinical trials on rare disease therapies with an orphan designation led to a peak in the number of applications between 2014 and 2016.[307] However, it is still too early to see results in the new orphan medicines authorised.

Another example of EU research funding is the AlphaMan project,[308] leading to the development of an enzyme-replacement therapy for a rare genetic disease called alpha-mannosidase. This resulted in the EU marketing authorisation of Lamzede[309] in 2018, the first ever treatment for this condition.[310]

A non-exhaustive list of successful EU projects can be found on the dedicated DG Research website.[311]

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305 Based on information from DG RTD.

306 See Chapter 3.3 of the Inventory of Union and Member State incentives to support research, development and availability of orphan medicinal products (SWD(2015) 13 FINAL).

307 Section 9.4 of Orphan study report (2019). See also Figure 3 in Chapter 5.1 of this SWD (effectiveness) with the number of designations granted per year (2000 – 2017).

308 ALPHA-MAN (Clinical development of Enzyme Replacement Therapy in alpha-Mannosidosis patients using recombinant human enzyme.)

309 Official Journal of the European Union, C 150, 27 April 2018.

310 Section 9.4 of the Orphan study report (2019).

311 https://ec.europa.eu/info/research-and-innovation/events/special-features/world-rare-diseases-day_en

**Member States' research initiatives**

It was also explored how the Orphan Regulation aligns with related measures taken at *national* level by Member States.

The number of Member States with a national plan supporting rare disease research into the development and availability of orphan medicinal products has grown substantially since 2009.[312] In that year, only four Member States had a national plan or strategy, whereas by 2017 the number had increased to 23 countries.[313] There was, however, no data available to further explore the link between these plans and the orphan designations and authorisations granted.

*Paediatric Regulation*

The Paediatric Regulation also interacts with EU legislation on the supplementary protection certificate for medicinal products ('SPCs') (Regulation (EC) 469/2009) and on clinical trials (Directive 2001/20/EC).[314]

- *SPC legislation*

As the Paediatric Regulation provides for the possibility to receive an extension of six months of the SPC when a PIP is conducted, any modernisation or recalibration of the SPC system following the ongoing evaluation of the SPC regulation[315] will influence the paediatric reward system. Any inefficiencies in the SPC extension system that are identified could be addressed in possible future measures following up that evaluation.

- *Clinical trial legislation*

The Paediatric Regulation resulted in an increase in paediatric clinical trials. The instrument for ensuring that such clinical trials are conducted, respecting the ethical principles[316] for protecting minors from unnecessary testing, and involving children in the decision to participate in a trial or not, is the EU Clinical Trials Directive and Regulation.[317]

312 The EPSCO council recommended the establishment of national rare disease plans in 2009.
313 Section 9.5 of the Orphan study report (2019).
314 The SPC Regulation is designed to offset the loss of patent protection for pharmaceutical products that occurs due to compulsory testing and clinical trials before a marketing authorisation can be obtained. The Clinical Trials Directive provides a legal framework for the conduct of clinical trials in Europe and contains specific provisions on clinical trials conducted with the participation of minors.
315 https://ec.europa.eu/growth/industry/intellectual-property/patents/supplementary-protection-certificates_en
316 Recital 7 of the Paediatric Regulation.
317 Directive 2001/20/EC (a new Regulation (EC) No 536/2014 on clinical trials was adopted in 2014, but has not come into force yet).

[318] In substance, the Paediatric Regulation and the EU Clinical Trials legislation can be considered complementary.

However, when a PIP is agreed and the clinical trials need to be approved and conducted, several problems have been reported, such as divergent ethical views at national level on the conduct of trials with children, including requests to delay the conduct of trials with children until after data from adults become available.[319] This may result in companies requesting a deferral of PIPs (or part of them), and consequently in delays in developing medicines for children.

While it is essential that trials are conducted in accordance with strict ethical principles and protect the safety of children, it is considered necessary for assessors to be better aware of the requirements of the Paediatric Regulation and the reasons for the various PIPs.[320] The joint Agency-Commission Paediatric Action Plan provides for measures to tackle these issues.[321] Moreover, the new Clinical Trial Regulation will further harmonise the conduct of multinational trials and increase paediatric expertise in the evaluation of clinical trials. This new legislation is consequently expected to help find solutions to those problems.

- *EU non-legislative activities*

In addition to identifying certain shortcomings of the Regulation, the Report on the 10 years of experience with the Paediatric Regulation[322] has also identified short-term measures designed to try to improve the implementation of the Paediatric Regulation. To follow up, on such points the joint action plan on paediatrics has been developed to respond to such conclusions.[323]

- *EU-funded research*

The impact assessment of the Paediatric Regulation deduced that certain tools set up by the legislation, and in particular the PUMA scheme, should have been complemented by EU research funding. This has not been done via a dedicated fund to promote independent

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318 The date of application of the Regulation depends on the Agency's finalising a database that is necessary for its operation.

319 Multi stakeholder workshop on 'How to better apply the Paediatric Regulation to boost development of medicines for children', https://www.ema.europa.eu/en/documents/report/how-better-apply-paediatric-legislation-boost-development-medicines-children-report-multi_en.pdf

320 This issue was discussed during a multi-stakeholder workshop held in March 2018 to draw up the Agency-Commission joint paediatric action plan.

321 Topic areas 2 and 3 of the action plan: https://www.ema.europa.eu/en/documents/report/european-medicines-agency-european-commission-dg-health-food-safety-action-plan-paediatrics_en.pdf

322 State of Paediatric Medicines in the EU – 10 years of the EU Paediatric Regulation: Report from the Commission to the European Parliament and the Council (COM(2017)626).

323 https://www.ema.europa.eu/en/documents/report/european-medicines-agency-european-commission-dg-health-food-safety-action-plan-paediatrics_en.pdf

research into the use of substances not covered by a patent or an SPC, as set out in the impact assessment, but via the standard EU research programmes.[324] [325]

Furthermore, to complement the PUMA scheme, the Committee on Proprietary Medicinal Products Paediatric Expert Group (the predecessor of the PDCO) at the time of the preparation of the legislation developed a list of 65 off-patent medicines considered priorities for research and development. This list continues to be updated by the PDCO; by 2017, 23 projects on 28 off-patent medicines (active substances) had received EU funding.[326]

Despite having provided significant results in neglected areas, such tools to support research have not resulted in a parallel success of the PUMA scheme.

- *Other national initiatives*

Member States have also put in place other initiatives which complement the provisions of the Regulation.[327] These include priority review of paediatric clinical trials applications, and fee waivers for the authorisation of paediatric clinical trials (clinical trials are authorised at national level), which streamline the conduct of studies agreed in a PIP. Furthermore, special measures have been put in place to determine the pricing of paediatric medicines or measures to reduce the use of off-label medicines when paediatrically tested alternatives are available on the market.

- *International*

The development of medicines is often a global affair. Products are studied and marketing authorisations are requested in various regions. Cooperation between international regulators therefore aims on the one hand to exchange information on how to address similar requests and, on the other hand, to provide similar advice and opinions to companies. These activities are ongoing at international level, mainly in 'clusters'.[328] In the paediatric cluster, the Agency works together with the regulators from the US, Japan, Canada and Australia. In the orphan cluster, it works together with the US regulators.

Analysis of international paediatric activities suggests that the Agency and the FDA's joint approach to paediatric medicines (the EU and the US have very similar legislative frameworks in this area) has the potential to help reduce regulatory costs for companies in

[324] Article 40 of the Paediatric Regulation.
[325] In the US, the FDA manages a specific fund to support research in off-patent products.
[326] Agency's 10 years report (Section 3.6.1.)
[327] Idem.
[328] A discussion forum facilitating regulatory discussions on global development of paediatric medicines. It was set up in 2007 as a joint Agency/FDA venture; in 2009 and 2010, respectively, Japan and Canada joined, followed in 2014 by Australia as an observer.

future if they submit in parallel in both regions.[329] The Study on the economic impact of the Paediatric Regulation involved a survey in which companies were asked whether they also used PIP data for their applications to the FDA. This revealed that data from 54% of PIPs were used in some degree when applying to the FDA and/or were subject to ongoing discussions with the FDA.[330]

**Coherence between the two legislations**

As around 90% of all rare diseases manifest themselves in childhood,[331] there is a clear need to develop orphan medicines that also cater for children. The main concern raised by 'non-industry' stakeholders is the limited development of products suitable for children with rare diseases.[332] [333] As previously described,[334] the Orphan and Paediatric Regulations, both alone and combined, have not provided sufficient incentive to foster the development of medicinal products for children with rare diseases.

[329] Technopolis Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016 (SANTE/2015/D5/023, Section 2.3.1).
[330] Study on the economic impact of the Paediatric Regulation, including its rewards and incentives (section 2.3.1).
[331] Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database, European Journal of Human Genetics, 2019.
[332] Only half of all currently authorised orphan medicines have been approved for use in children as well (Section 7 of the Orphan study report (2019)).
[333] Section 9.1.2 of the Orphan study report (2019).
[334] Chapter 5.1.4 of this SWD.

### 5.5 EU ADDED VALUE

**Main findings**

The Orphan Regulation has enabled the parties concerned to respond in a more concerted and effective way to the challenges of developing orphan medicines. Alongside other measures, it has contributed to an increase in R&D activities in nearly all main therapeutic areas. Between 2000 and 2017, 1956 medicines under development were granted an orphan designation. This would not have been reasonably possible at the level of Member States alone, given the lack of sufficient economic incentives for R&D and limited ability to conduct clinical trials on small numbers of patients without sufficient research networks and researchers.

However, if one compares the increase in the number of orphan medicines on the market with the baseline situation before 2000, the added value of the Orphan Regulation is somewhat modest. In terms of time-to-market and availability of orphan medicines, there are substantial differences between Member States, and the added value has been comparatively low for some of them.

The *Paediatric* Regulation has created a positive trend in developing new medicinal products for children, similar to what has happened in the US from the 1990s on, after the introduction of paediatric legislation there.

Both Regulations respect Member States' exclusive competences in fields such as the administration of health services, pricing, and reimbursement. Overall, the Regulations work in synergy with other instruments, such as EU research programmes and legislative acts.

EU added value refers to the changes and results observed in the areas of orphan and paediatric medicines across the EU which could not have been achieved through action at regional or national levels. Ideally, EU added value would have been established through a comparison with a counterfactual scenario in which the Orphan Regulation was not implemented (for instance, by making comparisons with another region that is similar to the EU in significant ways, but which has not introduced specific orphan legislation). However, comparable regions like the US and Japan have all introduced broadly analogous policies. There was thus no candidate comparator or source of data on which to construct such a counterfactual situation for orphan medicines.[335] In this way, the Orphan Regulation differed from the Paediatric Regulation, for which such a comparison was possible.

The assessment of EU added value has relied mainly on desk research, specifically on comparisons with the situation in the EU before the Regulations took effect, and on a

[335] See Section 10 of the Orphan study report (2019).

'comparator analysis'.[336] The analysis was complemented by feedback from interviews and the outcomes of the targeted consultations.

**Orphan Regulation**

The question of whether the Orphan Regulation has generated EU added value is linked with the question of whether the results achieved surpass those which could realistically have been expected at Member States' level (i.e. through national interventions alone).

The Orphan Regulation was the first legislative act concerning rare diseases in the EU. It represented the start of the development of a coordinated EU strategy to diagnose, treat and care for citizens with a rare disease. In 2009, the European Council of health ministers[337] issued a recommendation for action in the area of rare diseases and recognised the topic as an important public health issue. It encouraged the drawing up and adaptation of national plans and strategies, measures to boost research, and the pooling of expertise at EU level. In 2009, a focus on rare diseases was relatively new and innovative in most Member States and only a few had national plans in place. By 2019, plans had been established in 25 Member States.[338] [339]

Stakeholders agreed[340] that the Orphan Regulation has catalysed the development and marketing of orphan medicines and that it has contributed in ways that would not have been possible at national level alone, even when aggregated across Member States. At all events, action taken at national level alone could have led to distortions of the EU internal market.

- *Subsidiarity*

The authorisation of medicinal products, including orphan medicines, is fully harmonised at EU level. Thus Member States could not, and cannot, introduce specific provisions at national level in this field.

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336 A 'comparator analysis' involves comparing the results achieved by the Orphan Regulation with those that might realistically have been expected without it. For more details, see Sections 2.2. and 7.3. of the Orphan study report (2019).

337 Council recommendation on an action in the field of rare diseases (2009/C 151/ 22) June 2009, https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF
Implementation report on the Commission Communication on Rare Diseases: Europe's challenges [COM(2008) 679 final] and Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02), COM (2014) 548; https://ec.europa.eu/health/sites/health/files/rare_diseases/docs/2014_rarediseases_implementationreport_en.pdf

339 http://www.europlanproject.eu/NationalPlans?idMap=1

340 Section 10.1 of the Orphan report study (2019).

Experience in the US and Japan had shown that a key element in an effective policy of supporting R&D for orphan medicines was the creation of an official system of recognition and granting exclusive rights and incentives for a specific period.[341]

The Orphan Regulation addressed the issue of small populations and market fragmentation directly by creating economies of scale to an extent that would not have been possible through individual national policy initiatives. The market for individual orphan medicines was and is too small even in the larger EU Member States, so any national initiative would have needed to provide substantial incentives for firms to change their investment behaviour.

The Orphan Regulation itself does not prevent Member States from offering additional types of incentives, such as tax rebates or prizes for successfully developed products in chosen areas. These instruments can be helpful, and are part of the measures offered under the regulatory frameworks for orphan medicines in the US and Japan[342] and in some Member States.[343]

Nevertheless, it was found that few EU countries offered specific financial incentives for developers of orphan medicines. Particularly for smaller Member States, it was unlikely that these incentives would have made a clear difference to the pipeline for orphan medicines.[344] [345] [346]

The Regulation appears to have respected Member States' exclusive competences, for example in the fields of administration of health services and pricing and reimbursement, as well as in setting taxes and tax incentives for companies. In addition, the provision of healthcare, including prescription of medicines, is the responsibility of Member States. Such national measures have had a major impact on the current accessibility of orphan medicines, as described in the effectiveness section.

- Proportionality

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341 See Communication/Explanatory Memorandum about Draft Proposal (introductory text and second recital on page 12); the success of the US orphan system had encouraged other countries to follow (p. 2 of the same document).

342 At the time, for instance, all designated orphan products in the US were eligible for a federal tax credit equal to 50% of the spending on clinical research (see p. 2 of the Communication/Explanatory Memorandum about Draft Proposal).

343 Belgium and France, for instance.

344 Recital 3 on page 12 of the Communication/Explanatory Memorandum.

345 Section 10.2 of the Orphan study report (2019).

346 EU added value was also recognised in the outcomes of the targeted survey. A majority of academic researchers and experts who participated in the survey agreed with a statement that, at the time when the EU Orphan Regulation was introduced, there was a clear need for concerted EU action beyond the efforts of individual Member States. Representatives of patient and consumer organisations also agreed with this statement (Section 10.2 of Orphan study report (2019).

The Orphan Regulation can be seen as a proportionate[347] response to what is a major challenge for all EU Member States, with more than 6000 orphan diseases affecting 35 million European citizens, many of them children.

As mentioned previously,[348] the Orphan Regulation leaves scope for individual Member States to continue playing their part in promoting the development of orphan medicines. Member States maintain the freedom to invest national funds in rare disease research.

Thanks to the Regulation, a European orphan decision-making system was created, without which the EU might have had to rely on products coming from other markets, such as the US or Japan. This could have adversely affected both the number of orphan products and their timely availability to EU patients.

EU legislation also catalysed national initiatives in the fields of rare diseases and orphan medicines. Individual initiatives by Member States in these fields could have led to distortions of the EU internal market.

**Paediatric Regulation**

- *Subsidiarity*

As with the Orphan Regulation, Member States could not and cannot introduce specific provisions at national level concerning the authorisation of medicines for children, as this area is fully harmonised at EU level.

The impact assessment conducted in 2004[349] showed that certain Member States had attempted to boost the authorisation of paediatric medicines by encouraging industry to conduct research in children and, where data on use of a medicine in children already existed, to submit applications for marketing authorisations. Such actions by Member States were largely unsuccessful, as they did not result in any increase in the number of paediatric medicinal products or authorised paediatric indications.[350] That was why an intervention at EU level was considered necessary.

The value of the EU legislative intervention can also be assessed by comparing regions that have legislation on paediatric medicines with regions that lack such legislation. The number of new paediatric medicines authorised between 2007 and 2015 in the EU and the US, which have similar paediatric legislation, is twice the number of new paediatric medicines authorised in Canada (which has a voluntary scheme), and is six times higher than in Japan (which has no comparable legislation).[351] These figures suggest that a specific

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347 Proportionality means that, to achieve its aims, the EU will take only the action it needs to and no more (see Article 5 of the Treaty on European Union).

348 Chapter 2.2.2 of this SWD.

349 https://ec.europa.eu/smart-regulation/impact/ia_carried_out/docs/ia_2004/sec_2004_1144_en.pdf

350 Extended impact assessment on medicinal products for paediatric use.

351 Agency's 10 years report, section 1.7

EU legal framework for paediatric medicinal products was necessary to boost the development of medicines for children.

**Table 9: New paediatric medicines authorised in 2007-2015.**

| Region | EU* | US | Japan | Canada |
|---|---|---|---|---|
| New paediatric medicines | 80 | 76 | 12 | 38 |
| New paediatric indications | 141 | 173 | 38 | 107 |
| **Total** | **221** | **249** | **50** | **145** |

Note: The data provided by other regions included medicines that are not subject to the obligations of the Paediatric Regulation. For the purpose of this analysis, these medicines (generics, hybrid medicines, biosimilars, etc.) were excluded.

*EU data include centrally authorised products and national/DCP/MRP products.

The Regulation appears to respect Member States' exclusive competences. Member States remain responsible for fixing pricing and reimbursement decisions, as well as for setting taxes and tax incentives for companies. Such national measures have a major impact in determining the current accessibility of paediatric medicines on the market.

Moreover, healthcare provision, including prescription of medicines, is the responsibility of Member States. Complementary actions taken by Member States include reviewing clinical trials and data for paediatric medicines, adopting national legislation to reduce off-label use, providing financial support to research networks that focus on developing paediatric medicines, encouraging internal cooperation between networks and connecting existing networks, and creating research infrastructure for studies in children.[352] [353]

- *Proportionality*

The Paediatric Regulation can also be viewed as a proportionate[354] response to the lack of appropriately tested and authorised medicines for children. At the same time, it allows scope for individual Member States to continue to play their part in promoting the development of paediatric medicines. Member States maintain the freedom to invest national funds in paediatric research.

It can therefore be concluded that the Paediatric Regulation has helped set a positive trend in developing new medicines for children, similar to what has happened in the US from the 1990s on after the introduction of a comparable legislative framework.

[352] Draft European Parliament and Council Regulation (EC) on medicinal products for paediatric use – DG Enterprise: Extended Impact Assessment (page 14); Final Report of the Study on the economic impact of the Paediatric Regulation, including its rewards and incentives (December 2016); Section 4.4.

[353] A list of medicine-related incentives and benefits provided by Member States can be found in Section 4.4. (Table 22) of the Final Report of the Study on the economic impact of the Paediatric Regulation, including its rewards and incentives (December 2016).

[354] Proportionality means that, to achieve its aims, the EU will take only the action it needs to and no more (see Article 5 of the Treaty on European Union).

## 6. CONCLUSIONS

New, innovative medicines are essential for providing new opportunities to treat or prevent diseases. Over more than 50 years, EU pharmaceutical legislation has established a framework that encourages the development of such medicines, while also ensuring high standards of quality and safety and enabling the internal market to function smoothly. However, efforts to encourage R&D in the pharmaceutical field may not necessarily have focused on the areas of highest unmet need; rather, it but may have followed scientific leads and market opportunities. Certain therapeutic areas are better served than others. This problem has long been acknowledged for conditions with small target populations, such as rare diseases or specific patient groups, such as children. More recently, it has also been discussed in relation to areas such as antibiotics.

Efforts made through funding research programmes did not succeed in addressing this issue convincingly. That was why additional legislative tools were considered necessary to support the development of medicines to treat rare diseases and for use in children and to promote greater patient access to such treatments.

The EU Orphan and Paediatric Regulations were introduced in 2000 and 2007 respectively. The Regulations provide a set of incentives for developers of orphan medicines and regulatory rewards accompanied by obligations for paediatric medicines. They are designed to address issues underpinning market failures in these areas.

This evaluation has assessed to what extent these two Regulations they have proven effective, efficient and relevant and bearing EU added value. It has compared the current situation with the situation in Europe before the application of the two Regulations and analysed how they have performed in comparison with the expected outcomes, taking the impact of external factors into account. The internal coherence of the actions of the two regulations as well as their interaction with other policies has also been assessed.

*The Orphan Regulation*

Since the adoption of the Regulation in 2000, 142 orphan medicines have been authorised, of which 131 have remained on the market. The number of marketing authorisations for orphan medicines has not only increased over time, but actually grown substantially faster than for non-orphan medicines. It cannot be claimed that all these 142 products were developed thanks solely to the Regulation. However, it is estimated that between 18 and 24 orphan medicines are direct results of this legislation. Moreover, access has been accelerated. All orphan medicines were available on average nine months earlier and to more people across the EU than would have been the case without the legislation.

Of the 142 authorised orphan medicines, 40 (28%) targeted diseases for which there were no alternative treatment options. The 142 authorised products have helped up to 6.3 million European patients out of roughly 35 million patients in the EU suffering from rare diseases.

This is major progress in comparison to 2000, when only a limited number of medicines for specific rare diseases were on the market (and only in some Member States).

The legislation has helped through incentives to redirect investment into neglected areas and to transform therapeutic discoveries into therapies for some patients, but there is a long way to go to meet the needs of all EU patients with rare diseases. Around 95% of rare diseases have no treatment option yet (the same is true in the US). Moreover, legislation cannot replace the need for scientific leads or breakthroughs in research in the first place.

The available figures in efficiency analysis suggest that the market for orphan medicines has become more commercially attractive than it was before 2000. The Regulation introduced a designation process which identifies the pipeline of orphan medicines and, with the prospect of market exclusivity, enables new companies to attract venture capital. Between 2000 and 2017, 1956 medicines under development were granted an orphan designation, covering a large spectrum of therapeutic areas, with anti-cancer treatments accounting for around a third of all designations and authorised products so far. This number indicates a clear positive impact.

However, the transformation from concept (i.e. orphan designation) to authorised orphan medicine remains slow, even bearing in mind that medicines have long development cycles of as many as 10 to 15 years. In this regard, the EU is still lagging behind the US and Japan. In addition, the US has authorised 351 orphan medicines over the last 10 years. Differences between the US and EU may be explained to some extent by the EU's two-stage process, in which orphan designations must be confirmed at the time of marketing authorisation (as opposed to the US's one-off designation). Japan's high approval ratio is consistent with the approach of designating only products with a strong chance of approval.

The Orphan Regulation uses a prevalence threshold (the condition must affect no more than 5 in 10,000 patients in the EEA) as an important criterion for products eligible for support under the Regulation. The evaluation results raise the issue of whether the current prevalence criterion (on its own) is still an appropriate way to define a rare disease, whether a different method for calculating prevalence is needed, or whether a different criterion should be applied. Advances in science, such as personalised medicine approaches and the use of biomarkers, already allow to better target treatments to responder patients. The concept of personalised medicine could add another layer complexity to the current regulatory framework. While such developments may hold great potential for optimal tailoring of treatments to diseases, they should not lead to unnecessary multiplication of rare diseases out of common diseases, neither of exclusivity periods.

The Orphan Regulation uses several incentives to make a previous neglected area more attractive to developers of orphan medicines. However, these incentives come at a cost. The costs to the Member States' health systems for reimbursing orphan medicines between

2000 and 2017 totalled about €20-25 billion; in addition to the EU and national public funding invested in research.

On the other hand, thanks to orphan medicines, patients gained 210,000 to 440,000 quality-adjusted life years, which constitutes a substantial improvement in the quality of life of patients with rare diseases in the EU. Furthermore, as the costs and benefits are based on an assessment of the 2000-2017 period, it seems quite likely that lower costs and/or higher availability of treatments for patients will apply in the longer term, as more generics and biosimilars will enter the market once existing products' orphan status expires.

The evaluation gives a nuanced picture of the effectiveness of the incentives provided by the Regulation. Developers of orphan medicines, particularly SMEs, have benefited from scientific advice that seems to have improved the possible success rate of a development. The overall share of SMEs has risen so much that they now account for half of requests for orphan designation. However, SMEs may not necessarily bring orphan medicines to the market themselves, as promising medicines are often acquired by larger pharmaceutical companies at a late stage of development.

One of the shortcomings that has been identified is that research institutes and academia cannot benefit from the fee waiver for which the Regulation provides, as it is reserved for SMEs.

As regards the Regulation's design, market exclusivity is the main incentive it provides. While the evaluation provides no evidence that might cast doubt on the market exclusivity concept as such, it exemplifies the weaknesses of a one-size-fits-all incentive.

The findings of the evaluation suggest that for the 73% of orphan medicines the market exclusivity reward has helped to increase profitability for these products, without overcompensating the sponsor. However, for the 14% of orphan medicines, the 10-year market exclusivity may have led to overcompensation. Hence the 10-year exclusivity is thus not fully justified for certain orphan medicines. These are often well-established use products, or medicines authorised for multiple orphan conditions.

Low turnovers do not necessarily signify an 'insufficient' return on investment for orphan medicines, as this depends on the specific situation: it is important to take account of development costs and whether there is any generic competition after the expiry of any protection for a given product. Without any precise data on development costs, it was difficult to estimate what would constitute an appropriate reward for the reduced return on investment of an orphan medicine. Nor is it easy to estimate the level of return of investment above which no reward is needed.

The real effect of market exclusivity was calculated to be an additional protection period averaging 3.4 years (in addition to the protection provided by patents/SPCs). The corresponding value of this reward was estimated at 30% of revenues from sales of orphan

medicines. The cost-benefit analysis for the pharmaceutical industry due to the Regulation has been positive.

Generic competition, according to the evaluation study, has only been observed for very few products to date. As market protection incentives will only expire in the coming years for several authorised orphan medicines, it seems likely that there will be increased generic entry from that moment. For orphan medicines, however, the literature suggests a slower price fall upon generic entry in comparison to other medicines. Among other factors, this may be because an *application* for a generic of an can be submitted i.e. only on the day the exclusivity period of the orphan medicine expires.

While the Regulation includes a mechanism to reduce the exclusivity period if a product is deemed to be profitable, the conditions under which the market exclusivity can be reduced to six years ex post are difficult to apply and rarely used. This finding goes hand-in-hand with the fact that only one application has been received under the 'insufficient return on investment' criterion, and that was subsequently withdrawn. This has shown that it is hard to estimate future investments and the returns on them in advance, before the therapeutic indications for which the product may be used have been established, and before the price at which it is to be sold is clear.

In recent years, it has been suggested that the 'insufficient return on investment criterion' could be used by developers in the field of novel antimicrobials. However, so far it has failed to attract companies, despite the unmet need and the clear market failure in this area.

The Regulation's potential inefficiencies and undesirable consequences were identified in certain cases. There are 22 orphan products authorised for two or more orphan indications, each referring to distinct orphan conditions, which are entitled to multiple periods of market exclusivity ('indication stacking'). Although it is desirable to broaden the therapeutic areas for which an orphan medicine can be used and this should be encouraged to serve patients in need. However, it is often unclear whether the additional market exclusivity period was needed to recover the additional costs of R&D. Additional orphan indications have been also identified as a barrier to developing generic orphan medicines. However, the overall 'inefficiency' is limited as the number of products authorised for multiple orphan indications in the EU is relatively small, and in most cases there is a very big overlap in the periods of market exclusivity for each indication. Finally, indication stacking should be seen in the light of advances in personalised medicine.

Medicines that were n well-established use as a magistral or officinal formula before their authorisation as orphan medicines, or which are repurposed established medicines, account for 19% of orphan medicinesin the EU. This is a lower figure than in the US. However, recent cases in which producers substantially increased the price of a newly-authorised orphan medicine that was already available to patients as a magistral or officinal formula, at a much lower price, have raised questions about this authorisation route. These price

increases seem to bear no relation to actual R&D costs.. Although price setting lies beyond the remit of the orphan Regulation, additional market exclusivity seems to be the main factor influencing monopolistic price setting in these cases. Consideration should therefore be given to the possibility of the Regulation's providing differentiated incentives, depending on the type of application for marketing authorisation or the level of investment in R&D.

There may be room for simplification and streamlining of internal processes including different scientific committees within the European Medicines Agency to avoid the risk of inconsistencies and delays in some cases. Furthermore, some procedures create additional administrative burdens and it should be considered if they are still necessary and proportionate (e.g. the obligation for sponsors to submit an annual report on the orphan designation to the Agency).

The instruments for which the legislation provides have been supported by a variety of EU initiatives and programmes, such as collaborative research and innovation projects, all aiming to boost the development of treatments for rare diseases. In addition, Member States have funded national programmes to support patient care and research into rare diseases. Despite this remarkable financial effort, the information available does not allow a direct link to be made between the publicly funded research projects on rare diseases and the orphan medicines actually developed. The reason for this is that the Regulation and the specific research programmes lack monitoring arrangements.

It is worth pointing out here that the Regulation is only one element in a set of measures designed to improve the situation of patients with rare diseases. The timely diagnosis of a rare disease or the availability of expert centres in the EU, which are now supported by the European Reference Networks, are other examples. Although important, the Orphan Regulation is only one piece in this puzzle.

Finally, the tools provide by the Regulation to ensure that patients suffering from rare conditions have the same quality of treatment as any other patient have only proven partially effective. While the *availability* of orphan medicines has increased under the Regulation, their *accessibility* varies considerably across Member States, mainly owing to factors beyond the Regulation (such as strategic launch decisions made by marketing authorisation holders, national pricing policies and the characteristic of reimbursement systems). The Regulation does not impose any obligation to marketing authorisation holders to market an authorised orphan medicine in all Member States. Nor does it contain any provisions on such matters as transparency of R&D costs or return on investment, to facilitate downstream decisions that would influence the affordability and accessibility of orphan medicines.

*The Paediatric Regulation*

As regards the Paediatric Regulation, the main innovation to improve the landscape was the introduction of a legal obligation for all new medicines under development.

This has resulted in an increase of almost 50% in clinical trials including children and in over 1000 paediatric investigation plans (PIPs) agreed. While most PIPs are still ongoing, given the long development time of medicinal products, the number of PIPs completed is gradually increasing, and 60% of all PIPs have been completed in the last three years.

The number of paediatric products authorised has also increased after the adoption of the Regulation. By 2016, 101 paediatric medicines and 99 new paediatric indications had been centrally authorised. In the same period, 10 new paediatric medicines received a national authorisation and 57 new paediatric indications were added to nationally authorised products.

In addition, the submission and analysis of clinical data already available before the Regulation took effect have enabled information on use in children to be added to almost 200 medicines. This means that these medicines can now be used more safely to benefit children.

These results are consistent with the impact assessment, which predicted that it would take 10 to 15 years for all patent-protected medicines (unless specifically exempted) to be specifically tested for children, and up to 20 years for most medicines to be authorised for paediatric use.

In contrast to these positive results, the evaluation also found that new paediatric products such as orphan drugs are not being developed in the therapeutic areas where needs are greatest. The Regulation has no effective instrument for channelling R&D into specific therapeutic areas. Development has been boosted mainly in areas where adult development was already planned. It thus looks as if the Regulation works best in areas where the needs of adult and paediatric patients overlap. However, major therapeutic advances have mostly failed to materialise for diseases that are rare and/or unique to children, and which often receive equal amounts of support under the orphan legislation. The existing design of the obligations laid down in the legislation may not be up to the task of capturing all adult developments that could potentially benefit children. For example, medicines are increasingly studied on the basis of their mechanism of action. The mechanism of action of a product developed to treat an ‘adult-only’ disease could also be helpful in treating a different disease in children. However, the Regulation exempts products for adult-only diseases from the obligation of designing a PIP. Another example concerns innovative clinical trial design, which may face difficulties with fitting in with the way PIPs are currently designed and agreed.

Moreover, the existing design of the rewards may not be such as to support the prioritisation of product development in areas of specifically paediatric need. This is true of the main reward the Regulation offers: the possibility of obtaining a six-month extension of the supplementary protection certificate (SPC) to offset the cost of conducting the mandatory clinical studies in children. This reward has not proven effective in encouraging industry to develop medicines in line with children's most pressing needs, where these differ from the needs of adults. Economically speaking, it actually brings far greater benefits for products with larger sales volumes. Most such products are medicines developed for use in adults as well as children.

The other major rewards provided by the Regulation, the additional two years of market exclusivity (the 'orphan reward') and the paediatric use marketing authorisation, PUMA, have rarely been used. They have thus done little to boost development in areas of unmet paediatric needs. The orphan reward, which cannot be granted in addition to the six-month extension of the SPC, is considered less valuable by developers than the SPC extension. Consequently, developers prefer to seek an SPC extension whenever possible.

The PUMA scheme, designed to channel EU research funds into boosting the development of new paediatric indications in off-patent medicines, has yielded disappointing results so far. However, about 20 PUMA-related PIPs are currently under way, so outcomes may improve in the next few years. Factors beyond the Regulation are the main reasons for the PUMA scheme's failure to yield more than a limited number of products. One example is the difficulty of obtaining higher prices than those applicable to the existing product, to cover the cost of new clinical research. Another is the difficulty encountered in conducting paediatric clinical trials of old products that are already available on the market and often widely used off-label. This outcome did not come as a surprise; the impact assessment had already predicted it as a possible scenario.

The Regulation includes some instruments to ensure that a paediatric medicine is placed on all EU markets once its PIP is completed and it has been authorised. Yet accessibility of paediatric medicines on EU markets can still be problematic. Their launch in the various EU markets is closely linked to the launch of the adult equivalent. This results in what are known as 'staggered roll-outs'.

In economic terms, the cost-benefit analysis conducted reveals a balance that is positive for both industry and society if one weighs up all the Regulation's impacts, both direct and indirect. This shows that combining obligations and rewards is an appropriate way to boost the development of children's medicines. However, the use of rewards was limited to 55% of the potentially eligible PIPs completed. At the same time, the SPC extension resulted in over-compensation in some cases and under-compensation in others. These facts indicate that the current system has certain limitations.

There have been comments from industry that the SPC system, regulated by a separate EU legislative act, is complex. Companies have to apply independently for SPCs (and for extensions) to patent offices in each Member State, which grant them independently. The SPC legislation is currently undergoing evaluation. While any modernisation or recalibration may address some of the inefficiencies identified, it could also directly affect the functioning of the paediatric reward system and thereby the Regulation itself. This shows the risks of using an 'external' legal instrument to provide the main reward available under the Regulation.

The legislation itself is perceived as burdensome by industry because it requires companies to establish the paediatric research plan – including the design of the paediatric trials – with the Agency at an early stage of development. At those early stages, however, overall product development may be subject to considerable change, requiring changes to the PIP as a result. This means the companies concerned have to submit requests for modifications to the Agency. This is particularly problematic in the case of an innovative trial design, where development plans are often shaped by the results obtained in previous phases of clinical development. Developers also see the national authorisation of paediatric trials as potentially burdensome, since it may in certain cases contradict what has already been agreed on in a PIP.

These aspects can be expected to improve with the application of the new Regulation on clinical trials, which will better harmonise the conduct of multinational trials and the implementation of the ongoing joint Agency-Commission paediatric action plan, which explores possible ways to improve the PIP procedure.

*Outlook*

When the Regulations were designed, the main priority was to increase the number of products for patients with rare and paediatric diseases in the EU. The Regulations met these objectives. However, expectations have developed further. It is recognised that the marketing authorisation stage is an interim step which does not necessarily mean that a given product is available across the EU, let alone that it is affordable for national health systems. Moreover, even within the small area of orphan and paediatric diseases, needs differ or change over time. Clustering of products is observable in some areas, while in others R&D is wholly absent, leaving high unmet needs. The Regulations have no tools to boost development in specific therapeutic areas of orphan and paediatric medicines. Scientific leads, market forces and expectations regarding revenues continue to exercise a strong influence on investment decisions.

From the outset, the two Regulations were never intended to be isolated measures to address the challenges identified. They were added to existing instruments, such as research funding and other policy tools, which could not on their own fully compensate for companies' lack of interest in investing in this area.

Accordingly, this means that the effects of the Paediatric Regulation cannot be viewed in isolation. Although it is an enabler, its objectives need to be aligned with *other* policies in order to create a seamless ecosystem from R&D to marketing. Any future adaptations would need to take all stages of public intervention into account. They would also need to take account of where public intervention is most effective and ensure that different interventions complement one another. Such an approach is necessary to prevent market-driven considerations from dominating this priority area.

Publicly funded research is important in this regard. However, not enough information was available to show whether public funding for research programmes had produced new orphan medicines for unmet medical needs, let alone whether they were available and readily accessible to patients across the EU.

While the two Regulations had appropriate objectives in terms of tackling market failure, the instruments chosen have had some unintended effects and created inefficiencies which need to be corrected. For example, orphan designations are sometimes granted on the basis of the prevalence criterion to products that have high returns on investment.

Moreover, some scientific developments could challenge established concepts used in both Regulations. Current legal definitions, used in both instruments, are directly linked to the concept of a disease and, for orphan medicines, to the prevalence of the condition. These legal provisions require amendment to ensure that the Regulations accommodate new scientific developments.

Finally, new issues such as unequal access and affordability create tensions and call for action. However, the Regulations can only go so far in addressing such issues, which are largely dependent on *external* factors.

Any future response to the shortcomings and future challenges identified in this evaluation should strike a balance between incentives for innovation on the one hand, and availability and patient access (for orphan and paediatric patients) on the other. These aspects are closely linked with the key objectives of the Pharmaceutical Strategy for Europe, of which orphan and paediatric legislation is part. The purpose of the Strategy is to create a future-proof regulatory framework through a wide-ranging examination of the pharmaceutical sector. Any changes to the orphan and paediatric framework will need to demonstrate that it contributes to these goals. Such changes should encourage investment in research and technologies that will actually reach patients and meet their therapeutic needs, while addressing market failures.