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PART 1/2

COMMISSION STAFF WORKING DOCUMENT

IMPACT ASSESSMENT REPORT

Accompanying the documents

Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC

Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

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{SWD(2023) 191 final} - {SWD(2023) 193 final}

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.
Antibacterial/antibiotic	Any substance with a direct action on bacteria that is used for treatment or prevention of infections or infectious diseases.
Antimicrobial	Any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoals.
Antimicrobial resistance (AMR)	The ability of micro-organisms to survive or to grow in the presence of a concentration of an antimicrobial agent which is usually sufficient to inhibit or kill micro-organisms of the same species.
API	Active Pharmaceutical Ingredient.
ATC	Anatomical Therapeutic Chemical code.
Conditional marketing authorisation	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.
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 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 EU.
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 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, by the 2004 revision.
EEA	The European Economic Area includes all EU Member States and also Iceland, Liechtenstein and Norway.
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 the EU.
ERA	Environmental Risk Assessment
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).
Evergreening	’Evergreening’ strategies extend the effective patent period and thus allow drug companies to maintain a market share after their drug patents expire by introducing “follow-on drugs” – those with slight changes made to them after expired patents allow generic competitors to enter the market.
FDA	United States Food and Drug Administration.
GDP	Good Distribution Practices.
GDPR	General Data Protection Regulation.
GMP	Good Manufacturing Practices.
GMO	Genetically Modified Organism.
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 of its reference medicine.
HTA	Health Technology Assessment is a multidisciplinary process that summarises information about the medical, patient and social aspects and the economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased and robust manner.
HUMN	High Unmet Medical Need
IA	An impact assessment identifies and describes the problems 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.
ICER	An incremental cost-effectiveness ratio 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 analytical services organisation that collects data including global pharmaceutical sales data.
Killer acquisitions	'Killer acquisitions' is used as shorthand for: 'acquisitions' (in a wide economic sense) of innovative competitors which have as their object or effect the discontinuation of overlapping R&D projects to the detriment of innovation competition and ultimately consumers. Cunningham, C., Ederer, F. and Ma, S. (2021), "Killer acquisitions", Journal of Political Economy, Vol. 129, No. 3, pp. 649–702. 2
MA	A marketing authorisation is the mandatory approval process before a medicine enters the market of one, several or all EU 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 EU.
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 and applications for those medicines cannot be validated. 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.
MDGs	The United Nations Millennium Development Goals are 8 goals that UN Member States have agreed to try to achieve by the year 2015 to reduce extreme poverty. The MDGs have been superseded by the United Nations Sustainable Development Goals.
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 necessary to fully picture and illustrate the dynamics at stake. See also: The Megatrends Hub | Knowledge for policy (europa.eu)
MRP	The mutual recognition procedure (MRP) is a procedure through which an authorisation of a medicine in one EU Member State is recognised by another Member State.
MS	Member States 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 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.
Parallel import	Parallel import/trade is based on the principle of free movement of goods in the internal market (TFEU Articles 34 and 36). This trade is known as "parallel" to the extent that it takes place outside and – in most cases – in parallel with the distribution network that the manufacturers or original suppliers have established for their products.
Payer	An entity responsible for financing or reimbursing healthcare.

PDCO	The Paediatric Committee is EMA scientific committee responsible for activities associated with medicines for children. It supports the development of such medicines in the EU 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 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 scheme has been launched by the European Medicines Agency to enhance support for the development of medicines that target an unmet medical need. Through this voluntary scheme the 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 to enable accelerated assessment of applications.
QALYs	Quality-adjusted life years 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 EU considers diseases to be rare when they affect no more than 5 per 10,000 people in the EU.
Repurposed medicines	Medicines repurposing identifies new uses for licensed medicines that are outside of the scope of the originally intended use for the medicine. This typically involves taking an existing medicine that already has a marketing authorisation or licence for human use for a

	particular condition, and then using it to treat another condition. Alternatively, a repurposed medicine may be used in a different dose, or form, than its original licence (for example an inhaled product, rather than a tablet).
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.
Repeat use procedure (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 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.
SWD	Staff working documents 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 - see Annex 6 for possible criteria for unmet medical need.

1 INTRODUCTION: POLITICAL AND LEGAL CONTEXT

This impact assessment covers Directive 2001/83/EC[1] and Regulation (EC) No 726/2004[2] ("general pharmaceutical legislation"). 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 is complemented by the *specialised* legislation for medicines for rare diseases ('Orphan Regulation')[3], medicines for children ('Paediatric Regulation')[4], currently under revision, and advanced therapy medicines ('ATMP Regulation')[5]. The general legislation applies to these specialised medicines, while the specialised frameworks provide additional measures to address their specific characteristics. In particular, they address market failures by providing specific *incentives* for development of medicines for small number of patients affected by rare diseases and *rewards* for companies that fulfil the *obligation* to screen adult medicines under development for use in children[6]. The ATMP regulation adapts the technical requirements for the authorisation of medicines based on genes, tissues or cells.

The general pharmaceutical legislation governs the granting of marketing authorisations for all 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 took place in 2004 while targeted revisions on post-authorisation monitoring (pharmacovigilance)[7] and on falsified medicines[8] were adopted subsequently. 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. The roles of 'big pharma' and SMEs have changed, with emerging biopharma companies – often SMEs – increasingly driving innovation and development, with these developments taken over by 'big pharma' through acquisitions or licence agreements.[9] Science and technology have evolved at a rapid pace. However, there continues to be unmet medical needs[10], i.e. diseases without or only with suboptimal treatments. Moreover, some patients may not benefit from innovation because medicines may be unaffordable or not launched (i.e. placed on the market) in the Member State concerned. There is

[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] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products
[4] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004
[5] 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
[6] See Annex 6 for further details on the coherence between the two initiatives.
[7] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, OJ L 348, 31.12.2010, p. 74, and Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance, OJ L 299, 27.10.2012, p. 1.
[8] 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 entry into the legal supply chain of falsified medicinal products, OJ L 174, 1.7.2011, p. 74.
[9] See Annex 9 for further description of the pharmaceutical ecosystem.
[10] Possible criteria to define unmet medical need are described in Annex 6.

also a greater awareness of the environmental impact of medicines. More recently, the COVID-19 pandemic has stress tested the framework.

This impact assessment (IA) analyses policy options designed to address shortcomings highlighted in the evaluation[11] of the general pharmaceutical legislation, taking into account the lessons learnt from the COVID-19 pandemic. It was conducted in parallel with the evaluation (a 'back-to-back' exercise).

The revision is part of the implementation of the Pharmaceutical strategy for Europe[12] and aims to:

- Promote innovation, in particular for unmet medical needs, while reducing regulatory burden and the environmental impact of medicines;
- Ensure access to innovative and established medicines for patients, with special attention to enhancing security of supply and addressing risks of shortages, taking into account the challenges of the smaller markets of the EU;
- Create a balanced and competitive system that keeps medicines affordable for health systems while rewarding innovation.

This revision focuses on provisions relevant to achieve its specific objectives; therefore it covers all but provisions concerning advertising, falsified medicines, homeopathic and traditional herbal medicines. The revision of the general pharmaceutical legislation will be presented as a 'package' with the revision of the orphan and paediatric legislation. The ATMP regulation is not revised, but the revision of the general legislation will address some of the issues, e.g. broad application of hospital exemption, innovative or specific manufacturing methods for these products and burdensome procedures, identified[13] through the experience accumulated since the entry into force of the ATMP Regulation and will help translate research into ATMPs available to patients across the EU while maintaining a high level of public health protection.

1.1 Political context

Since the 2004 revision of the general pharmaceutical legislation, certain aspects such as unequal patient access, affordability, shortages, or the environmental impact of medicines have become more prominent and moved up the political agenda. This is evidenced by recent Council conclusions[14] and resolutions of the European Parliament[15] which called for a balanced system of incentives, rewarding innovation while improving access. Member States called for revised mechanisms and incentives for medicines development tailored to the level of unmet medical need, while ensuring patient access and availability of medicines in all Member States. The COVID-19 pandemic has spotlighted some critical issues in the European pharmaceutical policy.

The Pharmaceutical strategy for Europe[16] – adopted in November 2020 – is an important building block of the European Health Union[17] and more than a response to the pandemic. The strategy is a holistic answer to the current challenges of the pharmaceutical policy with 55 legislative and non-

[11] Annex 5.
[12] COM(2020) 761 final.
[13] COM(2014) 188 final.
[14] Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States, OJ C, C/269, 23.07.2016, p. 31. Strengthening the European Health Union: improving accessibility to and availability of medicinal products and medical devices. Council Conclusions on Access to medicines and medical devices for a Stronger and Resilient EU, (2021/C 269 I/02).
[15] European Parliament resolution of 2 March 2017 on EU options for improving access to medicine (2016/2057(INI)) Shortages of medicines, 2020/2071(INI).
[16] COM(2020) 761 final https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en
[17] COM(2020) 724 final, available at https://ec.europa.eu/info/strategy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_en.

legislative actions interacting together to achieve its overall goal of ensuring Europe's supply of safe and affordable medicines and supporting the European pharmaceutical industry's innovation efforts[18]. The revision of the general pharmaceutical legislation and the ongoing revision of the legislation on medicines for children and rare diseases[19] are flagship initiatives of the strategy. Although the revision of the general pharmaceutical legislation is a key element in addressing the objectives of the strategy, its effect needs to be seen with the other actions of the strategy, actions under EU4Health[20] and other relevant EU and national policies.

The **research and development stage** for medicines is supported by Horizon Europe[21] – a key funding programme for EU research and innovation – as well as the Innovative Health Initiative[22], co-funded by Horizon Europe, to promote innovation of medicines, including planned, specific partnerships to address unmet medical need[23] and AMR[24]. The Mission on Cancer[25], together with Europe's Beating Cancer Plan[26] will allow to better support development of cancer treatments. The budget for health research under Horizon Europe amounts to €8.2bn[27]; additional health research is funded by national programmes. In 2016, Member States from which data are available collectively budgeted about €11.3bn for health-related R&D; this figure excludes most tax incentives and funding for higher education and publicly-owned corporations[28]. In the EU, private investment in R&D in medicines and biotechnology has doubled from around €20bn in 2000 to more than €40bn in 2018; in the US, starting from a higher level at €40bn it almost doubled to around €75bn in the same period[29].

The European Health Data Space[30]- under the European strategy for data[31] – will provide a common framework across Member States for access to high-quality real world health data. Use of these will allow progress in research and development of medicines and provide new tools for pharmacovigilance. The revision of the general pharmaceutical legislation will better accommodate **digital tools and the use of health data** fitting the ambitions of 'Shaping Europe's Digital Future'[32]

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[18] mission-letter-stella-kyriakides_en.pdf (europa.eu)

[19] Medicines for children & rare diseases – updated rules, available at https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-rare-diseases-updated-rules_en.

[20] E.g. a joint action to support the cooperation between competent authorities by organising trainings, improving scientific assessment capacities and inspections, and an action to contribute to implement the Pharmaceutical Strategy as it concerns supporting Member States in national pricing and reimbursement policies.

[21] Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe – the Framework Programme for Research and Innovation, laying down its rules for participation and dissemination, and repealing Regulations (EU) No 1290/2013 and (EU) No 1291/2013, OJ L 170, 12.5.2021, p. 1.

[22] 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 L427, 30.11.2021, p. 17.

[23] European Partnership on Rare Diseases will develop a European Clinical Research Network to accelerate clinical trials for rare diseases; support access to data, information resources to translate research results into safe and effective medicines; support the scientific work of the International Rare Disease Research Consortium; and integrate basic, pre-clinical and clinical research. This partnership is planned for the work programme 2023/4.

[24] European Partnership: One Health Anti-Microbial Resistance will contribute to achieving the objectives of the European One Health Action Plan against AMR[24] and the World Health Organization Global Action Plan on AMR[24], by reducing the threat of AMR and contribute to achieving the objectives of the Health Emergency Preparedness and Response Authority (HERA). This partnership is planned for the work programme 2023/4.

[25] EU Mission: Cancer, available at EU Mission: Cancer | European Commission (europa.eu)

[26] COM/2021/44 final.

[27] European Commission, Directorate-General for Research and Innovation, *Horizon Europe, budget: Horizon Europe - the most ambitious EU research & innovation programme ever*, 2021, https://data.europa.eu/doi/10.2777/202859.

[28] OECD, Pharmaceutical Innovation and Access to Medicines, OECD Health Policy Studies, 2018.

[29] Analytical report, indicator RI-8, Annex 10.

[30] COM(2022) 197 final.

[31] COM(2020) 66 final.

[32] COM(2020) 67 final.

and the digital transition. By facilitating access to and use of health data the two initiatives together will support the **competitiveness and innovation capacity** of the EU's medical industry.

In 2021, the Health Emergency Preparedness and Response (HERA) was created in the aftermath of the COVID-19 pandemic to prevent, detect and rapidly respond to health emergencies. While HERA can address medicines shortages related to a health emergency, it will not play a role in addressing the challenges of **systemic shortages** targeted by the revision of the general pharmaceutical legislation.

The European One Health Action Plan against **Antimicrobial Resistance** (AMR)[33] aims to reduce AMR and develop alternative treatments or prevent diseases treated with antimicrobials. The revision of the general pharmaceutical legislation would contribute to the implementation of this action plan, together with the planned Council Recommendation on AMR.

The revision will also address **environmental challenges** together with European Green Deal[34] initiatives such as: the EU Action Plan "Towards a Zero Pollution for Air, Water and Soil"[35], the revision of the Urban Waste Water Treatment Directive[36], the revision of the Industrial Emissions Directive[37] and the revision of the list of surface and groundwater pollutants[38] under the Water Framework Directive[39] to include some medicines in order to protect the environment and the public health. Moreover, the EU Strategic Approach to Pharmaceuticals in the Environment[40] lists measures to address challenges from medicine residues.

Finally, this initiative supports the United Nations' **Sustainable Development Goals** (SDGs)[41] and in particular SGD 3 ('ensure healthy lives and promote well-being for all at all ages'), SDG 9 ('build resilient infrastructure, promote inclusive and sustainable industrialisation and foster innovation') and SDG 10 ('reduced inequalities'). The objectives and proposed measures relating to unmet medical need, affordability and unequal access to medicines across the EU are linked to SDG 3 and SDG 10, while those relating to environmental challenges and addressing inefficiencies of the regulatory system contribute to SDG 9.

1.2 Legal context

Directive 2001/83/EC and Regulation (EU) No 726/2004 form one policy intervention, the 'general pharmaceutical legislation' that regulates the authorisation, manufacturing, distribution and monitoring of medicines. It also provides regulatory protection periods to reward innovative medicines.[42] The legislation is based on cooperation and division of responsibilities between the EU and Member States. It provides for common standards but different pathways for an authorisation at EU and at Member State level.[43] Member States are responsible for the authorisation of manufacturers and wholesale distributors and they conduct inspections of companies.

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[33] A European One Health Action Plan against Antimicrobial Resistance (AMR) (June 2017).
[34] COM (2019) 640 final.
[35] COM/2021/400 final
[36] Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment, OJ L 135, 30.5.1991, p. 40.
[37] 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, and COM(2022) 156 final.
[38] Integrated water management – revised lists of surface and groundwater pollutants (europa.eu).
[39] Directive 2000/60/ EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy, OJ L 327, 22.12.2000
[40] COM(2019) 128 final.
[41] Home - United Nations Sustainable Development
[42] These regulatory protection periods are described in section 6.1 and in the evaluation SWD, section 3.3, Annex 5.
[43] For certain categories of medicines it is a requirement and for others it is an option for companies to apply for a marketing authorisation granted by the European Commission through the centralised procedure. This authorisation is valid in all Member States and based on a scientific assessment performed by the EMA. Medicines may also be authorised through national procedures. The different authorisation procedures are outlined in Annex 7.

Pharmacovigilance is a shared responsibility. The legislation does not affect the Member States' powers regarding the setting of medicine prices or the inclusion of medicines in the scope of national health insurance schemes.

The general pharmaceutical legislation has touchpoints with other legislation. The ongoing revision of the legislation on medicines for rare diseases and medicines for children is coherent with this revision in it aims to address unmet medical needs and improve patient access to medicines; a description of how the initiatives complement each other can be found in Annex 6.

The Clinical Trials Regulation[44], applicable since 2022, allows a more efficient approval of clinical trials in the EU, while the extended EMA mandate, as part of the European Health Union, strengthens the role of the Agency for a coordinated EU-level response to health crises[45] to ensure access to medicines in such crisis. The EMA fees legislation[46] is currently under revision. The fees support EMA and national competent authorities and contribute to the sustainability of the EU regulatory system.

The revision of the EU legislation on blood, tissues and cells (BTC)[47] is relevant as some substances of human origin are starting materials for medicines. Coherence between the two revisions is key to ensure clarity as to which legislation applies to some BTC based therapies.

For **access to medicines**, in addition to the general pharmaceutical legislation, the intellectual property frameworks (patents and SPCs) as well as the HTA Regulation and the 'Transparency' Directive[48] play a role. The Intellectual Property Action Plan[49] under the Industrial Strategy[50] includes the modernisation of the system of supplementary protection certificates (SPC) in the form of a "Unitary SPC" which does not intend to modify the maximum period of a SPC, but may lead to wider coverage of the SPCs; an impact assessment on these changes is under development.[51] SPCs extend patent rights to protect **innovation** and compensate for lengthy clinical trials and marketing authorisation procedures. At the same time, they impact the effect of regulatory protection periods provided by the pharmaceutical legislation and therefore the entry of generic and biosimilar medicines and eventually **patient access to medicines and affordability**. Member States' decisions on pricing and reimbursement of medicines also influence access. The 'Transparency' Directive regulates procedural aspects of the Member States' pricing and reimbursement decisions but do not

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[44] 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.

[45] 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, OJ L 20, 31.1.2022, p. 1.

[46] 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.

[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, 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.

[48] Council Directive 89/105/EEC, of 21 December 1998, relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of the national health insurance systems, OJ L 40, 11.2.89, p. 8.

[49] COM(2020) 760 final.

[50] COM(2021) 350 final.

[51] Medicinal & plant protection products – singles procedure for the granting of SPCs

impact on the level of price. The Health Technology Assessment (HTA) Regulation[52] will engage national HTA bodies in joint clinical assessment to provide evidence-based information on the comparative effectiveness of medicines to help national decisions on pricing and reimbursement. This contributes to improve affordability and access across the EU. Annex 14 further describes the multiplicity of factors having an impact and framing access to affordable medicines.

A description of the pharmaceutical ecosystem and legislative landscape can be found in Annex 9 together with a visual overview of the lifecycle of a medicine in Annex 8.

2 PROBLEM DEFINITION

2.1 What are the problems?

The evaluation of the general pharmaceutical legislation showed that the legislation continues to be relevant for the dual overarching objectives of protection of public health and harmonisation of the internal market for medicines in the EU. The legislation delivered on the objectives of the 2004 revision; albeit not to the same extent for all. The objective to ensure quality, safety and efficacy of medicines was achieved to the largest extent, while patient access to medicines in all Member States was achieved only to a limited extent. As to ensuring the competitive functioning of the internal market and attractiveness in a global context, the legislation has performed to a moderate extent. The evaluation found that the achievements or shortcomings of the 2004 revision vis-a-vis its objectives depend on many external factors outside the remit of the legislation, e.g. R&D activities and international location of R&D clusters, national pricing and reimbursement decisions, business decisions and market size. The pharmaceutical sector and development of medicines are global; research and clinical trials conducted on one continent will support development and authorisation in other continents; likewise the supply chains and manufacturing of medicines are global. International cooperation to harmonise requirements to support authorisation exists, e.g. the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The evaluation identified six shortcomings which are not adequately addressed by the pharmaceutical legislation recognising that they also depend on factors outside its remit:

Medical needs of patients are not sufficiently met

The evaluation showed that the legislation has been less relevant to ensure development of medicines addressing unmet medical needs, including novel antimicrobials. This related to e.g. lack of adequate incentives for innovation by SMEs, academic/industry collaborations. Unmet medical needs with regard to medicines for rare diseases and for children are covered by the parallel revision of the specialised legislations supported by its own impact assessment.[53]

The number of authorised medicines, both innovative and those with well-known active substances (e.g. generic and biosimilar medicines) is constantly on the rise. 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[54]. However, there continue to be diseases with no or only few treatment options, e.g. neurodegenerative or infectious diseases. These unmet medical needs affect millions of EU citizens[55]. In the public consultation[56], all stakeholders found that the

[52] 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.
[53] Cf. Ongoing Impact assessment for Medicines for children and rare diseases: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-rare-diseases-updated-rules_en
[54] Analytical report, indicator RI-9, Annex 10.
[55] The number of people living with dementia in the EU27 is estimated to be 7,853,705 and Alzheimer's disease is the most common form of dementia, Other dementias | Alzheimer Europe (alzheimer-europe.org).
[56] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Evaluation-and-revision-of-the-general-pharmaceutical-legislation/public-consultation_en.

legislation moderately promotes the development of medicines for unmet medical needs, with industry having the most positive view in that regard. While the general pharmaceutical legislation is not alone responsible for the problem of unmet medical needs[57], it can be instrumental in addressing some of the problem drivers within its remit.

AMR - a specific case of unmet medical need

An important area of unmet medical need is drug-resistant infections due to the emergence and spread of pathogens that have acquired new resistance mechanisms leading to AMR. AMR is responsible for an estimated 33 000 deaths per year in the EU and amounts to an estimated €1.5bn every year in healthcare costs and productivity losses[58]. At the same time the pipeline for novel antimicrobials that can fight resistant pathogens is very weak.[59] There is an apparent market failure and the lack of market incentives has led to underinvestment by big pharma companies in new compounds. Annex 15 further describes the market failure in this area.

Unequal access to medicines across the EU

The evaluation showed that the legislation has limited effect and relevance to ensure patient access to medicines. Access also depends on external factors[60] such as strategic decisions by companies whether and when to launch a product in a given Member State and national pricing and reimbursement policies. However, the general pharmaceutical legislation can have an impact on access through its incentives.

The number of authorised medicines in the EU has increased over time: 1 160 centrally authorised medicines (CAPs) were authorised in the period 2005-2020 and more than 17 000 medicines, primarily generic medicines, were authorised through mutual recognition and decentralised procedures in the same period[61]. However, patient access to medicines varies considerably across the EU[62]. The number of EU countries in which CAPs are launched has been steadily decreasing[63]. Substantial differences have been reported in terms of time to entry on the market[64].

Most medicines are – after authorisation – subject to national pricing and reimbursement decisions and, in particular for innovative and costly medicines, also HTA. The evidence requirements for these decisions (on relative/cost effectiveness of new medicines compared to existing treatments) are different than for the authorisation of those medicines, which is based on a positive benefit-risk balance for patients. Evidence required for HTA or pricing and reimbursement decisions are (often) not generated by companies by the time of the authorisation of the medicine and this may delay access. However, the recently adopted HTA Regulation intends to improve the situation, though its effects could not yet been taken into account in the evaluation and the consultations.

Evidence[65] shows that, whilst in Germany 133 out of 152 (i.e. 88%) new medicines authorised between 2016 and 2019 at EU level were accessible to patients, small Member States such as the Baltic Member States or Member States with comparatively low prices or with low GDP, like Romania, had fewer than 50 of these available[66]. The time to patient access is also significantly

[57] External factors (e.g. scientific barriers) are mentioned in the problem drivers for unmet medical need, see section 2.2.
[58] A European One Health Action Plan against Antimicrobial Resistance (AMR) (June 2017).
[59] Of 43 antibiotics in development, 15 were in Phase 1 clinical trials, 13 in Phase 2, 13 in Phase 3, and two have had new drug applications submitted. Historically, about 60% of drugs that enter Phase 3 will be approved.
[60] See Annex 14 on the factors influencing access to affordable medicines
[61] Analytical report, indicator ACC-1, Annex 10.
[62] Technopolis Evaluation study report, figure 10, 2022.
[63] 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
[64] Bergmann et al., 2016, Ferrario (2016). Access to innovative oncology medicines in Europe. Annals of Oncology, 27(2), 353-356. https://doi.org/10.1093/ANNONC/MDV547
[65] Data from European Federation of Pharmaceutical Industries and Associations (EFPIA) and IQVIA.
[66] Newton et al. (2021). *EFPIA Patients W.A.I.T. Indicator 2020 Survey*.

longer for most of these latter countries, e.g. approximately two years or more after marketing authorisation in Romania compared to four months in Germany. Similar observations were made across different subsets of medicines. As a result, patients may not have had access to any appropriate treatment for their disease.

Although access depends, as explained above, on a multiplicity of factors, most respondents in the targeted survey, except industry agree that there is still room for improvement of the EU legislation in terms of access.

Most of the nationally authorised medicines are generic medicines[67]. Generic and biosimilar medicines can be marketed only after the expiry of regulatory and other intellectual property protection periods of the original medicine. They normally drive prices down and improve access. Low volume markets still experience limited access to generics.

Affordability of medicines is a challenge for health systems

Innovative medicines are often costly. Medicine prices vary significantly between Member States[68]. A study showed that list prices were the highest in Germany and the cheapest in many different EU countries but never in those with lower GDP like Bulgaria or Romania[69]. The medicines analysed were unaffordable for many EU health systems. Pharmaceutical budgets also put pressure on health systems. Medicines in hospitals account for over 20-30% of hospital expenditures and are growing[70].

In 2013-2019, the average household out-of-pocket (including regulated co-payments) share of non-hospital medicines is stable, at around 28-30%, but there are big differences between the MS with countries like Germany and France having shares below 20% and Poland and Bulgaria over respectively 60 and 70%.[71] Out-of-pocket payment for medicines is outside of the remit of the pharmaceutical legislation. Other external factors are described in Annex 14.

Against this backdrop, generic and biosimilar entry can be an important factor in terms of competition, to achieve lower prices, broadening patients' access and alleviating healthcare costs[72]. In the EU, the share of generics in total medicines sales revenue modestly increased (from 13% to 16%) between 2002-2020[73]. An analysis shows that the EU is on a similar trend as other comparable markets (Japan and USA)[74]. Nonetheless, inquiries show that originator companies sometimes use various practices (such as "evergreening" or "killer acquisitions" early in the pipeline) to delay or prevent generic/biosimilar entry. These anti-competitive practices can be prosecuted by EU competition authorities. The evaluation confirms that further efforts can be made to fully exploit the savings generated by the generic and biosimilar competition; although measures in this regard are primarily outside the scope of the general pharmaceutical legislation, the revision can improve the conditions for generic and biosimilar authorisation and competition.

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[67] 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.
[68] The desk research suggests for example an almost 11-fold difference between interferone-beta list prices in Germany (€1451.17) and Croatia (€132.77); list prices do not include the confidential rebates (if they exist) or 'price freezes' and may therefore not correspond to the actual price.
[69] Zaprutko T, Kopciuch D, Kus K, et al. Affordability of medicines in the European Union. *PLoS One*. 2017;12(2):e0172753.
[70] European Commission, State of health in the EU: companion report 2019 (ISBN 978-92-76-10194-9)
[71] OECD, Eurostat and World Health Organization (2017), A System of Health Accounts 2011: Revised edition, OECD Publishing, Paris. http://dx.doi.org/10.1787/9789264270985-en).
[72] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective
[73] Evaluation SWD, section 4.1.1.4, Annex 5.
[74] Ibid, footnote 67.

The probability of competition is lower for (a) biosimilars than for generics; (b) products with manufacturing complexity and (c) products with smaller turnover (e.g. for rare diseases).[7576]

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

Shortages of medicines

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[77]. There are a number of root causes. These include: more complex and diversified global supply chains, quality and manufacturing challenges and commercial decisions or unexpected increase in demand. Evidence shows that medicine shortages are placing a significant burden on health systems, health professionals and are ultimately putting patients at risk of sub-optimal care and health systems at risk of higher healthcare costs[78].

Medicine shortages have also 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 EU, depending on the supply chain.

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 that the legislation is the least effective in addressing issues related to security of supply and medicine shortages.

The general pharmaceutical legislation can provide harmonised tools to allow Member States to better handle medicine shortages and thus act as enabler for addressing the problem.

The regulatory system does not sufficiently cater for innovation/unnecessary administrative burden

While the system for authorisation and monitoring of medicines in the EU overall meets the objectives of the general pharmaceutical legislation, rapid scientific and technological developments have resulted in new challenges for the system, which has become more complex over time, as reflected by the expansion of the number of EMA scientific committees and their interactions[79]. New types of medicines (e.g. personalised medicines), approaches and processes, may raise questions about whether they fully fit within the scope of the legislation and can find themselves subject to unintended barriers to innovation, development, production or marketing authorisation. Products combining medicines with technologies regulated under other frameworks (e.g. medical devices, artificial intelligence) or products using new platform technologies[80] face uncertainty about the applicable framework. Likewise, the current framework is not adapted to novel production technologies or methods (e.g. decentralised manufacturing). Borderline issues for ATMPs with the BTC framework, which provides starting materials, were also highlighted in the evaluation.

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[75] SWD(2020) 163 final, p. 58.
[76] Understanding Net Pharmaceutical Expenditure Dynamics in Europe, April 2022, IQVIA.
[77] 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.
[78] 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.
[79] COM(2021) 497 final.
[80] 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.

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 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.

Digital transformation has been changing the health sector. However, there is an overall lack of transparency and interoperability; digital expertise and infrastructure are not sufficiently available across the Member States and the EU regulatory network. All stakeholders agreed that EU telematics systems play an important role in contributing to the efficiency of the system, but also identified room for improvement (like a very complex governance system for EU telematics).

An assessment of the current authorisation system[81] 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[82].

Medicines in the environment

While the positive effect of medicine for treatment of diseases is undisputed, pollution caused by medicines is a well-documented risk to the environment and human health, particularly in relation to antimicrobial resistance. Residues of medicines may enter the environment during their manufacturing, use by patients and disposal, with the largest source being the use[83]. Residues of medicines have been found in surface and ground waters, soils and animal tissues across the EU at concentrations depending on the medicine and the proximity of sources[84]. Traces have also been found in drinking water. Residues of medicines in the environment is a global problem[85]. The evaluation confirmed that the current requirement for an environmental risk assessment (ERA) before marketing authorisation has some weaknesses as regards compliance, content and scope.

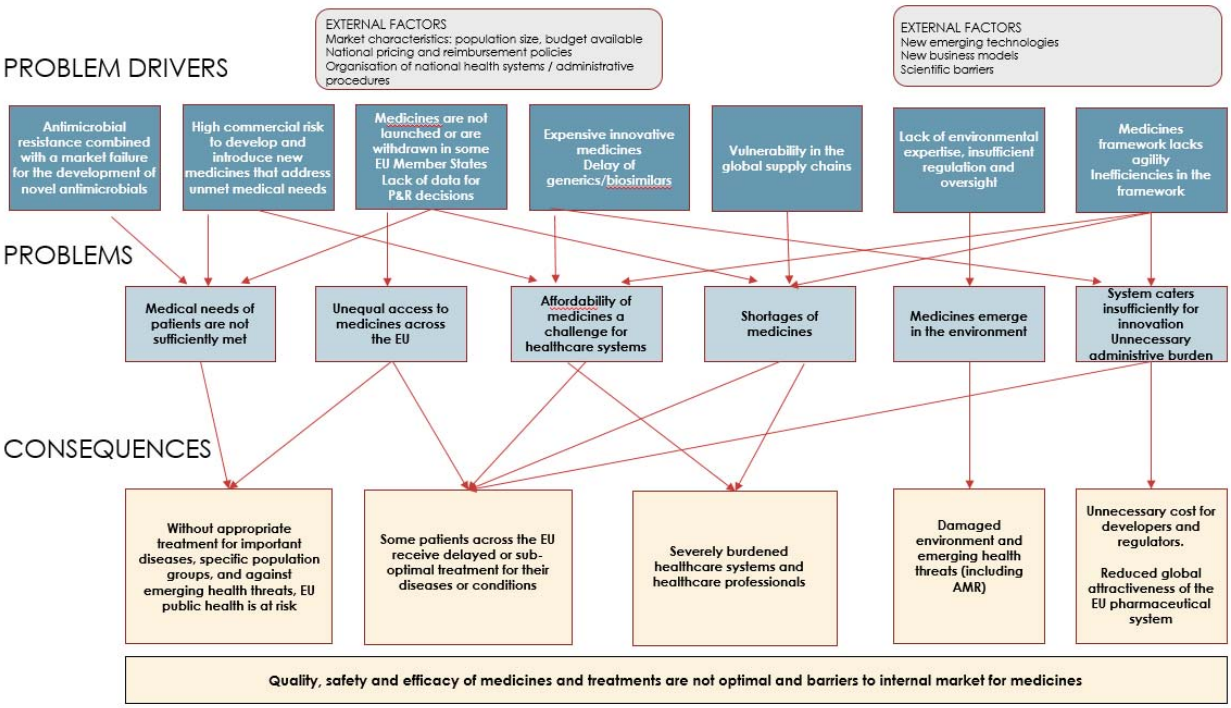
In the targeted consultations, the stakeholders (industry, civil society and public authorities) ranked reducing the environmental impact of medicines among the objectives where the general pharmaceutical legislation had been the least effective. In the public consultation, the stakeholders across the board found that the legislation has performed moderately in 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.

2.2 What are the problem drivers?

Figure 1 provides an overview of the problem drivers and their link with the problems identified.

[81] COM(2021) 497 final.
[82] 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 two fee regulations (Council Regulation (EC) No 297/95 and Regulation (EU) No 658/2014).
[83] COM(2019) 128 final.
[84] Analytical report, indicator E-1, Annex 10.
[85] Idem.

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



The problem drivers that are causing underperformance on the ground are a series of complex, interlinked factors.

Drivers for unmet medical needs

Despite the fast-paced advances in science and technology, scientific barriers prevent the development of medicines to treat or cure some diseases such as Alzheimer's. For unmet needs, there are a series of different drivers, e.g. market failure, complexity of disease pathologies, knowledge gaps in molecular and physiological underpinnings of diseases, high risk R&D. While the EU has a world-leading, research-intensive pharmaceutical industry[86], evidence suggests that R&D costs per new medicine have increased over time with estimates ranging from US$944m to US$2,826m with great variability across therapeutic fields[87]. This is one among the drivers that have increased the commercial risk of developing new medicines for **unmet medical need**.

Big pharma companies tend to disinvest from riskier upstream research and to choose R&D investments that will maximise their future profits through licensing or acquisitions of products that are already in later clinical trial stages with good probability for marketing authorisation, sales and high price.[88] Such business strategies are not always aligned with the public goal of directing efforts towards the greatest unmet medical needs. Furthermore, the pharmaceutical legislation makes no distinction in regulatory incentives granted to highly innovative medicines addressing unmet medical need and those for incremental innovation, such as 'me-too' medicines (similar to existing medicines) without added therapeutic value. This gives less incentive to invest in higher risk development of the former. There is a concentration of investment in areas where there is less

[86] The Pharmaceutical Industry in Figures, Key Data 2021 (EFPIA, 2021).
[87] Simoens, S., & Huys, I. (2021). R&D costs of new medicines: a landscape analysis. *Frontiers in medicine*, *8*, available at https://www.frontiersin.org/articles/10.3389/fmed.2021.760762/full.
[88] EPRS_STU(2021)697197_EN.pdf (europa.eu): European pharmaceutical research and development. Could public infrastructure overcome market failures?

financial risk, e.g. oncology. When companies invest in less risky areas, even incremental innovation can lead to an economically viable or profitable product.

The **growing resistance of pathogens to antimicrobials (AMR)** combined with the weak global pipeline of major new classes of antimicrobials are a special driver for unmet medical need. A growing market failure derives from the fact that the typical cost of surpassing the scientific challenges involved in developing new antimicrobials is very high and at the same time the typical income and profit that can be derived from sales of these products are very limited because healthcare systems want to keep new antimicrobials in reserve or limit their use so as not to fuel the vicious cycle of AMR, by inappropriate use of already authorised antimicrobials.

Drivers for access to medicines

A key **access problem driver** is that authorised **medicines are not launched in all Member States or are subsequently withdrawn**. Currently, companies have the choice where and when to launch centrally authorised medicines, the legislation only requires them to place their product on the market in at least one Member State within three years of its authorisation (the so-called 'sunset clause'). Other than that, companies have a free hand; this creates an unpredictable situation for patients and Member States. With some Member States companies enter into pricing and reimbursement negotiations only very long time after marketing authorisation or not at all. The decision for the company to launch and when depends on different factors for example the size of the patient population, or national pricing and reimbursement policies, and the organisation of health systems. These factors influence whether the company can successfully pass a HTA in that Member State and finally negotiate a price and a reimbursement status for the product.

Access may also differ due to organisational differences in Member States (different medical protocols, access to specific equipment/infrastructure needed for administration, different characteristics of the health systems).

The pharmaceutical legislation has no direct influence on HTA and pricing and reimbursement processes or the organisation of the national health systems. However, the general pharmaceutical legislation and its system of regulatory incentives can be an enabling factor to improved access by incentivising market launch by companies, strengthening the position of national pricing and reimbursement bodies, facilitating collaboration among decision makers along the lifecycle of a medicine and by increasing competition from generics and biosimilars.

For a more detailed analysis on the factors and dynamics behind the market launch, the access chain, HTA, pricing/reimbursement process and on pharmaceutical expenditure please refer to Annex 14.

Withdrawals of medicines disrupt the established access chain (from authorisation to entry into the health system). An available product abruptly or gradually withdrawn from the market (often for commercial reasons) can create **shortages** and leave patients without treatments.

Drivers for affordability of medicines

Pharmaceutical expenditure is largely subsidised by national health systems in order to ensure the adequate provision of medicines to all their respective citizens. New, highly **innovative medicines** may place pressure on public budgets due to their prices. Therefore, 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). Member States follow different **price and reimbursement policies** and the pharmaceutical markets remain very fragmented by country (for a review of pricing policies[89]). The External Reference Pricing (ERP) policy, for which the price set for the same product in one or several countries is used as a benchmark for setting the product's price in a given country, is the most frequently used pricing policy in Europe. As a consequence of

[89] WHO guideline on country pharmaceutical pricing policies, Geneva: World Health Organization; 2020.

differences in prices, the use of ERP and parallel import, and differences in market size, the availability and entry date of medicines strongly differ among Member States.

The prices by country do not depend only on the government regulation (such as price controls and reimbursement decisions) but also on several other factors, such as income per capita, the size of the market, the characteristics of the product (innovative or old, its therapeutic advantages etc.), the patent status, the presence of competitors and research costs incurred (also for unsuccessful development of medicine)[90]. 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 are relevant for the downstream actors and may facilitate their decision-making.

Delay in generic and biosimilar entry is also a driver for expensive innovative medicines.

The general pharmaceutical legislation has only an indirect impact on the affordability of medicines by facilitating competition and early market entry by generic and biosimilar medicines. In a similar way, it streamlines procedures and makes the regulatory framework more efficient thereby lowering costs for authorisation or manufacturing which could have an impact on the price of the medicine.

Drivers for shortages of medicines

Vulnerability in the global supply chains has arisen from global industry consolidation with increased complexity in supply chains, in which many different intermediate suppliers may be connected, and, in particular for generic medicines, from reliance on a few, specialised overseas suppliers that produce at lower prices. In addition, the notification and obligation to ensure appropriate and continued supply, varies across Member States with e.g. 4 months in advance notification of shortages in Italy and at least 6 months in Romania[91].

While Member States 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.

Drivers for medicines into the environment

The **lack of relevant or insufficient regulation and oversight** currently influences the effects medicines use may cause for the environment, while a lack of environmental expertise influences the understanding of the effects on the environment from medicines. The largest source of medicines entering the environment is the use of medicines; due to the chemical and/or metabolic stability of some medicines, as much as 90% of the active substance is excreted or washed off into the environment in its original form[92]. Pharmaceuticals mainly reach the environment through:

- the discharge of effluent from urban waste water (sewage) treatment plants – containing excreted pharmaceuticals as well as unused pharmaceuticals thrown away into sinks and toilets, despite the existence of collection schemes;
- the spreading of animal manure; and
- aquaculture, in which pharmaceuticals are often dispensed with the animal feed.[93]

Another source is the discharge of effluent from manufacturing plants (especially those outside the Union) with potential impacts that may significantly effect on a local scale when manufacturing

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[90] Zaprutko T, Kopciuch D, Kus K, et al. Affordability of medicines in the European Union. *PLoS One*. 2017;12(2):e0172753.
[91] European Commission, Directorate-General for Health and Food Safety, *Future-proofing pharmaceutical legislation: study on medicine shortages: final report (revised)*, 2021, https://data.europa.eu/doi/10.2875/211485.
[92] COM(2019) 128 final.
[93] Idem as 92.

emissions of wastewater are inadequately managed.[94] Environmental legislation, such as the Urban Waste Water Directive – currently under revision – and other environmental legislation and initiatives mentioned in section 1.1, is the main instrument for addressing reduction of medicines residues and hence the environmental impact of the industry; however, not even the best and most expensive current wastewater treatments are 100% effective. The measures in this revision complement environmental legislation.

Drivers for lack of innovation and inflexible regulatory framework

The rapid pace of the scientific and technological development is a driver for – and an external factor to – the problem that the regulatory system does **not sufficiently cater for innovation**. The general pharmaceutical legislation is often prescriptive, and it takes a long time to amend it. Hence, the **medicines framework lacks agility** to respond to rapid developments.

Inefficiencies in the regulatory framework were identified in the evaluation, e.g. redundant requirements like the 5-year renewal of marketing authorisation, leading to unnecessary administrative burden. 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 insufficient pan-European digital infrastructure and legal basis for optimal use of electronic tools for companies or medicine authorities which contributes to a loss of competitiveness. Better use of digitalisation in the framework, e.g. through electronic product information, could help combat shortages, increase access in smaller markets and also support competition, while improving information on medicines.

2.3 How likely is the problem to persist?

If no EU action is taken, the problems described will persist. While more medicines are expected to be authorised (for CAPs this might increase to 40-60 medicines containing new active substances per year[95]), these medicines will not necessarily address unmet medical needs to a greater extent than today. For example, recently approved antibiotics[96] and the clinical pipeline are insufficient to tackle the increasing emergence and spread of antimicrobial resistance[97]. The market failures in this area will not be corrected without interventions on several fronts, including the general pharmaceutical legislation. The persistence of the problems is also confirmed by some of the megatrends identified by the EU Joint Research Centre[98]. The megatrend on shifting health challenges describes demographic changes and environmental challenges that could create new unmet medical needs and public health burdens as demonstrated by the COVID-19 pandemic.

Authorised medicines will continue to be inaccessible at affordable prices in some Member States. The 'access chain' mechanism mentioned above and analysed in Annex 14 is affected by deficiencies that are systemic in nature and some of the 'links' lie outside the remit of this legislation. Nevertheless, the analysis of the policy options in section 6 shows that the revision of the legislation can act as a key enabler for access and can influence affordability. The policy interventions in the legislation shall be complemented by other actions of the pharmaceutical strategy, e.g. best practice exchange between Member States on pricing, payment and procurement.

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[94] Larsson DGJ. 2014 Pollution from drug manufacturing: review and perspectives. *Phil. Trans. R. Soc* ***369****:20130571*.
[95] Described in section 5.1.1.
[96] Since 2015. 11 antibacterials with new active substance have been granted a Union marketing authorisation, though none of these products constituted a new class of antibiotic.
[97] Antimicrobial products in clinical development for priority pathogens (April, 2021), 68 products are in development (41 antibiotics and 27 non-traditional antibacterial agents) see https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antibacterial-products-in-clinical-development-for-priority-pathogens.
[98] The Megatrends Hub | Knowledge for policy (europa.eu)

Since new scientific and technological developments will continue, some problems may exacerbate if the legislation is not future-proof. Current work-arounds which are based on 'creative' interpretation will become bottlenecks, especially for complex products. Borderlines between product categories may be more blurred and determination of applicable legal frameworks and their interaction may become complex, leading to longer development or authorisation processes for innovative medicines and thus a longer time to reach patients. This impacts negatively innovation while some innovative products may remain unregulated with negative effect on public health.

If the efficiency of the regulatory system will not be improved and administrative burden not reduced, e.g. by digitisation, valuable resources might not be available to facilitate the development and the assessment of innovative medicines. Likewise, resources might not be available to invest in the expertise needed to cope with new scientific and technological developments. For the industry, there might be less investment in new medicines and hence fewer new medicines authorised, reduced innovative capacity and competitiveness. The megatrend on accelerating technological change and hyperconnectivity is particularly relevant both in terms of development and innovation of medicines and of digitisation of the regulatory system.

Likewise, the problem of medicine residues in the environment will persist if no EU action is taken with risks to flora, fauna and habitat due to the pharmacological characteristics of the active substances. The megatrend on increasing demographic imbalances with the ageing population in the EU may exacerbate the environmental challenges from medicines as elderly people tend to use more medicines than young people; this could also put further pressure on national health systems.

3 WHY SHOULD THE EU ACT?

3.1 Legal basis

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 a shared competence of the EU and Member States, once the EU adopts harmonised legislation in such an area, Member States can no longer exercise their own competence. This is the case for the general pharmaceutical legislation. Any future legislative proposals, supported by this impact assessment, will be based on Articles 114(1) and 168(4)(c) TFEU. It 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.

As per Article 168(7) of the TFEU, Member States are responsible for the definition of their health policy and for the organisation and delivery of health services. Consequently, coverage and pricing decisions for medicines are outside the scope of the legislation.

3.2 Subsidiarity: Necessity of EU action

Diseases do not know borders. 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, given that the authorisation of medicines is fully harmonised at EU level.

The objectives this revision intends to achieve benefit all Member States. EU action relies also on the single market to achieve a stronger impact as regards access to safe, effective and affordable medicines, as well as the security of supply across the EU. National actions are likely to create disharmonised solutions resulting in fragmentation, and possibly exacerbate some of the problems to be solved, 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[99]. A harmonised approach at EU level also provides greater potential for incentives to support innovation and for concerted action for development of medicines in areas of unmet needs.

The legislation respects Member States' exclusive competence in the provision of health services, including pricing and reimbursement policies and decisions. In this respect, the Pharmaceutical Strategy provides for supporting non-legislative actions such as cooperation mechanisms, e.g. through a group of competent authorities, based on mutual learning and best practice exchange on pricing, payment and procurement policies. These exchanges can be facilitated at EU level.

3.3 Subsidiarity: Added value of EU action

This initiative revises a system with recognised EU added value for the EU patients/citizens, pharmaceutical industry and medicines authorities through e.g. timely authorisation, patient access and continuous supply of innovative and established medicines and strong cooperation[100].

This revision is expected to bring further benefits by addressing unmet medical needs and contributing to reducing the unequal patient access to medicines across the EU. At the same time, simplification and streamlining of processes are expected to reduce administrative burden for companies and authorities and hence improve efficiency and attractiveness of the EU system.

This revision can influence positively the competitive functioning of the market through the review of the incentives and other measures to facilitate early entry on the market of generic and biosimilar medicines and hence improve patient access and affordability.

These benefits and cost-savings can best be achieved by EU action, while recognising that external factors such as national pricing and reimbursement policies and company decisions to launch medicines have great impact on patients' access to medicines. Furthermore, science and technological developments, as well as R&D policies and company investment decisions influence innovation, especially for unmet medical needs.

The measures to support security of supply under this initiative relate to the responsibilities of marketing authorisation holders and supply chain actors like wholesalers. Those actors are already covered by the EU pharmaceutical legislation. However, measures supporting security of supply go beyond legislative measures; many actions do actually take place already at national level and will continue to do so. National and EU levels are not alternatives to each other, but complementary.

In a few instances, the evaluation identified problems with a harmonised implementation of the Directive across Member States[101]. However, these problems relate to vague legal wording of the respective provision rather than the legal instrument used. Moreover, in 2019, a REFIT Platform Opinion[102] considered a suggestion to turn the Directive into a Regulation, though that suggestion did not receive overall support. The opinion showed that many Member States considered the system sufficiently harmonised and would not see a need for a Regulation.

4 OBJECTIVES: WHAT IS TO BE ACHIEVED?

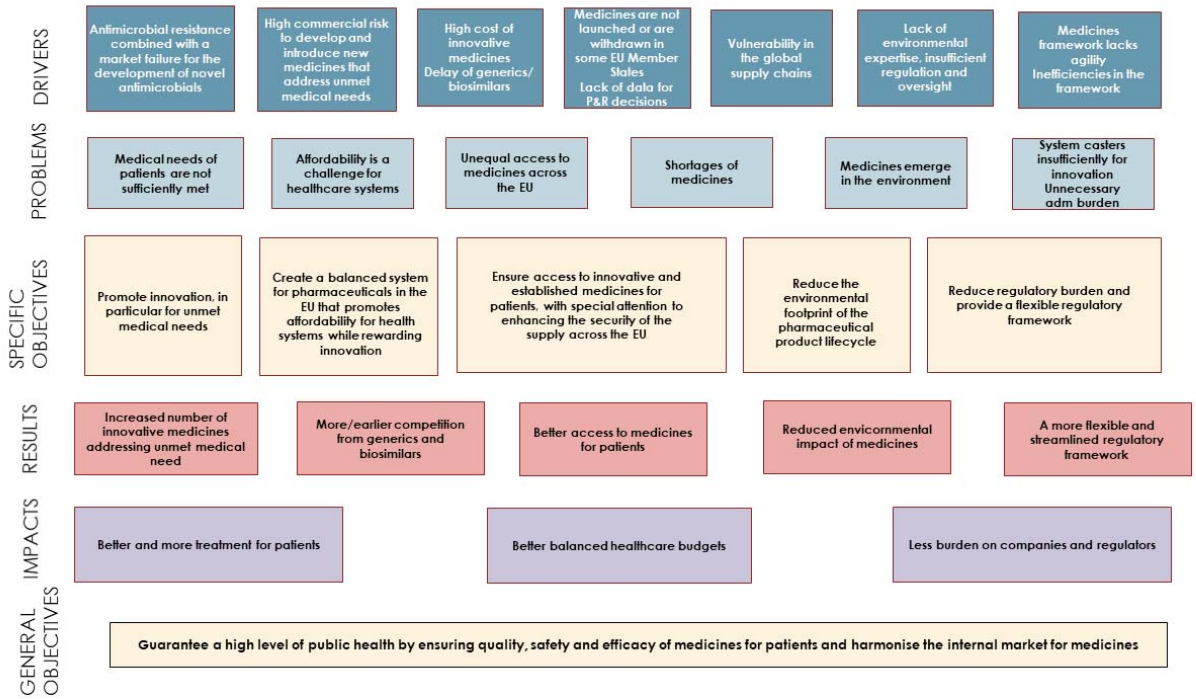
4.1 Introduction

This section sets out the general and specific objectives as well as the logic (Figure 2) underpinning the revision. It addresses the problems identified, and provides a focus for assessing and comparing

[99] European Commission, Directorate-General for Health and Food Safety, Future-proofing pharmaceutical legislation : study on medicine shortages : final report (revised), 2021, https://data.europa.eu/doi/10.2875/211485
[100] Evaluation SWD, section 4.2, see Annex 5.
[101] E.g. application of the Bolar provision – see page 7 of the evaluation SWD
[102] https://wayback.archive-it.org/12090/20200308120955/https:/ec.europa.eu/info/sites/info/files/xi.9.a_medicinal_products_for_human_use.pdf

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 objectives of the revision remain unchanged 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

In response to the problems identified, this revision aims to:

1. **Promote innovation, in particular for unmet medical needs**

The objective is to promote innovation with special focus on medical conditions not yet addressed and which represent a significant EU health burden (unmet medical needs). The revision should enable major biomedical research advances and ensure a pipeline of innovative new medicines for use across the EU. It should also support pharmaceutical R&D and strengthen the competitiveness of the research-based EU pharmaceutical sector.

The objective is also to address the market failure related to the development of novel antimicrobials through novel incentives that can finance the research required while respecting the need for a as limited as possible use of antimicrobials to reduce the tendency of pathogens to develop resistance.

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

This objective aims to enable competition, to promote affordability of medicines for health systems across the EU and ensure healthcare costs are sustainable for Member States. Affordability should not though be promoted at the expense of innovation, which also benefits patients. Thus, 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. This is expected to drive down costs for medicines with the additional benefit of strengthening the EU generic and biosimilar industry.

Affordability is a new objective of the revision, which can only indirectly be impacted by the general pharmaceutical legislation.

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, including in smaller Member States, after a timely authorisation under the EU pharmaceutical system. After a medicine has been developed and become available after a timely authorisation under the EU pharmaceutical system, patient access has two dimensions: (i) equal access to/market entry of innovative medicines across the EU and (ii) continuous supply and limited shortages of all medicines. As regards the first, the aim is to provide a motivation to companies to rapidly reach an agreement with Member States and engage Member States in effective negotiations. Facilitating competition from generic and biosimilars will also serve the same objective. As regards the second dimension (shortages and keeping products on the market), the aim is to enhance and harmonise notification requirements and obligations to ensure appropriate and continued supply across Member States.

4. Reduce the environmental impact of the pharmaceutical product lifecycle

This objective aims to reduce the environmental impact of pharmaceuticals through minimising medicine residues in the environment from their production, use, and disposal. This would entail an enhanced assessment of environmental risks of medicines and appropriate risk mitigation measures, including on their prudent use, especially for AMR.

5. Reduce the regulatory burden and provide a flexible regulatory framework

This objective aims to create a more flexible regulatory framework, to future-proof innovation and reduce regulatory burden. Through simplifying and integrating regulatory requirements and pathways and reducing burden for industry and public authorities alike, this objective aims to increase the attractiveness of the EU regulatory system. The goal is to provide clarity on the appropriate regulatory pathway, reduce approval times and costs while maintaining 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.

Objectives 1, 2 and 5 work in synergy for promoting innovation as do objectives 2, 3 and 5, with a range of measures to achieve access to affordable medicines. Trade-offs have to be considered between objectives 4 and 5 as measures to reduce the medicine residues in the environment are likely to increase the administrative burden. Trade-offs have also to be carefully considered for measures under objective 3 to address the risk of shortages while reducing regulatory burden. Trade-offs between achieving access (objective 3) through possible costs of additional market launches and affordability (objective 2) may also be necessary. Trade-offs are also inherent in objective 2 between rewarding innovative medicines and affordability often achieved by generic/biosimilar competition.

The specific objectives are consistent with the European Green Deal and Digital agenda principles 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[103]. In particular objectives 1 and 3 on innovation including for unmet medical needs and on access to medicines will have a positive effect on the access of patients to the medicines they need which relates to Article 35 of the Charter of fundamental rights of the EU which establishes the right to benefit from medical treatment under the conditions established by national laws and practices and a high level of human health protection in

[103] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A12012P%2FTXT

the definition and implementation of all the Union's policies and activities. Objective 4 which is expected to reduce medicines' residues in the environment from their manufacturing, use and disposal is in line with the objectives set out by Article 37 on environmental protection.

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 where no policy changes are made.

The current system provides 8 years of data protection and 2 years of market protection for all innovative medicines, to give time to developers to recoup their investment by delaying the entry of generic or biosimilar medicines. Other incentives also exist in parallel that delay generic/biosimilar competition (patent, SPC, orphan market exclusivity, paediatric protection extensions), usually offering a longer than 10-year protection if a medicine is eligible. However, the regulatory data and market protection is the broadest in terms of eligibility, as it applies to all innovative medicines, and it is almost impossible to infringe it[104].

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

Currently, there are no special incentives or obligations for the development of new antimicrobials or prudent use of existing ones, nor for conducting comparative clinical trials.

There are no incentives or obligations on MAHs to place their products on the markets that do not offer a sufficient business case. In essence, even when receiving an EU-wide marketing authorisation, a company is completely free to choose where and when it will market its product. There is no predictability for Member States who have no way of obliging the company to initiate negotiations for pricing and reimbursement. The steps from a medicine's marketing authorisation to access and the influencing factors are described in Annex 14. There is no requirement for MAHs to be transparent about public contribution to R&D costs either.

With regard to shortages, the current system focuses on notifying supply disruptions; it obliges MAHs to notify competent authorities 2 months in advance if they expect a temporary or permanent withdrawal of a medicine. Moreover, MAHs and wholesalers have to ensure appropriate and continued supplies of medicines, however without effective means to enforce the obligations.

The ERA is the main mechanism within the current legislation for addressing environmental impact of pharmaceuticals. It is required for all new MA applications and covers the environmental risks of the use, storage and disposal of pharmaceuticals. It does not include environmental effects of manufacturing. While it provides data to assess the impact of medicine residues released into the environment, there are gaps in timely enforcement and possible risk minimisation measures.

SMEs have a fundamental role in the development of medicines. According to a recent report from IQVIA[105], emerging biopharma companies (defined differently than SMEs in the EU, but essentially the same category) 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. The trend is that small companies dominate the earlier development stages, which are not too expensive but very risky. Once the molecule reaches a

[104] Before authorising a generic/biosimilar product, national competent authorities check against the data protection or market exclusivity of the reference medicine and do only authorise the generic if these protections have expired.
[105] 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022.

certain maturity and still looks commercially promising, the SME typically partners[106] with big pharma companies, which come in at the stage of the expensive late-stage clinical trials, marketing authorisation and market launch that often require vast capital and global infrastructure.

5.1.1 Projections

The life sciences sectors continue to invest in and advance innovative therapeutics and vaccines, the total number of products that are in active development globally exceeds 6 000, up 68% over the 2016 level.[107] Rich pipelines translate to more medicine authorisations, and we assume that the current annual 30-40 authorisations of medicines with new active substances in the EU will expand to 50-60 in the next 15 years. In our **dynamic baseline**, we will take the middle value at the middle of the next 15-year period, **45 innovative medicines per year** to analyse the impacts of the various policy measures proposed.

Against the backdrop of the overall positive outlook for innovation, research efficiency declines and it costs more money and requires more failures to develop a new medicine[108]. Investments in R&D are driven by commercial interest rather than public health needs, leaving important unmet medical needs unaddressed. We expect that **15-20%** of the new innovative medicines, or **7-9 medicines per year will address a real unmet medical need** without changes to the baseline, based on the current ratio of accelerated assessments at the EMA[109].

According to WHO, drug-resistant bacterial 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 and no new antibiotics are developed and authorised.

Regarding access to medicines, a IQVIA survey[110] shows no major improvement over the last year, with a **90% variance** between Northern and Western European countries and Southern and Eastern European countries **in terms of patient access to new medicines**, which also largely **corresponds** to the launch patterns according **to market size and purchasing powers** described in section 2.1 and Annex 14 due to pricing and reimbursement policies. The average delay between market authorisation and patient access can vary by as much as a factor of seven across EU, from as little as 4 months to 29 months. Maintaining the baseline would likely conserve the problem at today's level.

Available evidence suggests that across the EU the frequency of shortages and their impact on patients and healthcare providers is increasing[111].

If no changes are made to current requirements, the effect of the ERA to manage environmental risks would remain limited. The main effect to reduce medicines in the environment should come from environmental legislation.

5.2 Description of the policy options

In order to respond to the specific objectives, we considered more than 70 potential policy measures deriving from the consultation process and initial analysis. These measures were organised around nine policy blocks reflecting the objectives of the revision and its broad scope[112].

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[106] Big pharma may acquire the rights for the product, the whole company, or they develop, authorise and market the medicine in a joint partnership (e.g. the Pfizer-BioNTech COVID-19 vaccine).
[107] 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022.
[108] idem
[109] Annex 5 – Evaluation SWD, p.22
[110] EFPIA Patients WAIT Indicator 2021, see: https://www.efpia.eu/media/636821/efpia-patients-wait-indicator-final.pdf
[111] European Commission, Directorate-General for Health and Food Safety, Future-proofing pharmaceutical legislation : study on medicine shortages : final report (revised), 2021, https://data.europa.eu/doi/10.2875/211485

In a second step, taking into account the preliminary evaluation findings, we designed the three high-level options which represent alternative ways to reach all the objectives of the revision. Each option is constructed around specific underlying principles behind the grouping:

- Option A builds on status quo and achieves the objectives mainly through new incentives;
- Option B reaches the objectives through more obligations and oversight;
- Option C adopts a 'quid pro quo' approach in the sense that positive behaviour is rewarded and obligations are only used when there are no alternatives.

Each option contains pivotal and non-pivotal measures. Non-pivotal measures are complementary to the pivotal ones and form an integral part of the policy options. A thorough multi-criteria impact analysis for each policy measure, based on data, literature review and stakeholder feedback can be found in Annex 11.[113] Finally, the options are complemented by horizontal measures. Contrary to the non-pivotal measures, they apply across the board and deliver on simplification and innovation.

The IA report focuses on the 'pivotal' measures and the 'pivotal horizontal measures'. These pivotal measures were selected on the basis of the magnitude of their impacts and their political importance. **Table 1** shows how the pivotal measures map on to the specific objectives.

[112] Directive 2001/83/EC merged 11 prior directives related to medicinal products, and together with the Regulation (EC) No 726/2004, consists of 220 articles, offering numerous "levers" to adjust the policy.

[113] To give an example, a pivotal measure to support market access is making the last 1 or 2 years of regulatory data protection subject to market launch in all EU countries and this is discussed in the main body of the IA. Access in all Member States will be supported by other measures, such as facilitating multi-country packs to make launches in smaller Member States easier, but those measures are rather considered in Annex 11.

5.2.1 Tabular overview of policy options

Table 1 Mapping of **pivotal elements** to the **specific objectives**

Objective	Baseline	Option A	Option B	Option C
Promote innovation, in particular for unmet medical needs.	8 years DP +2 years MP	8 years DP +2 years MP Special incentive: +1 year DP for medicines that address UMN +6 months DP to include comparative trials Digitalization, simplification elements from horizontal measures	6 years DP +2 years MP Special incentive: + 2 years DP for originators that address UMN. Digitalization, simplification elements from horizontal measures	6 years DP +2 years MP Special incentive: +1 year DP for medicines that address UMN + 6 months DP for comparative trials Digitalization, simplification elements from horizontal measures
Incentives to promote the development of novel antimicrobials	No special incentives for the development of antimicrobials	Transferable exclusivity vouchers for antimicrobial products	Pay or play model for antimicrobial products	Transferable exclusivity vouchers for antimicrobial products
Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation	Generic and biosimilar entry after DP/MP periods are over providing a predictable framework for competition from generic and biosimilar medicines.	Baseline + additional rewards for innovation and access. Comparative trials may lead to public cost savings.	Earlier entry of generics and biosimilars with 2 years shorter protection than baseline +2 years MP for medicines with no return on investment. Require public transparency on any relevant public contribution or funding, including of research and development costs	If market launch condition not met, earlier entry of generics and biosimilars Require transparency on public contribution to R&D costs in relation to clinical trials included in the MA application Comparative trials may lead to public cost savings.
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	+6 months 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)	Obligation to place a centrally authorised medicine on the market in the majority of MS (small markets included) within 5 years	+2 years (or 1) DP extension if medicine is placed on all EU markets within 2 years of authorisation and appropriately and continuously supplied
	Obligation to notify a withdrawal 2 months before the interruption in market supply of the product	Notification requirement same as in baseline	Notification requirement same as in baseline	Improve data on medicines shortages, through adequate notification periods for withdrawals and serious shortage risks; shortage prevention, increased transparency of the supply chain, mitigation plans for all medicines and stockpiling of critical medicines Monitoring of shortages is reinforced with a mechanism of information exchange between MS.
Reduce environmental impact of the pharmaceutical product lifecycle	An ERA is required for all new MA applications. Potential risks from medicines to the environment are assessed by regulators and precautionary measures are taken	Same as baseline ERA	Strengthen the conditions of use for medicines and ERA requirements, including the assessment of the environmental risk of manufacturing and its impact to AMR	Same as option B with the inclusion of AMR aspects in GMP.
Reduce regulatory burden, and provide a flexible regulatory framework	Not applicable / non legislative measures	Horizontal measures* *The horizontal measures are applicable to all options, for details please refer to section 5.2.5.	Horizontal measures*	Horizontal measures*

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 need

5.2.2 Policy Option A

Option A addresses the identified problems through **incentives** rather than setting further obligations coupled with a stronger enforcement of existing obligations and information requirements.

To stimulate **innovation**, Option A maintains the current system of regulatory incentives (8 years data + 2 years market protection), supplemented by a targeted incentive, an additional 1 year of regulatory data protection for products addressing unmet medical need (UMN). Clarifications of the scope and new definitions should facilitate innovation. It also foresees the introduction of a new **incentive 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.

Option A stimulates the development of novel **antimicrobials** that can fight resistant pathogens through **transferable exclusivity vouchers**. A transferable regulatory protection voucher (transferable exclusivity voucher) allows the developer of a novel antimicrobial that reduces AMR to benefit from an additional year of RP on another product in their portfolio or sell the voucher to another company. This is a measure supported mostly by industry as a way to underpin the substantial R&D costs of bringing new classes of antimicrobials to the market[114]. This will be supported by measures on harmonisation of the summary of product characteristics for nationally authorised antimicrobials to support good prescription practices.

Option A promotes patient **access** with a 6 month regulatory data protection incentive if a product is placed on the market in all Member States within 5 years of MA. 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 timeframe within which they do so, by offering them a reward in exchange.

Measures on **security of supply** retain the current requirement for notifications of withdrawals (at least two months in advance).

The current **ERA requirements** continue with an additional obligation to include the information on the environmental impact of supply chain actors in the application dossier. The latter proposal is part of the package of suggestions to support quality and manufacturing aspects (QMC) for medicines.

Among the **non-pivotal measures** of Option A are a non-binding system for scientific assessment of evidence for repurposing off-patent medicines to include new indications for allow for innovation, measures to facilitate multi-country packs to enhance access and inclusion of new manufacturing methods into the framework to both ensure best quality manufacturing and to cater for innovation.

5.2.3 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 in the lifecycle of a medicine to foster patient access, affordability and security of supply.

To stimulate **innovation**, especially for unmet medical needs, it introduces a modulated **system of incentives**, with a reduction in the current standard regulatory protection periods. The new standard protection[115] for all originator medicines would consist of 6-years data protection and 2-year market protection. 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. Other medicines will be entitled to strengthened protection only if they can demonstrate no return on investment in view of investment costs, including for research and development.

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[114] Previously explored in the Joint Action on Antimicrobial Resistance and Healthcare Associated Infections.

[115] Baseline protection is the current regulatory protection of 8 years of data protection and 2 years of market protection which also applies in Option A; (new) standard protection is the regulatory protections of Options B and C of 6 years of data protection and 2 years of market protection.

Option B also encourages the development of novel **antimicrobials** that can fight resistant pathogens through 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 also includes measures for prudent use of antimicrobials including monitoring consumption, optimising package sizes and stricter rules for the use and disposal of antimicrobials for human use and tightening of prescription requirements for example through the mandatory use of diagnostics prior to prescription of antimicrobials thus target pathogens better.

Access measures in Option B consist primarily of an obligation to launch centrally authorised medicines on the market in a majority of Member States (small markets included) within 5 years. If the obligation is not fulfilled, the medicine loses its protection, and generics can 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[116] 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** and conditions of use for medicines are strengthened. This option also foresees the assessment of the environmental risk of manufacturing in the ERA as part of the marketing authorisation. Moreover, it proposes improving oversight of sites through modification of rules on inspections and a mandatory joint audit scheme for national GMP and GDP inspectorates.

Non-pivotal elements in Option B include the 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 pharmaceutical legislation and simplifying/clarifying the regulatory framework for certain categories of medicines (e.g. borderline products) should facilitate innovation. Anti-competitive practices such as introducing multiple marketing authorisations are restricted, interchangeability of a biosimilar medicine with its originator medicine will be elaborated in the product assessment and the Bolar exemption (legal exemptions from patent infringements for acts relating to the regulatory submission of testing data) will be broadened to facilitate generic entry. Together with obligation for all MA applicants to publicly disclose any relevant public funding received (R&D **transparency**) this should address **affordability**.

5.2.4 Policy Option C

Option C proposes a 'quid pro quo approach' with a modulated system of **incentives combined with obligations**.

The regulatory protection for originator medicines in option C is split into a standard and a conditional period. The standard is 6 years data protection and 2 years market protection (as in option B) while the conditional period is 2 years (or 1 year, see box below with a variation of the option). The conditional year/years are granted only if the product is placed on all EU markets within 2 years of authorisation and appropriately and continuously supplied thus increasing **access** to patients. To be pragmatic, the provision has some exemptions (e.g. the possibility for a Member State to waive[117] the obligation within its territory for the purpose of the incentive). For it to be predictable for generic and biosimilar companies, a time limit is set (i.e. 2 years before the DP expires) for a final decision on the prolongation or not. If a company fails to comply with the market launch requirement, there will be earlier generic competition and increased **affordability for health**

[116] 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, OJ L 174, 1.7.2011, p. 74.
[117] In the case that a MS does not wish to be supplied at that moment.

systems[118]. Moreover, originator medicines addressing an UMN would receive an additional 1 year of data protection to stimulate more innovation in areas of unmet patient need.

The system of special incentives in options A and C are similar but transparency on public contribution to the costs of clinical trials will be required for all medicines in option C. There is a special incentive (6 months) to stimulate developers to conduct comparative trials. **Incentives can be cumulated**, however the total regulatory protection period is **capped at 11 years**, which is a difference compared to Option A.

Variation to Option C

Option C aims at a balanced mix of obligations and incentives, which in individual cases may result in a higher level of protection for companies than the current baseline. To mitigate this result, a variation[119] to Option C is assessed, where no medicine could reach a 'beyond-baseline' level of protection. The variation consists of a reduction of the conditional **2 years** protection period to **1 year**, and a capping of cumulated incentives at 10 years.

The next sections will consider Option C with 2 years conditional period as default. The differences in impacts between the default option C and the variation are discussed in section 8.1.

Variation to Option C
6 years DP + **1 years DP if placed in all EU markets** +2 years MP
Special incentives:
+1 year DP for medicines that address UMN
+ 6 months DP for comparative trials
Incentives capped at 10 years.
Transferable exclusivity vouchers for antimicrobial products

With respect to **innovation**, the changes to the scope, definitions and classification advice with regard to medicines and the codification of rolling reviews and PRIME would be similar to option B. However, this option also foresees the inclusion of a sandbox environment (i.e. a structured form of testing before formal regulation) which would more readily accommodate innovation in breakthrough areas where the current framework does not sufficiently cater for this innovation. 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. To incentivise development of novel **antimicrobials** that can fight resistant pathogens, a system of transferrable exclusivity vouchers (as in option A) is explored. The fight against AMR is corroborated with a strong emphasis on prudent use measures which are similar to those proposed 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- and Member State-level actions to mitigate and prevent **shortages** and build on the shortage provisions in the EMA reinforced role legislation[120]. 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 the possibility of information sharing by Member States on critical shortages and supply chain vulnerabilities.

The **ERA requirements** are similar to option B. It would also strengthen conditions of use of medicines on a case by case basis to limit the environmental impact without affecting the

[118] An alternative consequence could be repealing marketing authorisation of companies not launching in all EU, however this would deprive patients' access to the concerned medicine, hence this measure was discarded.
[119] During the evaluation several stakeholders from patients' groups and academia argued that incentives are overly generous within the EU.
[120] 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, OJ L 20, 31.1.2022, p. 1.

appropriate therapeutic use. It will include AMR aspects in GMP to allow a more holistic assessment of environmental risk along the pharmaceutical lifecycle.

With regard to **non-pivotal elements**[121], this option foresees stronger oversight of manufacturing supply chains through changes to inspections, reinforced Member State inspection capacity (joint audits of inspectorates) and increased EMA coordination. The strengthened Bolar provision to promote competition and hence **affordability** listed in Option B is retained and the transparency obligation on public funding is limited to clinical trials. Improvements to the current Hospital Exemption will continue allow for the use of ATMPs without marketing authorisation, but under stricter conditions to ensure quality, safety and efficacy of these therapies.

Transferable exclusivity vouchers and r*estrictions on their granting and use*

The transferable exclusivity voucher is a tool to **generate funds for the development of novel antimicrobials**. The analysis in section 6.1.1.4 points to the conclusion that even though vouchers can be an expensive solution, they represent a credible measure against AMR if applied under strict conditions; their benefits and costs need to be weighed against the cost of inaction and the impact of AMR on health and economy[122].

By setting strict criteria for antimicrobials that can benefit from the voucher, its value would be calibrated to benefit the developer of the antimicrobial more than the buyer. The analysis in section 6.1.1.4 explains why vouchers can work only if they are very restricted to a limited number (i.e. max 1 per year). This is also the reason why they score differently in the impact assessment for orphan and paediatric medicines where such limitation is not possible (see details in Annex 4).

To achieve strict limitations, only those medicines that are 'game changing' antimicrobials for reducing AMR can receive '**novel antimicrobial' status** by the Agency, based on clear criteria set out in the legislation. The antimicrobial is considered novel, and thus eligible for the voucher if preclinical and clinical data underpin a significant clinical benefit with respect to antimicrobial resistance and it either represents a new class of antimicrobials or it has a new mechanism of action that is distinctly different from the mode of action of any authorised antimicrobial (criteria to be assessed by qualified experts). Moreover, the active substance should not have been previously authorised in a medicinal product in the EU that addresses a multi-drug resistant infection or a serious or life threatening infection. This will also direct investment and research into those game changing products. Even if found eligible, additional supply requirements, transparency conditions on funding received and on the sale or transfer of the voucher and other conditions will be set in the legislation.

There would be moreover a review clause in the legislation to evaluate the application of the vouchers after some years and decide on the continuation or not of the measure. It may take some time until an antimicrobial is authorised that is eligible for a voucher, a voucher may not be used immediately after it has been granted and the effect of the extension of data protection due to a voucher may also take some time to be seen. Several vouchers have to be granted and been used to gain sufficient experience for a review of the measure.

5.2.5 Horizontal measures

All options are complemented by a series of horizontal measures. These are necessary to improve the effectiveness and efficiency of the regulatory system overall and will act on core elements of the authorisation and lifecycle procedures. They respond to the specific objectives of **innovation**, and **reducing the regulatory burden and providing a flexible regulatory framework**.

Generic marketing authorisations will be simplified by enabling a common assessment of manufacturing data across products, as generic medicines often source active substances from the

[121] See Annex 11 for details.
[122] AMR-Tackling-the-Burden-in-the-EU-OECD-ECDC-Briefing-Note-2019.Pdf

same site. A more efficient repeat use procedure[123] will be provided to reduce administrative and cost/burden and prevent medicine shortages. Furthermore, the sunset clause and renewal of MAs after five years will be abolished to simplify procedures. Likewise, the envisaged reduction in the number of notifiable variations reduces the administrative costs incurred by MAHs and regulators.

Provisions of the legislation will be reviewed with regard to novel combined products (e.g. where medicines are coupled with medical devices, software, or artificial intelligence). To address shortcomings highlighted in the evaluation[124] the legislation will ensure complementarity with the medical devices regulation/in vitro diagnostic regulation in relation to benefit/risk assessment, responsibilities of the medicine developer, and joint scientific advice.

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 these changes would not constitute a complete derogation from the GMO legislation.

New concepts will be integrated, such as adaptive clinical trials and full use of health data (real world evidence), applying the digital by default principle, notably through electronic submissions of applications, variations to MAs and electronic product information. The provision of authorised electronic product information for EU medicinal products would enable easier access to data contained within the product information, taking into account needs of patients, consumers and healthcare professionals, as well as the risk of digital exclusion.

The working methods of EMA and the European medicines regulatory network will be adapted, especially with regard to the functioning of the centralised procedure and the decentralised procedures, the use of expert assessment teams and multi-expert inspections teams to ensure a better use of the available network resources. The evaluation also identified suboptimal coordination between the EMA committees that duplicate work, create administrative burden and risking delays especially in the assessment of medicines for rare diseases and for children[125] and ATMPs. An EU-wide centrally coordinated process will be foreseen offering early dialogue and more coordination among clinical trial, marketing authorisation, health technology assessment bodies and pricing and reimbursement authorities for integrated medicines development and post-authorisation monitoring, pricing and reimbursement.

6 WHAT ARE THE IMPACTS OF THE POLICY OPTIONS?

6.1 Economic impacts

The general pharmaceutical legislation rewards innovators through the **regulatory data and market protection (RP)**. By protecting data on the safety and efficacy of the product, RP guarantees that during the data protection period no generic/biosimilar medicine can obtain a marketing authorisation referring to the originator's data. This effectively protects innovators from generic or biosimilar competition[126] for 10 or 11[127] years after authorisation. In comparison with other jurisdictions, the EU ranks high (see **Table 2)**.

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[123] See glossary.
[124] See Annex 5. The evaluation showed 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.
[125] SWD(2020) 163 final.
[126] RP does not prevent companies willing to undertake their own clinical testing to seek marketing authorisation for the same medicinal product if they do not infringe on any patents or SPCs. However, that would be rather costly for entering a market, where the originator medicine is already present, and hence rarely occurs.
[127] An extra year is granted for an additional indication with significant clinical benefit. Historically around 1 in 8 medicines qualify for that.

Table 2 Basic regulatory protection periods for medicines globally[128]

Country	Protection	Duration
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
Japan	New Chemical Entity	8 years

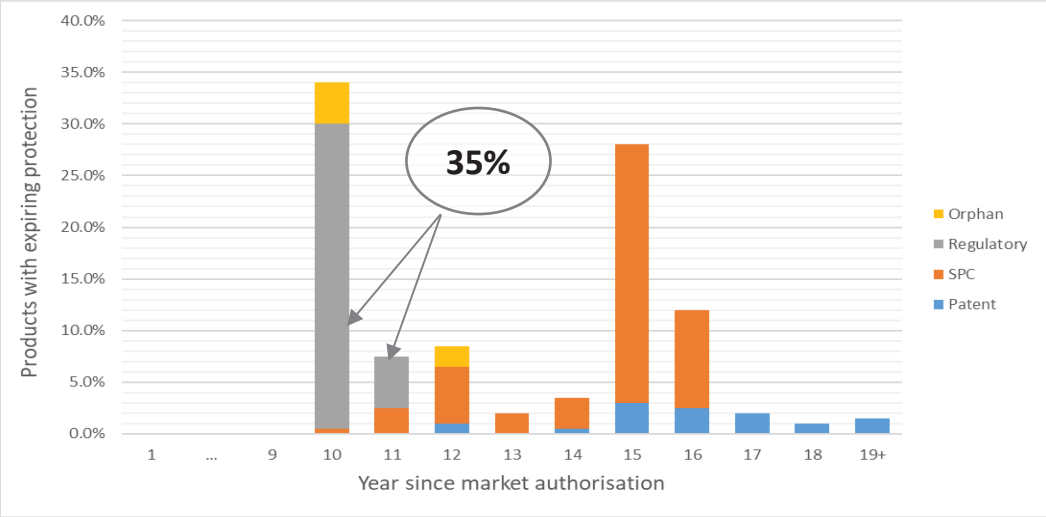
In addition to RP, medicines are also protected by patents (20 years), SPCs (up to 5 year extension of primary patent, but maximum 15 years from marketing authorisation), and medicines for rare diseases also benefit from 10 years market exclusivity (+2 years if paediatric studies were carried out)[129]. The patent and SPC protection start from the patent filing, and depending on the time until authorisation they may offer longer or shorter protection than RP. It differs case by case which instrument provides the longest protection period after entering the market, as demonstrated by **Figure 3** on a representative sample of 200 medicines. Medicines protected by patent or SPC not only enjoy a longer protection, but on average they generate 2-3 times higher revenues than those protected only by RP (Table 3).

Table 3 Medicines' protection period and revenues by their last layer of protection

Last line of protection	Number of products	Avg. protection duration	Avg peak annual sales[1]
Regulatory protection	69	10.1 years	**€ 158.7 m**
Market Exclusivity	12	10.7 years	**€ 41.7 m**
SPC	95	14.3 years	**€ 368.3 m**
Patent	23	16.7 years	**€ 300.5 m**
Grand Total	**199**	**12.9 years**	**€ 268.2 m**

We expect this ratio among protection types to remain in the next 15 years, therefore the changes to the RP would **concern around 1/3 (i.e. 35%) of the new medicines**, which have a **23% share among all originator medicine sales in the EU**.

Figure 3 – Ratio of medicines by the length of last layer of protection and type of protection

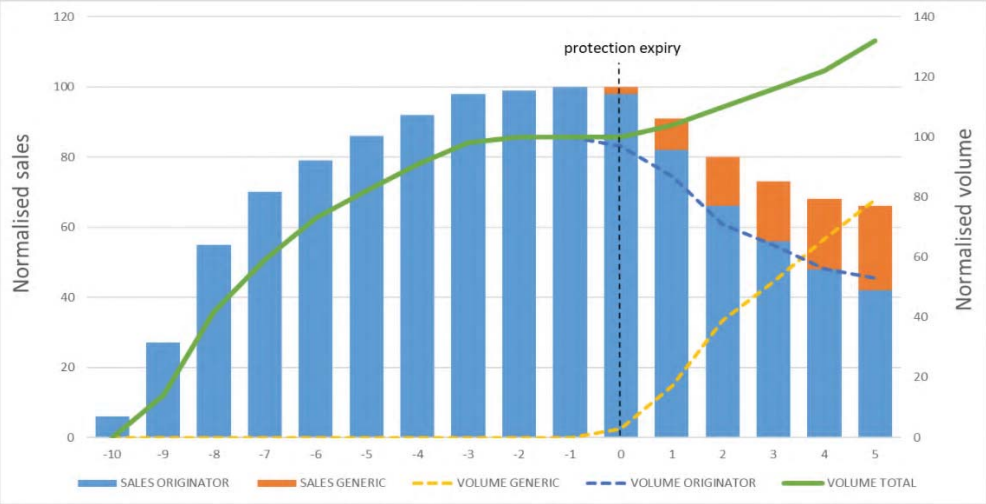


We provide a conceptual model to explain the economic impacts of the changes in the RP, on the different stakeholders. The model is based on the commercial lifecycle of a representative innovative

[128] Data collection by Technopolis Group, 2022.
[129] A diagram with the current regulatory and IP protections in the EU can be found in Annex 9.

medicine, an analogue, for which RP is the ultimate protection. To create this analogue, historical data[130] were examined, and the evolution of sales followed from market authorisation 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. It is assumed that the pricing strategy of the manufacturers remain unchanged. The calculations were done based on the public, list prices (not the actual, confidential prices).

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



The SPC evaluation[131] 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 considers the average evolution of sales volumes and values across all the RP-protected medicines in a nine-year cohort, including those medicines that were not contested by generics after protection expiry. The model represents well real-life at systemic level, even though some medicines – for example, those that face a high number of competitors – might show a much steeper erosion, whereas others might see persistently high sales after expiry in the absence of competitors.

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[132]. 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 health 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 RP, we use the above baseline and the 16 years observation period, which we consider as the commercial lifetime of an RP protected medicine. This allows to understand how the stakeholders' positions change under the different scenarios. Extending the protection allows innovators to seek longer monopoly rents, but it delays cost savings

[130] 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.
[131] SWD(2020) 292 final.
[132] The evaluation (Annex 5) found that originator products can maintain a 30% premium over their generic competitors.

and broader access for the public and delays revenues for generic companies. Decreasing protection has the exact reverse effect.

Profit, sales, cost, volumes – how we measure economic impacts for key stakeholders

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. We will indicate the monetary value of the volume difference as "Δ of patients treated (monetised)".

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 but we have good data on sales (revenues) from the IQVIA database. By deducting the cost of sales from the revenues, we can calculate the gross profit. The gross profit only includes the variable costs of manufacturing and distribution, but not the fixed costs, such as R&D and investment in infrastructure. In our model we distinguish three categories of revenues, each with a different margin of gross profits.

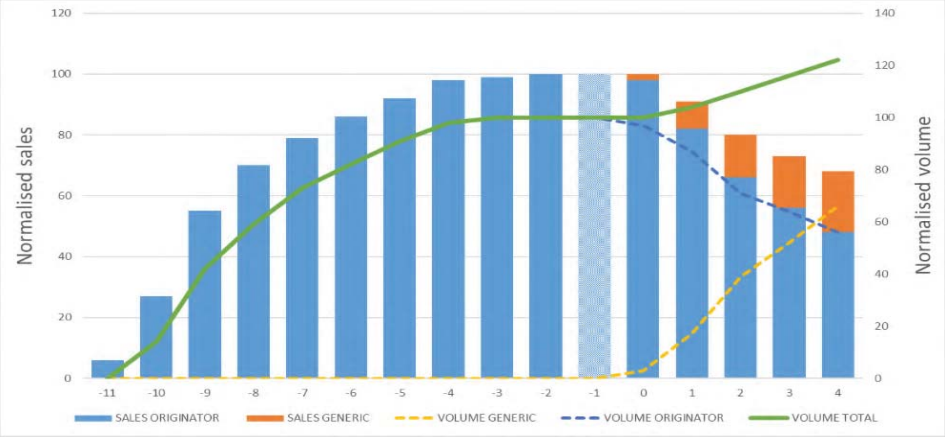
- **Protected originator sales**: this is the most profitable category during the protected period of new medicines. Based on a sample of reports from publicly listed companies we apply a 80% gross profit margin on the revenues (20% cost of sales)
- **Contested originator sales**: once generics enter 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.

6.1.1 Economic impacts of key policy measures

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

To understand the economic impact of an increased regulatory protection (either offered for UMN, comparative trials or market launch) we have added an extra year of protected sales to our model, and analysed the gains/losses for the different stakeholders during the observed 16 years (**Figure 5**).

Figure 5 - Normalised sales and volume for products with 8+2+1 years of RP protection



The longer protection translates into higher profits for the innovator but increases the costs for patients and payers, and also delays revenues for generic manufacturers. 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). The exact monetary impact depends on the length of additional protection, and on the number of medicines expected to benefit from a certain incentive. Below we assess the special incentives one by one.

Special incentive: 1 year extension of RP for medicines addressing UMN (Option A, 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 45 annual new authorised

medicines as per our dynamic baseline, **on average 3 special UMN incentives per year are expected**. It is worth noting that for orphan medicines too an incentive for high unmet medical needs is foreseen, extending the market exclusivity period beyond the modulated RP protection for those orphan medicines.

Table 4 – Impact of change of +1 year regulatory protection for UMN

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
Patients monetised gains/losses	-€28m	-€84m
Patients + payer monetised gain/loss	**-€82m**	**-€246m**

Table 4 summarises the monetary gains and losses of the different stakeholders at a single product level, and also at systemic level, counting with 3 incentives a year. For affected medicines, the **innovators'** gross profit will increase by €282m a year, and the incentives would increase the cost for payers by €162m. Taking into account that some patients will not have access to the medicine due to the sustained higher price, the total **cost will be €246m to the public**.

In exchange for this public cost, the UMN incentive would directly reward investment in UMN R&D and likely would have a spill-over effect: national and EU-level research and innovation funding could be specifically channelled to UMN, and national pricing and reimbursement systems could differentiate the UMN addressing medicines, making them even more viable commercially.

We expect that the incentive would attract more investment in UMN and **result in 1-2 additional UMN medicines per year**, for the benefit of the patients and creating savings for the health systems. This important and non-monetised[133] benefit has to be seen together with the costs.

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 would introduce uncertainty for businesses as the ultimate duration of the regulatory protection period would not be fully clear when their investment decision is made[134].

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

Similar to the previous incentive, this measure could benefit medicines for which RP is the last layer of protection, making around **35% of all new medicines eligible**. Conducting comparative trials may not be feasible for some medicines, and if the cost of the comparative trial is too high as opposed to the reward, companies will decide to decline the incentive. Taking these factors into account, we expect that half of the RP products or **8 medicines annually** could benefit from the incentive. Table 5 shows the economic impacts on the main stakeholder groups of this incentive both at individual product level and at systemic level, for the 8 medicines per year.

Table 5 – Impact of change of +6 months year regulatory protection for comparative trials

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

[133] Monetising the benefits of an additional new medicine has several challenges: there is a large variation between medicines' value, defined by the patient population and severity of disease. Moreover, monetising a medicine's value requires putting a monetary value on patients' life and health, as well as on the physical and emotional burden of their families and carers. We thus have chosen not to monetise these impacts, but quantify them as much as possible.
[134] See Annex 14 for further details on the factors influencing access and affordability.

Patients + payer monetised gain/loss	**-€41m**	**-€328m**

Comparative clinical trials have a cost. In the absence of publicly available data, we estimate the cost of a comparative clinical trial at €20-50m (the model uses the middle value of the range), referring to the paediatric trials as a benchmark[135]. Due to the revenue extending nature of the incentive, higher sales medicines would have a higher compensation, independent from the cost of the trial.

For the public, 8 trials a year would cost €328m, but at the same time it would generate important non-monetised benefits: comparative trial data will enable 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.

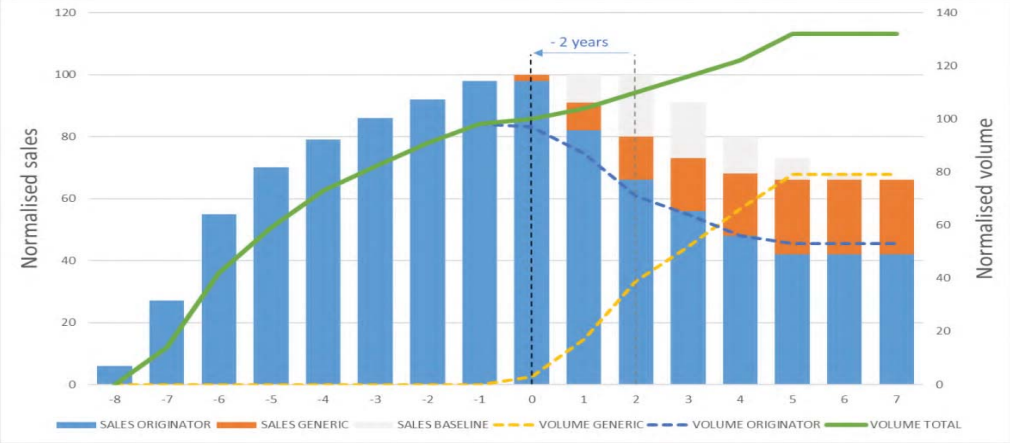
In the consultations, industry stated that comparative data is already provided at authorisation stage when possible and that some products (e.g. ATMPs, products for ultra-rare diseases) will not benefit from this incentive. Patients and public authorities on the other hand supported comparative clinical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

6.1.1.2 Decreasing standard regulatory protection (Option B)

A key feature to support affordability in Option B[136] is a decreased regulatory protection, from 8+2 years in the baseline to 6+2 years, except for a minority of medicines: UMN addressing medicines and medicines with no return on investment can maintain 8+2 years RP.

To model for the change, 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[137] (**Figure 6)**.

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



This measure would only concern medicines that have RP as the last layer of protection, about 1/3 of the 45 new medicines. Out of this 15 medicines, 20% may be UMN addressing or low revenue thus exempted from the measure. Some of the RP protected medicines are eligible for SPC protection between year 8 and 10 from market authorisation, partially offsetting the RP reduction. Overall, **9-12 medicines may be affected** by the reduction annually. **Table 6** summarises the impacts at product and systemic level for the different stakeholders.

Table 6 – changes between baseline and RP 6+2 per stakeholder

2 year decrease in RP	**Product level change**	**% change**	**Systemic change (9-12 medicines)**

[135] The joint evaluation of the orphan and paediatric regulation estimates the cost of paediatric studies at €22m.
[136] This section discusses Option B solely, the eventual loss of protection in Option C for some medicines not complying with the access condition is discussed in 6.1.1.3.
[137] More on the assumptions in Annex 4.

Originator gross profit	-€188m	**-15%**	**-€1.97 b**
Generic gross profit	+€25m	+56%	**+€266 m**
Cost to public payer	-€107m	-6%	**-€1.13 b**
Δ of patients treated (monetised)	+€71m	+5%	+€745 m
Patients + payer monetised gain/loss	+€178m	+9%	**+€1.86 b**

Compared to the baseline, affected **originators** would lose their two highest-revenue, most-profitable years. The product would **lose 15% of its lifetime profits**. For the originators this sums up to €2bn loss annually in gross profits from the EU. More than 75% of originators replying to the targeted survey expressed a negative stance towards a reduction of protection period for products that do not address an UMN.

On the other end, the measure would generate €266m additional gross profit for the generic industry, and €1.13bn direct cost reduction for health payers. Thanks to the lower price, 5% more patients could benefit from the concerned medicines and accounting for the extra patients served in a monetised form, the total benefit for the public is €1.86bn, or 0.9% of the total EU pharmaceutical expenditure. An additional benefit would be a higher proportion of UMN among newly approved medicines, due to the relative higher reward.

Because of all the other co-existing protections (SPC, patent, market exclusivity), option B **would leave 75-80% of new medicines unaffected. The saving for payers and patients, would be borne by a dozen of medicines, which would lose 15% of their profits.**

Apart from the imbalanced impact, the measure would have additional costs. With a lower reward, some developers may decide not to enter the EU market, or delay entry and seek return on other markets first. An estimated **€670m will be lost for innovation**[138] 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. 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.

Would the RP reduction harm EU competitiveness?

A direct link between EU incentives and EU competitiveness is hard to establish because while the incentives make the EU markets more attractive, they are agnostic to the medicines' geographical origin. Around 20% of new medicines authorised in the EU are from the EU, the others are mainly from US, UK, Switzerland and Japan that are equally eligible to all EU incentives. Equally EU based innovative companies can benefit from incentives elsewhere, if they sell their products there.

In June 2016, the Council requested the Commission to conduct an evidence-based analysis of the impact of incentive mechanisms, notably SPCs. Two studies have been commissioned. One from Max Planck Institute[139] questions whether the availability of patent or SPC protection affects companies' decisions to locate research facilities in one jurisdiction or another, emphasising that other factors are likely of greater importance. The Copenhagen Economics study[140] argued that SPCs could play a role in attracting innovation to Europe, pointing out that taxation, education, and other factors are probably more significant in that respect.

[138] 20% of lost protected sales, the typical R&D rate of revenue for originator companies, calculated in Annex 4.
[139] Max Planck Institute. Study on the legal aspects of supplementary protection certificates in the EU, 2018.
[140] Copenhagen Economics. Study of the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards, 2018.

6.1.1.3 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. As all options modulate RP, they all would impact those medicines that have RP as the last layer of protection, 35% of new medicines, **15-16 medicines a year**. Option A offers a +6 months RP extension incentive for medicines launched in all EU markets within 5 years of authorisation. Option B instead requires companies to launch their product in the majority of all EU countries within 5 years, otherwise they lose their protection and generics are allowed to the market. Option C requires market launch in all EU MS (except those not interested in the product) within 2 years of authorisation as a conditionality to parts of the protection period. Complying medicines would gain 2 years of conditional 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. 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.

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 savings to the public have been calculated (**Table 7**). 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 4).

In option B and C the concept is reversed. If a medicine complies with the requirements, the stakeholders' position do 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 (section 6.1.1.2). Again, the average peak-sales value was adjusted, assuming that the low-sales medicines will be the ones not complying.

Table 7 – Comparative table of measures improving access

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* -2 years, if not in all EU	66% (10-12 medicines)	-€469 m gross profit -15% gross profit for 5 non-complying medicines	€444 m gain from non-complying medicines

* The differences in impacts between the default option C and its variation are discussed in section 8.1

To determine compliance we use assumptions and this inevitably carries uncertainties. Originator industry is better off with higher compliance and worse off with low compliance, which then results in profit losses. For the public, high compliance is the desired outcome, resulting in faster and increased access. However, non-compliance lowers the cost by shortening the protection period and thus contributes to affordability, also an improved outcome compared to the baseline.

The access measures benefit society, above all patients. These benefits are elaborated in the social impacts section (6.2). Option B has the disadvantage that it is unpredictable. Until reaching 5 years on the market, the generic industry will not know for sure whether the originator medicine complies or not. If generic companies prepare for non-compliance, and start development and production, the innovator's compliance would delay their entry by 3 years. And in case of non-compliance without the generic companies being prepared, there will be no generic competition for quite some time, neutralising part of the expected impact of the measure.

Practical details and impact of modulation of data protection for market launch (option C)

The access conditionality would be a first-of-its-kind policy measure that addresses a problem specific to the EU, and the primordial goal of it is to increase and accelerate EU patients' access to new medicines, regardless of the country they reside. The measure is successful if it is widely used and a high proportion of new MAHs comply with the requirements and benefit from the incentive. A low success rate would discourage companies and would not achieve access in all Member States.

Lack of access in a particular Member State can have many reasons. Sometimes companies decide not to launch or delay launch in a market because of low profitability, small patient populations, perceived cumbersome procedures, pricing policy, parallel trade. In other cases, Member States deny access because no therapeutic value is seen, the medicine is not cost-effective according their HTA assessment, or it would have an unbearable budget impact. There may also be objective roadblocks, such as the need for highly specialised delivery infrastructure or diagnostic tools for the therapy that do not exist in the Member State.

The proposed measure in option C targets companies to do their utmost to launch the medicine in all EU markets within a specific period after authorisation (e.g. 2 years) and ensure a continuous supply. This includes that companies shall file for pricing and reimbursement in all 27 Member States, they have to conduct negotiations in good faith, and upon positive decision ensure supply that covers the Member States' needs[141]. However, companies could still receive the market launch incentive if due to reasons beyond their control the market launch is delayed or not happened at all (e.g. the Member State doesn't wish to be supplied at that particular moment or doesn't have the specialised infrastructure e.g. in case of orphan medicines or ATMPs).

The Commission would grant the extra protection (2 years or 1 year for the variation to option C) based on a system where Member States will be obliged to confirm within a certain period after marketing authorisation compliance with the conditions of the incentive, justify a refusal by a statement of reasons based on objective and verifiable criteria or give a waiver to the company. Non reaction of a Member State will be considered as tacit confirmation of compliance.

Companies should not find it difficult to comply with the conditions of this incentive, as EFPIA already made a voluntary commitment[142]: their members would file for pricing and reimbursement in all EU27 Member States within 2 years from authorisation. This is already a step forward from the current situation, but it is voluntary, restricted to EFPIA members and there are no controls in the system. Hence, it does not work to the extent of the incentive, which relates to actual launch and supply not just filing. The proposed measure adds a significant financial incentive for complying, and it can also prevent dishonest applications[143]. By making ignoring certain markets or abusive negotiating practices very expensive, Member States, and especially smaller Member States would have a more balanced position when dealing with global firms.

The instrument to work adequately would also require Member States to act timely and in good faith, because if compliance is made unduly difficult and unpredictable, the access goals will not be met. Considering the common goal of both industry and Member States to ensure wide patient access in the EU, we expect this change to contribute positively to the negotiations between the two parties and that blocking the incentive will indeed be reserved to the objectively justified situations. Ultimately, any alleged abusive behaviour can be subject to judicial control at Member State level and a revision clause could be built in to take stock of performance after a certain time.

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[141] The Transparency Directive allows 180 days for Member States to make their pricing and reimbursement decision, therefore filing at 18 months shall allow a market launch in 2 years.

[142] EFPIA Access to medicines (efpia.eu)

[143] We have seen examples in the past that a small member state was offered 4-6 times higher price than Germany.

The specific situation of **SMEs and not-for-profit entities** and their capacity to engage in multiple parallel pricing negotiations will be taken into account by allowing longer period to comply with the market launch conditions, **3 years from authorisation**.

We can expect this measure to spur a **long term behavioural change** of both industry and public actors to engage more towards increasing access, which is a strong demand from public authorities and citizens. Ideally, launching new medicines in all 27 Member States in a timely fashion would be the standard for all medicines, and not only for the 35% of them (with RP as the last layer of protection) that are directly affected by the incentive.

Such incentive has not yet been tested on the market, however stakeholders were willing to share their views about it. Public authorities in the targeted survey and a workshop were overall positive to linking incentives with market launch, while industry was against. For industry, access depends on factors that are not under their control (e.g. variations in national reimbursement decisions); however, they agreed that the measure can be a financial incentive to launch in smaller markets. To address this concern, the design of the measure includes the safeguards explained above. Civil society organisations, patients, researchers and public authorities considered this measure as very important. They stressed the need to provide 'real' effective access and continuous supplies. Some public authorities argued that this measure should be an obligation. Member States have highlighted in a series of Council conclusions[144] that incentives need to be proportionate to the goal of encouraging innovation while improving patients' access to innovative medicines. They considered that deferred or missed market launches, and business behaviour, including high priced essential medicines pose a high burden for patients and health systems. They called the Commission to evaluate the system and take action.

Would a decreased protection translate into price increase?

Companies may try to increase prices to compensate for a shorter RP if they do not get the incentive, however, this will result in lower volumes sold, less Member States and fewer patients could afford the increased price. Rationally behaving companies should not have different pricing policies because of the length of protection, a higher price does not automatically lead to higher profits[145].

The Evaluation[146] compared prices of the top-selling almost 200 medicines in the EU, US, Australia, Canada, Japan and Switzerland. **We could not find any correlation between the prices and data protection periods**, however in the US prices for the same medicines are often 3-5 times higher than in other countries despite offering very long effective protection[147].

6.1.1.4 Measures addressing AMR (Options A, B, C)

Annex 15 describes innovative financing solutions – outside of the general pharmaceutical legislation – introduced in some EU Member States and some international initiatives to incentivise development of new antimicrobials.

Pay or play model (Option B)

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[144] Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member Stateshttps://www.consilium.europa.eu/en/press/press-releases/2016/06/17/epsco-conclusions-balance-pharmaceutical-system/; Council conclusions on innovation for the benefit of patients: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52014XG1206(03)&from=SK; Conclusions on strengthening the European Health Union: https://data.consilium.europa.eu/doc/document/ST-14029-2021-INIT/en/pdf

[145] A recent and extreme example is the case of Zynteglo®, a gene therapy authorised in the EU in 2019. The company insisted on a high price (more than €1m) that not even the richest markets were willing to pay, and led to zero sales and zero profits in the EU market.

[146] Notably the indicator AFF-1.2 on p100 of Annex 10, Analytical report.

[147] On the other hand, more new medicines and much faster than in the EU are made available to US patients, at least for those who can afford a premium insurance scheme.

In this model, a company co-finances the innovation and either holds an antimicrobial in its portfolio or it pays to a fund to finance the development of novel antimicrobials. A recent analysis[148] found that a pay or play model would impose additional costs on EU pharmaceutical businesses with the risk that the costs would be passed on to health systems (insurers and/or patients) through higher prices 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 likely view the surcharge as an unavoidable cost to be factored into their wider pricing policies. In addition, the fund would generate only limited amount of money so that only a 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).

The pay or play model would not directly increase the number of novel antimicrobials and may increase prices of other medicines, creating substantial social costs. The benefits of the incentive would depend on the use of the collective fund, which is 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, they raised concerns that the model would unfairly penalise companies (particularly SMEs) with no expertise in AMR product development.

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

These would benefit in particular SMEs as they would be rewarded as early as regulatory approval for a new antimicrobial. It would also increase the attractiveness of the field for private financing mechanisms, such as venture capital. According to EFPIA[149], the value of such voucher in the EU should be between €280 m and €440 m per product, based on assumptions around a "fair European share", a proportionate contribution of the EU towards the development of a novel antimicrobial product that would benefit the global population. The voucher could be an important part of the EU response to AMR for the **development of novel antimicrobials**, i.e. not just products that are already in the (weak) pipeline. Such response could also include other initiatives, outside the legislation, such as joint procurement for antimicrobials under HERA to **guarantee revenue** paid to producers **for ensuring access** to existing or new antimicrobials.

Cost and benefit of transferable exclusivity vouchers

To understand the impacts of a voucher, the model of RP extension has been used, with some adjustments. The buyers and thus users of the vouchers would be companies that hold the products with the highest sales among the RP protected medicines. The commercial lifecycle of these products differs from the average, as their market is more attractive for generics/biosimilars. It results in a faster erosion of price and sales, therefore an additional year of protection has a higher value for the originator, and a higher cost for the other stakeholders. We have examined over a 10-year period the highest selling RP protected medicines, and identified the champions for each year. We used in our model a €545 m average peak annual sales for these champions (More details on the model in Annex 4). **Table 8** summarises the effects to the various stakeholders.

Table 8 – Changes to baseline with the voucher and value of voucher

Stakeholder	change	change %
Originator gross profit	**+€387 m**	+10.1%
Generic gross profit	**-€54 m**	-23%
Cost to public payer	**+€283 m**	+4.7%
Patients monetised gain/loss	-€158 m	-3.8%
Patient + payer monetised gain/loss	-€441 m	-7.3%

[148] (https://academic.oup.com/cid/article/71/8/1994/5736365?login=true).

[149] Representative of innovative industry: A new EU pull incentive to address Anti-microbial Resistabce (AMR) Recommendations from EFPIA.

The €545m 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 €283m 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 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 RP protected medicines in a given year, we can visualise the impact. (**Figure 7, Table 9**).

Figure 7 Distribution of buyer and seller advantage if 1 or 3 vouchers issued a year

Table 9 – share of value among buyer, seller and the public

1 voucher		**3 vouchers**	Voucher 1	Voucher 2	Voucher 3	Total
Seller rent	**€205 m**	Seller rent	€89 m	€89 m	€89 m	**€267 m**
Buyer rent	**€154 m**	Buyer rent	€270 m	€97 m	€50 m	**€417 m**
Cost to public in nominal value	**€283 m**	Cost to public in nominal value	€283 m	€147 m	€109 m	**€539 m**
Cost to public incl. unserved patients	**€441 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.

The voucher not only generously rewards the buyer without merits, but the public has to pay a high price to the developer. We present the cost for the public payer to reward the developer with 1€ in **Table 10** 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 10 - 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[150].

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 put on balance with the current **€1.5bn in health care costs and productivity losses from AMR**[151] 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. Benefits are further detailed in the social impact section (6.2).

In the consultations, some civil society organisations concurred that company profits would rise as a result of a transferable voucher and thus create an incentive to develop products to 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 the costs for public health systems. Alternative solutions such as small milestone rewards or longer regulator protection periods should be considered according to civil society organisations, public authorities, healthcare professionals and citizens. In the public consultation, innovator industry defended the benefits of transferable vouchers. Public authorities, civil society and the generics industry expressed opposing views about the voucher citing arguments linked to overcompensation, high cost to health systems and loss of competitiveness for generics.

Impact of prudent use measures

The use of smaller packages would enable more sustainable use of antimicrobials and less release of unused antimicrobials in the environment. On the opposite side, it would increase manufacturing costs and package waste. Stricter rules on prescription of antimicrobials and mandatory use of diagnostics would impact prescription behaviour positively, however, it would also result in switching from broader spectrum antimicrobials to more specific (and expensive) antimicrobials and costly diagnostic tests. Requirements to adopt AMR lifecycle monitoring plans[152] would help the EU reduce its overall consumption of antimicrobials and hence AMR. This measure would come with some cost both to businesses and Member States, however the establishment of appropriate mechanisms to share information with regulators could mitigate this burden.

6.1.1.5 Horizontal measures[153]

The horizontal measures are intended to deliver wide-ranging improvements in terms of efficiency and effectiveness. **Table 11** presents a qualitative assessment of the benefits of each of the 10 pivotal horizontal measures, rating the likely benefits – against the baseline – on a 3-point scale (High, Medium, Low) 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.

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[150] Unserved patients refer to those patients that were not served due to the delayed entry of generics, i.e. the lost volume

[151] 201020_EUJAMRAI_policy-brief_WP7_appropriate-use-of-antibiotics-one-health-perspective.pdf (eu-jamrai.eu)

[152] Such AMR lifecycle monitoring plan could cover stewardship, risk mitigation measures to limit AMR, report resistance to the antimicrobial, educational material to inform more efficient use, monitoring and reporting on the use.

[153] Detailed analysis of the measures are in Annex 11.

Table 11 - Qualitative assessment of the benefits of pivotal horizontal measures for key stakeholders

	Business	EMA	NCAs	SMEs	Health Systems	Environ-ment
Streamlining and de-duplication						
#1 Streamlining of procedures	H	M	M	H	L	L
#2 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
Digitisation						
#5 Legal basis to allow network to analyse real world evidence	M	M	H	H	H	M
#6 Legal basis for setting up electronic product information for medicines	L	M	M	L	M	L
#7 Electronic submission of applications	H	H	M	H	L	L
Enhanced support and regulatory flexibility						
#8 Optimise regulatory support to SMEs and non-commercial organisations	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

Stakeholders' views are more convergent vis-a-vis horizontal measures. Reducing regulatory burden (e.g. through efficient governance of EMA committees and authorisation procedures, elimination of the renewal procedure and digitisation) can be considered as common ground both for industry and public authorities and improve the competitiveness of the EU as a global destination for businesses.

The introduction of electronic product information is supported by all stakeholder groups. For healthcare professionals and patients it is important to keep paper package leaflets in certain cases to ensure access to information for all patients. Member States want that the different national levels of 'digital readiness' are respected. The electronic product information will complement the current paper package leaflet of authorised, statutory information for each medicine, though in certain cases Member States could allow electronic product information only. It could have positive effects on shortages and will be more appropriate to the EU's multi-lingual environment. The electronic product information will have a limited, positive environmental impact from reducing the number of paper package leaflets and streamlining the logistics chain.

An EU-wide centrally coordinated process for early dialogue among authorities responsible for clinical trials, marketing authorisation, health technology assessment, and pricing and reimbursement will improve business predictability for companies (including SMEs). Such early dialogues are expected to provide guidance to companies on evidence generation along the medicine lifecycle. Clearer and more coherent evidence requirements will reduce uncertainty and investment risks for developers of innovative medicines, in particular in areas of unmet medical need (where developers often already face significant challenges due to the complexity of the diseases concerned). Early dialogues can therefore contribute to guiding and steering the investment and clinical development decisions of companies towards innovations with high added value for health systems and patients. They will also ultimately contribute to timely patient access to innovative medicines by providing clarity on evidence requirements of downstream actors for timely generation of appropriate evidence, facilitating and speeding up their decision-making.

Overall, these measures are expected to generate net benefit of up to €100m a year, shared among businesses and authorities (Annex 3) in the best case scenario.

6.1.2 Option A – combined impact of the measures

Conduct of business: Retention of the current period of RP for all new medicines and special incentives for UMN, comparative trials and EU-wide product launch would have a positive effect on businesses that can benefit from the incentives. However, this would 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.

Public authorities: Incentives providing longer data protection periods in general (whether to promote innovation or EU-wide market launch) would carry a significant cost to national health systems and payers by delaying generic entry. There would 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 for comparative trials would offset an additional period of high prices for payers against a more robust evidence base for HTAs and payers.

The high cost of a transferable voucher given to developers of novel antimicrobials would be borne by healthcare payers. 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.

Sectoral competitiveness, trade and investment flows: The special incentives for UMN, including the transferable voucher and EU-wide market launch are expected to improve competitiveness and attractiveness of the EU pharmaceutical sector, especially SMEs and support increased investment in medicine development to address UMN and AMR respectively.

Research and innovation: 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 a medicine and its comparators.

Functioning of the internal market: The slight increase in the number of new innovative centrally authorised medicines owing to incentives and the increase in access to those medicines through the market launch incentive will 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.

Administrative burden on business: Changes to RP for medicines to make them contingent on market launch should be expected to make the system considerably more complex. It will require reporting by MAHs on market launches resulting in higher administration costs. The horizontal measures however would significantly cut red tape.

SMEs: 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. As mentioned in the 'SME test' Appendix D of Annex 12, other measures in Option A present no major positive or negative impacts.

6.1.3 Option B – combined impact of the measures

Conduct of business**:** For originators affected by the reduced RP, the overall income and profitability from new medicines would be significantly reduced (22% loss in commercial value). It may happen that developers increase their prices 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.

Public authorities: 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 monitoring shortages will require a significant investment from authorities. However, shortages avoided reduce the burden of finding substitutes or new suppliers.

Sectoral competitiveness, trade and investment flows: Reduction in the standard regulatory protection could weaken the global competitiveness of EU based originators overall, compared with the current situation. The reduction will affect equally all companies selling their products in the EU, no matter where their R&D is placed. 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.

Research and innovation: The reduction of the regulatory protection would cause an estimated annual €670m loss for R&D.

Functioning of the internal market: Earlier generic entry due to lowering of the standard data protection period for most new medicines (except those addressing an 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.

Administrative burden on business: 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 methodology that businesses would need to follow. The transparency requirements would put an additional burden on companies. The horizontal measures however (discussed in section 8) would significantly cut red tape.

Obligations on MAHs to place centrally authorised medicines on the market in a majority of Member States may carry additional costs to the MAH that would have to bear the consequences of the reduced regulatory protection. The MAH will also have to provide additional information to regulators to demonstrate their compliance with obligations, raising costs. These obligations will also increase the costs to MAHs for interacting with HTA bodies in the Member States.

Administrative costs would also be expected for AMR measures in relation to the pay or play model and prudent use measure, e.g. monitoring of consumption.

SMEs: 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. On the other hand SMEs could benefit from the UMN incentive as they are often willing to invest in more risky R&D.

Obligations for market launch in a minimum number of Member States, including smaller markets, may be more challenging to meet for SMEs that do not yet have market presence.

6.1.4 Option C – combined impact of the measures

Conduct of business: 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. In addition, generic companies have the opportunity to enter the market earlier when originators have not fulfilled the RP prolongation conditions.

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.

Public authorities: It is a win-win for public authorities, partly because their role in market launch is strengthened and no longer depending on companies only. Either after a successful price or reimbursement negotiation the medicine will become available to patients, or if there is no compliance, the measure will allow earlier market entry of generics and biosimilars thus reducing prices through generic and biosimilar competition. The strengthened role of Member States comes though with increased responsibilities for timely decisions at national level. The special incentive for comparative trials would lead to increased availability of such data to regulators at time of authorisation and may provide a better evidence base for HTAs and payers.

There may be additional costs 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 shortages will increase the complexity and administrative burden of monitoring shortages for Member States' authorities, although use of a common template and streamlined reporting for reporting could enable cost savings in the long term. Monitoring of supply at Member State level is economically advantageous for NCAs as it builds upon the existing system of national monitoring.

To support market launch of products in Member States, HTA, pricing and reimbursement bodies would have to conduct a greater number of procedures, in a reduced time period. It is observed that national pricing and reimbursement decisions for new medicines often take longer than the legally maximum of 180 days.[154] This can be partly offset by the efficiencies in the new HTA regulation, in particular better sharing of evidence on the therapeutic benefits of the treatment. Greater transparency around public support for clinical trials would strengthen pricing and reimbursement agencies' negotiating position with MAHs.

Member States would have new burden from supplying marketing authorisation holders with confirmations, refusals or waivers on the compliance with conditions for market launch extension. For AMR, public authorities would need extra capacity to assess AMR lifecycle monitoring plans.

The EMA and NCAs may require additional capacity and expertise or incur greater administrative burden in reviewing and assessing products based on the additional requirements for ERA and GMP (AMR aspects).

Sectoral competitiveness, trade and investment flows: By providing additional incentives (UMN, AMR, comparative trial) companies could get the same regulatory protection period as in the

[154] The Directive 89/105/CEE sets a maximum period of 180 days. For compliance issues see e.g. SWD(2012) 29 final.

baseline (8+2), and the EU pharmaceutical sector would remain attractive. In recent years, global venture capital investment has seen accelerating growth driven by advances in drug research and residual unmet need for which it is often easier to demonstrate value to patients/the healthcare systems[155]. The conditional EU-wide market launch incentive would apply to both EU and non-EU based companies, therefore the relative competitiveness of EU companies would not be driven down. The greater obligations and requirements to monitor and prevent shortages (including reporting and stockpiling requirements) and to address environmental challenges could affect more the EU pharmaceutical sector, but these measures are proportionate to achieving the objectives of security of supply of medicines at all times and reducing the environmental impact of pharmaceuticals. The overall balance of the measures on competitiveness would still be positive.

Research and innovation: Impacts on research and innovation would be similar to Option A.

Functioning of the internal market: The increase in the number of new innovative medicines owing to incentives and the increase in access across the EU through the market launch incentive will improve patient coverage and functioning of the internal market. Transferable vouchers would delay the start date of competition for the product to which the voucher is transferred, but the systemic impact would be limited due to the low number of vouchers and products benefiting from them.

Administrative burden on business: Additional regulatory data protection period for medicines contingent on appropriate and continuous supply will require MAHs to seek confirmation of supply from Member States resulting in higher administration costs. Similarly, an increase in notification period for withdrawals (12 months) and shortages (6 months) will increase the administrative burden of reporting shortages for MAHs. Introduction of a common template for reporting withdrawals and shortages could help reduce the additional administrative burden 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 shortage prevention and mitigation plans for all medicines. The horizontal measures however (see section 8) would significantly cut red tape.

Increased transparency around public support for clinical trials is narrower than the proposal under 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 easy to retrieve and thus will incur less substantial administrative costs.

For AMR, prudent use measures would increase the administrative burden for businesses, e.g. for AMR lifecycle monitoring plans. Strengthened ERA would also increase the administrative burden for businesses.

SMEs: There may be additional administrative burden on SMEs to meet the strengthened requirements for ERA. The greatly expanded obligations and requirements for withdrawal/shortage reporting and management would also put a relatively larger burden on SMEs compared to their larger counterparts. On the other hand, SMEs should benefit from the introduction of regulatory sandboxes to support development of innovative products and scientific support from the Agency, as well as fee reductions. Incentives for UMN and AMR are also expected to benefit more SMEs, including biopharmaceutical companies, as they are more active in risky early-stage drug discovery.

6.2 Social impacts

Public health and safety is the key impact assessed under the social dimension of the legislation and includes patients' and health system interests.

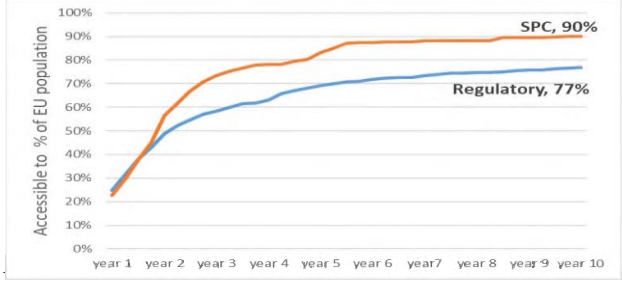


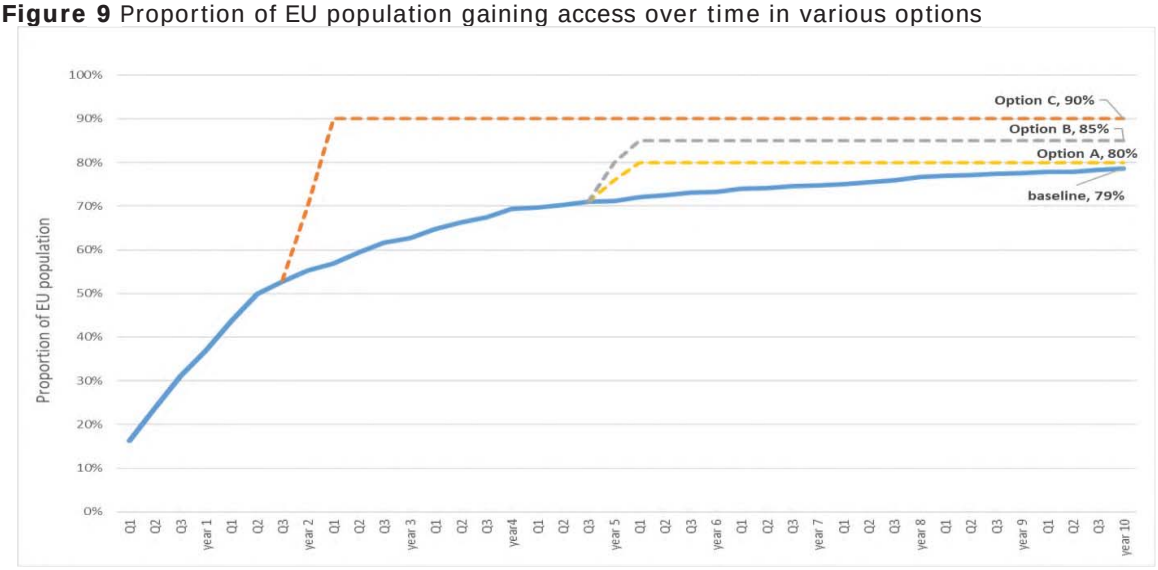
Figure 8 Avg product accessibility to EU population

[155] The financial ecosystem of pharmaceutical R&D: https://www.rijksoverheid.nl/documenten/rapporten/2022/02/28/th

Among the specific objectives of this revision, the one on **access** is directly impacting patients. Analysis of historical data[156] reveals that access to newly authorised medicines in the EU is unequal and there is a large variation in time to access. Moreover, medicines whose last layer of protection is SPC are more accessible than RP protected ones (**Figure 8**).

All policy options seek to address this objective, using either incentives or reducing protection in case of non-compliance. **Figure 9** 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 RP protected medicine.

Figure 9 Proportion of EU population gaining access over time in various options



Based on the assumed compliance rate (Option A – 50%, Option B – 75%[157], Option C - 66%) and time limits to comply, we modelled when and what percentage of the EU population can gain access to the average RP protected medicine (see also section 6.1.1.3).

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 (65.3%). 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[158] compared to the baseline.

The special incentives under Options A and C should support increased R&D investment, especially in areas of UMN and this should flow through to an increase in treatment options and benefit more patients. Comparative trials will 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 and provide better information to healthcare providers for evidence based treatment decisions.

The reduced regulatory protection in Option B would allow earlier generic/biosimilar entry, lower prices and eventually increase the number of patients treated with the concerned 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.

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[156] See Annex 4 (analytical methods and methodology) and Annex 5 (evaluation SWD).
[157] Not all, but for majority of markets.
[158] 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.

The transferable exclusivity voucher in Option A and C would help develop novel antibiotics. While the scheme would apply to a limited number of novel antibiotics which need to be used selectively, i.e. as a last-line therapeutic option (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. So far, these events are sporadic within the EU, but can develop into a dangerous public health emergency in the future. Novel antibiotics on the shelf can protect citizens from such a crisis and the health and economic cost of AMR in case of inaction may be much higher. Moreover, strict conditions for defining a 'novel' antibiotics will help to ensure that this incentive is not just a windfall profit for products already in the (weak) pipeline, but encourage additional investment in research.

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). For AMR, the highest ranking measure to address AMR was introduction of a ‘pay or play’ model (Option B) mostly supported by civil society organisations and opposed by the industry which supported additional market protection period for novel antimicrobials and the transferable exclusivity voucher.

6.3 Environmental impact

To address the issue of pharmaceutical residues in the environment, and in drinking and natural waters, different measures have been considered under the policy options. The general pharmaceutical legislation addresses the impact of pharmaceuticals in the environment through requirements for an environmental risk assessment (ERA) and related conditions of use and mitigation measures along the lifecycle of medicines. These measures complement those under the environmental policy and legislation to reduce the environmental impact of medicines; several specific environmental legal acts are under review, see section 1.1.

A common measure across all policy options is the more prudent prescription rules for antimicrobials, which should result in fewer antibiotics entering the environment.

For Option A, the current **ERA requirements** continue with an additional obligation to include the information on the environmental impact of the supply chain in the application dossier. The impact of Option A would not be very different to the baseline, though a greater environmental awareness of the supply chain actors could be envisaged.

Option B increases the requirements for ERA, by including the assessment of the environmental risk of manufacturing as part of the marketing authorisation process. Option C would in addition strengthen the conditions of use of medicines and include AMR aspects in GMP to allow a more holistic assessment of environmental risk along the pharmaceutical lifecycle.[159]

The overall impact of options B and C should be less residues (e.g. genotoxic substances, antimicrobials) in the environment and less disruptions to the ecosystem and human health. Strengthening the ERA in the general pharmaceutical legislation is expected to have a positive effect by increasing environmental awareness and responsibilities in the pharmaceutical sector. Furthermore, a strengthened ERA will also provide an improved basis for taking environmental risk minimisation measures, enhanced obligations for ERA updates, monitoring of medicines use and conditions for prudent use. Enforcement should be strengthened as well. The inclusion of assessment of environmental risk of manufacturing in the ERA would allow tracking the environmental risks of manufacturing across the supply chain providing a more comprehensive assessment of the potential

[159] Annex 11 describes the assessment of the proposed measures (tables 47 and 64) in qualitative terms.

environmental impact of a new medicine, but the measure could result in high costs and administrative burden and pharmaceutical inspectors may not have expertise to check compliance.

For option C, inclusion of AMR aspects into GMP would help minimise amounts of antibiotics entering the environment via manufacturing and thus prevent or reduce emergence of AMR from manufacturing of medicines. Companies would have additional costs to comply with AMR requirements in GMP and public authorities would have additional enforcement costs.

Some limited positive environmental impacts are expected from digitalisation such as electronic package leaflet and electronic submission of applications in terms of reduced use of paper and streamlining of the logistics chain.

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 on EU actions. There is variable stakeholder support on strengthening the ERA which ranges from support for it to cover all stages of pharmaceutical lifecycle, from raw materials to end-product (public authorities and citizens) to views considering existing measures (controls, benchmarking on the manufacturing and disposal of products in the environment) stringent enough (industry). According to the targeted survey (Annex 2), the inclusion of assessment of environmental risk of manufacturing in the ERA was mostly negatively rated by industry while all other stakeholder groups viewed this option as bringing a positive impact. A workshop conducted for this IA confirmed the general view that there is a tension between reducing regulatory burden while expanding environmental obligations.

The policy options are aligned with the EU climate-neutrality objective and consistent with ensuring progress on adaption to climate change. The policy options aim at reducing medicine residues in the environment and thereby reducing the environmental footprint.

7 HOW DO THE OPTIONS COMPARE?

This section compares the expected impacts of the options in relation to the baseline in terms of their effectiveness, efficiency, coherence, EU-added value, proportionality and subsidiarity.

The comparison focusses on the pivotal elements as these have the most significant impacts and will allow clear differentiation between the options. The horizontal measures together with the pivotal elements respond to the objective of **innovation and** will impact on the objective of reducing regulatory burden and providing a flexible regulatory framework. The other objectives are mainly impacted by the pivotal elements alone. The overall comparison of the options against the relevant criteria is presented in **Table 12**. The complete analysis of all the elements is provided in Annex 11.

Table 12 Overall comparison of policy options

Criteria	Baseline	Policy Option A	Policy Option B	Policy Option C
Effectiveness: contributing to achieving the policy objectives				
Promote innovation,	0	++	-	+
in particular for unmet medical needs	0	+++	0	+++
Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation	0	--	++	+
Ensure access to innovative and established medicines for patients with special attention to enhancing security of supply across the EU	0	+	++	+++
Reduce environmental impact of the pharmaceutical product lifecycle	0	+	++	+++
Reduce regulatory burden and provide a flexible regulatory framework	0	+++	++	++
Effectiveness: other impacts				
Competitiveness, SME, single markets	0	+	+	++
Social impacts (patients, public health and safety)	0	++	+	+++
Environmental impacts	0	+	++	+++

Criteria	Baseline	Policy Option A	Policy Option B	Policy Option C
Efficiency				
Administrative and compliance costs	0	++	++	+
Savings and benefits	0	+	++	+++
Coherence	0	+	++	++
EU added value	0	++	++	+++
Proportionality and subsidiarity	0	+	+	++
Overall	**0**	**+**	**+**	**+++**

For efficiency, effectiveness, coherence and EU added value, the scores are given on the expected magnitude of impact as explained above: + + + being strongly positive, + + positive, + moderately positive, 0 neutral, – moderately negative, – – negative and – – strongly negative.

7.1 Effectiveness

Innovation

Option A offers the same default incentives for innovation as the baseline with some additional ones in particular for UMN and AMR. Overall, Option A is slightly more generous towards innovators, as in this option incentives can be freely cumulated. Option C on the other hand offers lower default incentives for innovation than Option A, however under Option C companies can still get the baseline protection period if they comply with certain conditions (market launch, UMN, comparative trials etc.). In Option C, the maximum period of RP is capped. Option B keeps the baseline protection period for UMN medicines, whereas for other RP protected originator medicines there will be a 15% loss in profits. We estimate that this translates into €670m loss to innovation funding annually. The pay or play model in Option B is considered less effective than the transferable exclusivity voucher of Option A and C in stimulating AMR related innovation. It is important to note that the revision does not affect the incentives pertaining to intellectual property rights (patents and SPCs). These offer IP protection to the invention(s) associated with the medicine and can extend the effective protection period beyond RP. As Figure 3 illustrates, for about half of the medicines on the market, SPC is the protection that expires last. This important incentive for innovation would still be available for most of the products on the market despite a modulation of regulatory incentives. The revised SPC regime will not change the duration, but streamlines the way an SPC can be obtained through a single granting mechanism or a unitary SPC and ensuring legal certainty for innovative companies.

Horizontal measures will facilitate the secondary use of health data, including real-world evidence, for innovators (including SMEs and academia), and for regulatory decision-making. Wider and more systematic access to real world evidence will be integrated in the lifecycle of a medicine, from early stage of development (complementarity with clinical trials data), to authorisation and post-marketing supervision. In this context, the European Health Data Space infrastructure will provide a significant positive economic impact of at least €5.4bn over the next 10 years, stemming from efficiency gains as a results of a less costly access to health data by reusers (€3.4bn), greater information transparency for policy-makers and regulators (€0.8bn), and increased value for patients, healthcare providers and innovators thanks to further reuse of health data[160]. The complementarity of this initiative with the European Health Data Space, via the facilitation of the secondary use of health data, will have a direct benefit for all pharmaceutical companies, including SMEs.

Option C combined with horizontal elements, especially simplification, regulatory flexibilities and digitalisation is more beneficial to innovation compared to the baseline.

[160] COM SWD(2022) 131 final https://data.consilium.europa.eu/doc/document/ST-8751-2022-ADD-3/en/pdf

Affordability

In terms of affordability, the general pharmaceutical legislation has a limited role to play, as pricing and reimbursement of medicines is a Member State prerogative. Nevertheless, the regulatory protection has an impact on affordability, as it delays generic competition and keeps prices higher. As demonstrated in section 6.1, two-thirds of the medicines are protected from generic competition thanks to their SPC or patent protection, therefore any change to the RP would have no effect on them. According to the draft impact assessment on the revision of the SPC legislation, the unitary SPC system would not significantly affect the entry of generics and biosimilars on less attractive (smaller or peripheral) markets in the EU; the larger and more central EU markets usually remain unaffected as SPCs are sought there anyway. This is possibly so as other factors play a far more important role in a decision to enter a market, such as: pricing and reimbursement rules, legal uncertainty connected to the country, quality and readiness of healthcare systems, differences in the value assessment process, overall levels of pharmaceutical spending and size of the market. The additional annual expenditure on medicines that might be a result of wider territorial SPC coverage due to the unitary SPC is estimated at €37m.[161]

With these limitations, Option B offers the most effective measure in terms of affordability, offering €1.13bn direct cost reduction for health payers with the reduced RP period (6+2 years). This reduction of 0.5%-0.6% of the EU pharmaceutical expenditure would heavily impact 20-25%[162] of the new medicines (they would lose 15% of their gross profits) while other, often more profitable, medicines would be unaffected. Option A keeps the baseline protection period. The R&D transparency requirements in option B and C are supposed to indirectly contribute to affordability too, better equipping with additional evidence national bodies for price negotiations.

The market launch in option B is an obligation with no additional period of protection whereas in option C market launch is linked to an incentive. In both cases, if the market launch does not take place, it would at least result in cost savings to the public as non-complying medicines would lose a part of their protection period resulting in an earlier entry of generics or biosimilars. In option A, the market launch incentive would come with an extra €455m 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 is counterbalanced 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.

Options B and C include an expansion of the so-called Bolar provision to facilitate market entry of generic and biosimilar medicines immediately after the expiry of regulatory or intellectual property right protection periods. Market entry of these medicines lower generally the price of the innovator product and are themselves cheaper[163] and thus make savings for the healthcare systems, e.g. in 2020, the list price savings (excluding confidential rebates and discounts) accounted for €5.7bn in savings from biosimilar medicine versus the pre-biosimilar cost of the originator[164].

Option C is the most advantageous by far from a patient/public health perspective, and it represents a fair balance between originator and generic industry, along with public authorities and payers.

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[161] Based on historic data (2010-2021) the country with the most significant estimated impact was Latvia in 2019, where additional spending could reach up to 0.48% of pharmaceutical expenditure, cf. section 6.6.2 of the draft SPC IA.

[162] Those having SPC or patent protection, having an orphan market exclusivity, or having an UMN or no return on investment status in option B would be exempt from the impacts of the decreased RP.

[163] Analytical report, indicator AFF-6, Annex 10.

[164] The Impact of Biosimilar Competition in Europe, December 2021, IQVIA.

Access and shortages

All options result in more and quicker market access of new medicines, compared to the baseline. The least increase is with Option A and that is the costliest measure for the public. Options B and C are not only more effective, but they are synergistic with affordability. In these options, the public wins in either case: more timely access across the EU if companies comply with market launch conditions, or earlier generic competition and affordability if they do not. The gain in access is highest with option C, thanks to the shorter deadline to compliance (2 years) and to the all-EU launch requirement (vs majority of Member States in option B).

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 even goes beyond that, and also requires earlier notification in case of shortages and withdrawals. As such, Option C has the highest positive impact on shortages, followed by B and A. There is a trade-off among shortages and administrative burden, better and more reporting is needed to address shortages but that comes with a certain administrative cost.

Environment

Option A does not impose additional requirements for the ERA, whereas Option B obliges companies to report about the environmental risks of manufacturing too as part of their MA application. Option C goes further than B, demanding more stringent conditions of use for medicines than the baseline. As with the shortages, there is a trade-off among environment protecting measures and administrative burden.

Regarding the impact on AMR, Option C offers the highest safeguards against the impacts of the release of antimicrobials into the environment, followed by option B, and with no impact for option A. All options feature prudent antibiotic use measures, to reduce antibiotics in the environment, and lower the risk of AMR. Options A and C are also the most effective in financing Europe's 'fair share' of the cost for novel antimicrobial development through a transferable exclusivity voucher while in Option B the 'pay or play' model would not directly increase the number of novel antimicrobials and may risk increasing prices in a broad range of medicines without resulting necessarily in the development of novel antimicrobials (while for the voucher this would concern only the product on which the voucher would be applied).

Regulatory burden and providing a flexible regulatory framework

Horizontal measures feature uniformly across the options, and they will represent a very significant burden reduction for companies and public authorities, through streamlining of procedures, digitisation, enhanced support and regulatory flexibility. In terms of regulatory burden, the difference among the options is restricted to the increased requirements due to more stringent shortages and environmental measures, where options C and B score worse than option A. However, this difference compared to the positive impacts from the horizontal measures is minor.

Impacts on competitiveness and SMEs

In terms of effect on **competitiveness**, the proposed incentives do not make a geographic distinction, they equally offer regulatory protection for products developed in the EU, or anywhere in the world which ensures a level playing field between EU-based and third country-based companies. While the EU regulatory framework is attractive for developers, competitiveness also depends on many other factors e.g. tax system and incentives; available grants, loans and other funding (e.g. the European Innovation Council Accelerator); pool of talents; proximity of top academia; clinical trials infrastructures; market size; security of supply chains; favourable reimbursement decisions.

The horizontal measures described in section 5.2.5 (e.g. simplification, digitalisation, elimination of duplications) and those pertaining to innovation and the futureproofing of the legislation (e.g. flexibility of the framework, clarification of scope, sandboxes, codification of rolling reviews and PRIME) are applicable to all options. They are set to enhance the attractiveness of the EU framework globally. In this context, other policies and initiatives working in synergy with this

revision, like the R&I policy, industrial strategy, the EU system of intellectual property rights (patents and supplementary protection periods), the creation of the European Health Data Space, are key factors to promote innovation and EU competitiveness.

In terms of **effects on SMEs,** Option A emphasises support for innovation, but otherwise presents no major positive or negative impacts for SMEs specifically. Option B includes several measures that are expected to negatively impact SMEs disproportionately. In terms of innovation, SME originators may find it more difficult to invest in riskier novel medicines given the reduction in the standard data protection period and their relatively weaker market position when it comes to negotiating prices. In terms of 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. The proposed measures in Option C would be the same for big pharma and SMEs, however some of the measures may have greater impact on SMEs, e.g. due to their limited ability to absorb such a reduction in market protection. Mitigating measures such as longer timeframes to comply with requirements for market launch for example would eliminate any disproportionate burden on SMEs. Regulatory sandboxes and the transferable exclusivity voucher for novel antibiotics could be especially beneficial to SMEs because they are more active in innovative fields than big pharma. Similarly, incentives for UMN would benefit SMEs, which are generally willing to make early-stage investments in areas of high risk, by giving more value to their assets even if they are acquired by big pharma in late-stage development. SMEs already enjoy fee exemptions and reductions for regulatory procedures and through the new horizontal measures SMEs will benefit from optimised scientific support with a greater likelihood of success for authorisation. Overall, with the increasing investment in biopharmaceutical R&D and the increasing share of SMEs among developers, biopharma SMEs in the EU and elsewhere would have excellent prospects for the future.

Overall, Option C scores the highest in the multi-criteria analysis, this option addresses the most effectively the specific objectives of the revision, and has the most positive economic, social and environmental impacts.

7.2 Efficiency analysis

This section compares the cost-effectiveness of the policy measures in the different options, based on the models and calculations in section 6. The data in tables are always compared to the baseline. The measures tackling access and affordability (changes in the regulatory protection period) and the incentives for UNM and AMR are the ones expected to have the most substantive economic impacts on the various stakeholders. Tables 13a, 13b and 13c compare the options with all relevant measures (the cost-benefit analysis of the variation to option C is presented in section 8.1).

Table 13a Cost-benefit table of key measures in **Option A**

Option A	Cost/benefit for public payer and patients	Cost/benefit for originators	Cost/benefit for generic industry
+1 year extension of RP for medicines addressing **UMN**	+ €246m cost + 1-2 new UMN addressing medicines	+ €282 gross profit (3 incentives)	- €39m gross profit
+6 months extension of RP for conducting **comparative clinical trials**	+ €328m cost + faster access and cost saving thanks to improved reimbursement decisions	+ €378m gross profit +€280m cost (8 medicines)	- €52m gross profit
+6 months extension of RP for all EU **market launch**	+€455 m public cost +3% access	+€527 m gross profit (7 complying medicines)	- €71m gross profit
Transferable exclusivity voucher	+€441m cost + 1 novel antibiotic	+€387m gross profit (1 voucher)	- €54m gross profit
Total balance	**+ €1.470m cost** + 1-2 new UMN medicines +comparative data +3% access +1 novel antibiotic	**+€1.294m gross profit**	**- €216m gross profit**

Table 13b Cost-benefit table of key measures in **Option B**

Option B	Cost/benefit for public payer and patients	Cost/benefit for originators	Cost/benefit for generic industry
2 year **reduction of RP** (except for UMN)	+€1860m gain innovation loss	**-€1.970m gross profit** (9-12 medicines)	+€266m gross profit
Loss of RP, if no **market launch** in majority of EU within 5 years	+€681m gain +5% access	**-€842m gross profit** (4 non-complying medicines)	+€101m gross profit
Total balance	**+ €2.541m gain** +5% access innovation loss	**- €2.812m gross profit**	**+€367m gross profit**

Table 13c Cost-benefit table of key measures in **Option C**

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 +15% access	-€469m gross profit (5 non-complying MP)	+€63m gross profit
+1 year extension of RP for medicines addressing **UMN**	+ €246m cost + 1-2 new UMN addressing medicines	+ €282m gross profit (3 incentives)	- €39m gross profit
+6 months extension of RP for conducting **comparative clinical trials**	+ €328m cost + faster access and cost saving thanks to improved reimbursement decisions	+ €378m gross profit +€280m cost (8 medicines)	- €52m gross profit
Transferable exclusivity voucher	+€441m cost + 1 novel antibiotic	+€387m gross profit (1 voucher)	- €54m gross profit
Total balance	**+ €571m cost** + 1-2 new UMN medicines +comparative clinical data +15% access +1 novel antibiotic	**+€298m gross profit**	**- €82m gross profit**

The tables provide an overview of the costs and benefits of the different options and on different stakeholder groups. Whenever it was possible, we presented the cost/benefits in a monetised form, however for certain social benefits putting a monetary value was either not possible or not appropriate. Therefore the societal benefits of new UMN addressing medicines, of improved access, of new innovative antibiotics and of comparative clinical data of new medicines are only mentioned in the table, without a monetary value.

In terms of efficiency, option A delivers quite well on all targets and creates the desired societal benefits, however at a significant cost for the public, missing the affordability target. Option B on the other hand is very cost-efficient for patients and public payers, offering altogether €2.5bn savings to the public, around 1% of the annual pharma expenditure. Option B does improve patient access and UMN medicines would receive a relatively higher support (though unchanged compared to baseline). The savings to the public would be borne mostly by the originator industry.

Option C distributes the cost of the additional societal benefits more evenly among the stakeholders, and also effectively delivers on all objectives. In terms of efficiency, option C offers the most cost-effective mix of policy measures. The variation to option C (presented in section 8.1) equally delivers on all objectives in a cost-efficient manner, with a slightly different distribution of cost to offer more gains for public payers and patients.

Horizontal and other measures

In Annex 3, the analysis concluded that the horizontal measures are – in the best case scenario – expected to generate up to around **€300m savings annually regardless of the selected option**, shared among businesses (one-third) and authorities (two-thirds). Additional administrative costs resulting from measures on shortages and environment would offset as a minimum 10% of these savings (min. €30m additional cost) for businesses; likewise for administrations.

Option C offers the most cost-effective solution to achieve the specific objectives, followed by Options B and A.

7.3 Coherence

Options B and C are consistent with the EU Strategic approach to pharmaceuticals in the environment and complementary to the ongoing revisions of the environmental legislation mentioned in section 1.1. All policy options are coherent with the EU Action Plan on Antimicrobial Resistance[165]**.** All three options contribute to SDG 3 ("health and well-being), SDG 9 ("innovation and infrastructure") and SDG 10 ("reduced inequalities") [166] (section 1).

The objective of patient access to affordable medicines is coherent with the objective of the HTA Regulation on timely patient access. Option C with its incentives for both EU-wide access and comparative clinical trials provides the best alignment followed by Option A.

Through the horizontal measures all options will ensure coherence with the sectorial legislations medicines for rare diseases and for children, EMA fees legislation and with EU legal frameworks on medical devices/in vitro diagnostic and on BTC through efficient interaction and synergies between these regulatory frameworks. In addition, options B and C will create more clarity on the interplay between these legal frameworks through the proposed changes in definitions and classification advice. More details available in Annex 6 with regard to medicines for rare diseased and children and in Annex 9 for BTC.

The access related measures in Option C such as the modulation of incentives or the additional obligations of supply will not only have a positive effect on access but also a systemic effect on public and private actors' behaviour, as explained in section 6. At the same time, the European Health Data Space will provide actors access to harmonised EU health data which unlocks possibilities and efficiencies along the pharmaceutical lifecycle in the development of medicines promoting innovation, in the monitoring of medicines for both regulators and marketing authorisation holders and in evidence generation for downstream decisions after marketing authorisation.

The revision of the general pharmaceutical legislation and the revision of the SPC regime with a unitary SPC are coherent in the objectives to promote innovation and reduce regulatory burden. However, the unitary SPC may have a small negative effect on affordability, as mentioned in section 7.1, and a hypothetical risk[167] of delaying generic or biosimilar entry in markets, where the originator has never been present which would have a negative effect on patient access. On the other hand, the predictability for generic/biosimilar companies will increase in the new SPC regime, through a central SPC database, effectively streamlining decision, less risk of litigation and, if litigation occurs, the avoidance of multiple litigation. Together with the measures undertaken under the pharmaceutical revision to support day 1 entry of generics and biosimilars this will facilitate patient access to those products.

HERA would support solutions from the public procurement side to the market failures in the area of antimicrobials. This unprecedented, combination of policy changes is a result of a combined set of actions in related areas (data, procurement, pharmaceuticals) that complement each other and should not be seen in isolation from each other. Together with the futureproofing and simplification elements of this revision they constitute a holistic response which can be expected to radically upgrade the EU's position globally as a place for medicine innovation.

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[165] A European One Health Action Plan against Antimicrobial Resistance (AMR) (June, 2017), available at: https://ec.europa.eu/health/system/files/2020-01/amr_2017_action-plan_0.pdf

[166] Sustainable development in the European Union, overview of progress towards the SDGs in an EU context, 2022 edition, Eurostat (2022)

[167] The risk is considered hypothetical because it is only in very limited cases that generic or biosimilar medicines enter a market where a SPC has not been requested or granted, i.e. a market where the originator has never been present.

7.4 Proportionality and subsidiarity

All three options are consistent with the EU's right to act under the Treaty of the Functioning of the EU (covering public health protection, the single market 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.

The principle of proportionality is strongly reflected in the discussion of certain trade-offs to be made between the different objectives (section 4). To give an example, trade-offs are inherent between the objective of innovation and affordability often achieved by generic/biosimilar competition. The incentives will remain a key element for innovation but they have to be adapted to better take into account 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.

With regards to subsidiarity, all options pursue the objectives of the revision and provide a clear demarcation between EU level and Member State level actions. They do not propose any change to the national health care systems which are in the exclusive power of Member States (Article 168 TFEU), but certain measure (e.g. transparency requirements, better evidence base, early dialogue between regulators, HTA bodies and payers) will facilitate decisions of Member States in these areas e.g. pricing and reimbursement.

7.5 Limitations of the comparison

There is a level of potential uncertainty in the findings described in section 7 owing to the influence of other contextual factors such as developments in the pharmaceutical sector, other relevant legislations (e.g. HTA Regulation, Urban Waste Water Directive and SPC Regulation) and policies at Member State level (see for details of factors influencing access to affordable medicines – annex 14). While the influence of external factors has been considered in the design of the options and their analysis there is an unavoidable risk that they may impact or delay some of the expected benefits. Their effects and anticipated unintended consequences (e.g. the effect of some measures on prices of medicines, or the effect of conditionality of certain incentives on innovation) are analysed to the extent possible in section 6. 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.

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. 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.

8 PREFERRED OPTION

The impact assessment indicates that policy option C is most effectively addressing all the objectives of the revision of the general pharmaceutical legislation in an efficient and consistent manner. The measures of option C address in a proportionate manner the underlying problem drives; a mapping of measures against problem drivers can be found in Annex 16.

This option proposes a modulated trade-off between incentivising innovation (for both unmet medical need and antimicrobial resistance) and improving access, R&D transparency, and security of supply of medicines as well as reducing the environmental impact of medicines. The costs and benefits of Option C for different stakeholder types are described below. The below section considers the pivotal measures but also **takes into account the other measures assessed in Annex 11**, along with the impacts of the horizontal measures.

The preferred option conforms to the principles of subsidiarity and proportionality. It respects the national competence on the organisation of the Member States' healthcare systems and provides clear demarcations between EU level and Member State level actions. Given the objectives the revision aims to achieve, the trade-offs and new burdens on companies and authorities are acceptable and proportionate.

It is expected that the revision will not change the current legal instruments, i.e. a Directive and a Regulation, for the general pharmaceutical legislation.

8.1 Costs and benefits of the preferred option

Table 14 reviews the most significant costs and benefits stemming from the pivotal measures, and also includes the variation to Option C described in section 5.2.4. The variation would decrease the 2 year conditional protection to 1 year. As a result, the overall protection level moves down by 1 year for all RP protected medicines, and only 1 year protection remains dependent on the launch condition. The 1 conditional year is a lower "prize" for compliance, thus we assumed that fewer medicines would meet the requirement (50% vs. 66% in the default). The variation allows the legislator to consider the impacts on the various stakeholder groups by "moving the cursor".

Table 14a Cost-benefit table of incentives in Option C (6+2+2) compared to baseline (8+2)

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 +15% access	-€469m gross profit (5 non-complying MP)	+€63m gross profit
+1 year extension of RP for medicines addressing **UMN**	+ €246m cost + 1-2 new UMN addressing medicines	+ €282m gross profit (3 incentives)	- €39m gross profit
+6 months extension of RP for conducting **comparative clinical trials**	+ €328m cost + faster access and cost saving thanks to improved reimbursement decisions	+ €378m gross profit +€280m cost (8 medicines)	- €52m gross profit
Transferable exclusivity voucher	+€441m cost + 1 novel antibiotic	+€387m gross profit (1 voucher)	- €54m gross profit
Total balance	**+ €571m cost** + 1-2 new UMN medicines +comparative clinical data +15% access +1 novel antibiotic	**+€298m gross profit**	**- €82m gross profit**

Table 14b 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 +8% access	-€378m gross profit (8 non-complying MP)	+€51m gross profit
+1 year extension of RP for medicines addressing **UMN**	+ €246m cost + 1-2 new UMN addressing medicines	+ €282m gross profit (3 incentives)	- €39m gross profit
+6 months extension of RP for conducting **comparative clinical trials**	+ €328m cost + faster access and cost saving thanks to improved reimbursement decisions	+ €378m gross profit +€280m cost (8 medicines)	- €52m gross profit
Transferable exclusivity voucher	+€441m cost + 1 novel antibiotic	+€387m gross profit (1 voucher)	- €54m gross profit
Total balance	**+ €377m gain** + 1-2 new UMN medicines +comparative clinical data +8% access +1 novel antibiotic	**-€602m gross profit**	**+€39m gross profit**

In the default Option C, the higher market access is achieved without extra cost to the public, even some gains could be expected in case of non-complying medicines. The other incentives would mean an extra cost to the public and to generics, nonetheless it is expected that the indirect benefits from the medicines addressing UMN and faster and better reimbursement decisions, would offset

these costs. The originator companies would have additional costs and benefits from the incentives and the market launch conditionality, and overall they would see an increase in their sales.

In the variation of option C the public would gain significantly compared to the baseline in monetary terms and also enjoy the benefits of the measures. The gains would even allow financing the transferable voucher to support development of novel antimicrobials, without turning the public monetary balance into negative. In the variation, all the costs of the positive social impacts would be translated into reduced revenues for innovator companies, though a significant proportion of the costs would come from non-compliance (e.g. not launching in all EU markets, not carrying out comparative trials), which companies should avoid by complying.

In the variation the cost is put only on a subset of innovator companies, e.g. high-sales, SPC protected medicines would be unaffected. The shorter conditional period for market launch (1 instead of 2 years) means a smaller loss of revenue if companies do not launch in all EU markets, therefore a lower compliance rate (50%) is assumed, resulting in smaller positive effect on patient access. The loss to innovators may translate into slightly less innovation.

Option C and its variant are both cost-effective alternatives to reach all the objectives, the slight difference between the two being the different focus on more access or more affordability (+15% access and €571m more cost vs. +8% access and €377m gains) for the public payer and patients.

Patients, Citizens and Healthcare services

Option C will bring **benefits to patients and citizens** by facilitating the work of healthcare professionals, pharmacies, hospitals and strengthening health. The new measures to promote access across all Member States, by incentivising companies to launch their products on all EU markets, coupled with lower revenues for companies in case of non-compliance will be the first EU-level legislative measure to address the long-standing inequalities **and will increase patient access to innovative medicines**. Facilitating the entry of generics and biosimilars will increase affordability and consequently increase the number of patients treated. The additional incentive for addressing UMN will incentivise the development of more medicines with high public health benefit. Transferable vouchers would lead to development of novel antimicrobials, reduce EU deaths and health system costs due to AMR, and ensure a better preparedness against the increasing threat of resistant bacteria. **Security of supply** measures will improve continuous availability of both critical and non-critical medicines, which will significantly reduce shortages of medicines and benefit patients and healthcare services. Citizens will also benefit from measures taken to reduce the impact of pharmaceuticals on the environment and on public health via the environment through a strengthened environmental risk assessment of medicines along their lifecycle and imposition of appropriate measures to mitigate these risks.

Several other measures discussed in Annex 11 will corroborate the impacts of the pivotal measures: Option C would give a push to repurposing of medicines, as a cost-efficient way to expand therapeutic uses of medicines instead of a rather selective and even risky off-label use (C.1.2., C.1.3.)[168]. Along with the measures facilitating generic entry right after protection expiry (C.1.4., C.5.1., C.5.2., C.5.4., C.5.5.), these will further expand patients' access to medicines. Prudent use measures for **antimicrobials** will help decrease the risk of AMR (C.2.3, C.2.4, C.2.5).

A harmonised system for authorisation of medicines in the EU – through the general pharmaceutical legislation – offers clear EU-added value for public health to enable access to and innovation of medicines. In addition, EU-level action is the most efficient mechanism – in the scope of this revision – to address the concerns Member States have raised about unequal access and affordability, in particular for the centrally authorised medicines.

[168] The codes in brackets refer to the codes of the measures in Annex 11for easier identification

Future proofing measures of Option C will ensure patient safety in areas of rapid technological change, including personalised medicine. Currently, Directive 2001/83/EC covers all 'medicinal products' that are "either prepared industrially or that are manufactured by a method involving an industrial process". "Delinking" the legislation's scope from the way medicines are manufactured will address potential regulatory gaps (without changing the overall scope) due to scientific and technological developments e.g. low-volume products, bedside-manufactured or single batch personalised medicines that do not involve an industrial manufacturing process[169] (C.3.3.). Adapted regulatory pathways, e.g. for less complex cell-based medicinal products, and regulatory sandboxes will also increase the chance of faster patient access to cutting edge medicinal products (C.3.5., C.3.6.). Lastly, allowing electronic product information will bring advances to readability for patients and opportunities for healthcare professionals to communicate information more effectively (Horizontal 6).

Industry

For the originator industry, the modulation of the regulatory protection means a lower standard **duration of regulatory protection**, but companies can achieve a similar/same (depending on the variant in this option) protection as of today if they comply with the **condition to launch in all EU-markets.** The extra condition would entail some additional administrative cost, but that would be somewhat compensated by burden reduction, such as allowing multi-country packs for certain types of medicines (C.4.2.). The special incentive for addressing UMN would offer a longer period of protected sales and thus a higher return on investment, a €282m additional gross profit at industry level. The special incentive for comparative trials will recompense the additional costs from carrying out the trials, and the data will help faster pricing and reimbursement decisions, and earlier market entry. It comes with €378m extra gross profit, but also with €280m cost. The trial data would allow better negotiating position for payers, which may limit company's profits. The transferable exclusivity voucher would reward developers of novel antibiotics, and also the buyers of the vouchers would have gains.

The incentives involving extension of data protection would delay generic entry and keep generic companies out of the market for longer. In the case of UMN incentive of an additional 1 year to originators, it represents a loss of €39m in gross profit per year for generic companies, and €52m 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 (C.1.5, C.1.6.). On the other hand, there should be an increase in R&D activity for generic/biosimilar medicines with a streamlined and clearer regulatory pathway (C.5.1.) and by measures facilitating generic entry right after protection expiry.

Option C also brings greater certainty for businesses by adding clarity and predictability to the regulatory system and the legal pathway (see references to "delinking" in the previous section, as well as adaptation of definitions), streamline the GMO assessment in the authorisation of clinical trials that involve investigational medicines with a GMO component (C.3.2.). These measures should promote **innovation** and attract investment to the EU. SMEs should also benefit from the introduction of regulatory sandboxes to support development of innovative products (C.3.6.) and enhanced support in addition to the current fee reductions.

The preferred option continues to provide a favourable incentive structure for innovation in the EU which remains competitive against what other regions offer. The incentives apply equally to all products, regardless of where they are developed – in the EU or elsewhere; in this regard, the EU competitiveness is not negatively impacted by this option.

[169] Organised in close coordination with other EU legal frameworks (medical devices, substances of human origin) to avoid shifts of therapies that are already regulated

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**, option C introduces several obligations and requirements on MAHs and wholesalers that likely will carry additional costs to these parties including costs associated with warehousing (for stockpiling), operations and capital (C.6.1. to C.6.9.). Stakeholder consultations estimated that increasing warehouse capacity to accommodate 10% additional stock will have a cost of €500k – 1m per warehouse. This policy option will also require more **transparency** and at the same time 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 substantial burden on SMEs in particular.

The horizontal measures on the other hand simplify the regulatory system and reduce burden on industry, reducing compliance costs and administrative burden in the range of €80-160m per year.

For industry, a harmonised and predictable medicines regulatory framework – through the general pharmaceutical legislation – offers clear EU-added value by reducing duplication, simplifying requirements and making the system easier to navigate. The preferred option aims at harmonising requirement concerning shortages.

Despite the new obligations for companies, the preferred option is proportionate when balanced with the efficiency gains, including those from secondary use of health data via the European Health Data Space (see section 7.1), and simplifications introduced and the recognition that other objectives such as patient access and the wider policy ambitions on strategic autonomy and green deal have to be factored in.

Competitiveness and future of innovation under reduced regulatory data protection

Industry stakeholders frequently claim that the reduction of regulatory data protection period would harm future innovation and EU competitiveness. In section 6.1.1.2 we demonstrated that the incentives are agnostic to the geographic origin of the medicines, therefore the reduction would not harm EU companies more than non-EU companies coming to the European market (non-EU companies develop 80% of new medicines introduced to the EU market).

However, lower profits may transform into less innovation at a global scale. Option C results in a slight gain in gross profits but the variation of option C estimates a total loss of €602m in gross profits. Industry re-invests on average 25% of their gross profit into R&D, consequently €150m may be lost for innovation. In 2021 the global pharmaceutical industry has invested €230b in R&D[170], hence the potential loss amounts to 0.07% of global R&D investment. If we wanted to translate this to medicines, only 1 in the next 1500 new medicines would not be developed because of the reduction, a likely invisible loss over the next 15 years.

Public authorities, agencies and payers

Incentives involving additional data protection periods will 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.

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 biosimilar medicines, 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

[170] $238b - EvaluatePharma - World Preview 2022, Outlook to 2028, page 20

voucher are estimated at €2m per year. The workload of pricing and reimbursement agencies would also increase with incentives for market launch driving up the number of applications, while their workload should decrease from better evidence provided from more comparative trials.

Health payers would also benefit from measures to promote post-authorisation studies and comparative trials, which would enable access to evidence that supports pricing and reimbursement decisions for HTA bodies. Rejecting immature marketing authorisation applications at time of validation would reduce workload of medicine regulators (C.9.1.) with estimated savings for the EMA and NCAs at 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 impact of pharmaceuticals will increase workload for EMA and NCAs, increased coordination, joint audits and data sharing could also result in efficiencies.

Academic/research institutions

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 (C.1.2), and obligations will be simplified to facilitate non-commercial entities (e.g. academic) to become MAHs (C.1.2). This option also brings increased requirements of efficacy and safety for use of hospital exemption (e.g. trial data and good manufacturing practices capability), dedicated pathways for less-complex cell based medicinal products and a regulatory sandbox (C.3.5. and C.3.6.), which may impact the activities of academic researchers and research institutions under this exemption, but should support data collection, safe and efficacious use and ATMP development. Academics and research institutions will also benefit from streamlining 'horizontal' measures such as fee reduction and more scientific support to help non-commercial entities to bring innovative medicines to the market.

8.2 REFIT (simplification and improved efficiency)

The review aims at simplifying the regulatory framework and improving its effectiveness and efficiency thereby reducing the administrative costs borne by companies and administrations[171]. The horizontal measures are envisaged in that regard and most of them will act on the core elements of the authorisation and life-cycle procedures, which are at the centre of this legislation. These measures can be grouped as follows:

Streamlining and acceleration of processes and coordination of the network

The proposed abolishment of the sunset clause and renewal of MAs after five years would avoid unnecessary duplication and a burden on MAHs and regulators[172]. The envisaged reduction in the number of notifiable variations could potentially reduce the administrative costs incurred by MAHs and regulators. For generic applications, in order to avoid duplicative assessments of the same data for medicines containing the same active substance, to reduce administrative costs for both administrations and companies, worksharing procedures and a more efficient repeat use procedure are proposed.

[171] A quantification of these costs is presented in Annex 3.

[172] The latter not adding value regarding safety, given the availability of Periodic Safety Update Reports that accumulate safety data and any impacts on the known benefit-risk balance.

The revision will also look to streamline efficient interaction (early dialogue) between different regulatory authorities (EMA, NCAs, HTA, etc.) as well as synergies between different but related regulatory frameworks, e.g. interplay with BTC framework, medical devices (for certain types of products) and health technology assessments. This, together with a structural simplification of EMA (e.g. as regards the committees) should further reduce the administrative costs for both the administration and the business.

Digitalisation

The envisaged revision aims at an enhanced digitisation of different applications to EMA and NCAs, which should result, overall, in cost reductions. This would induce initial, one-off, costs for the administrations but should bring efficiencies and therefore cost reductions with time. Finally, the envisaged use of the electronic product information, i.e. the electronic leaflet as opposed to paper leaflets, should also, in the long term, adduce additional administrative cost reductions.

Adaptations to accommodate new concepts and support SMEs and non-commercial organisation

The revision foresees adaptations to accommodate new concepts and regulatory processes such as adaptive clinical trials, use of real world evidence, and new uses of health data within the regulatory framework. This should result in cost reductions for businesses and administrations. It also envisages optimising the regulatory support to SMEs and non-commercial organisations. This should in turn result in additional reductions of administrative costs for these parties.

8.3 Simplification and burden reduction for businesses, supporting the one in one out approach

This section evaluates the administrative costs induced by the implementation of the *preferred* option for businesses and citizens/patients, in comparison to the baseline. Moreover, all options include some administrative costs related to horizontal elements, which are also evaluated in comparison to the baseline[173].

As regards companies, there are a number of cost reductions resulting from the implementation of the *preferred* option. The reduction is done for reasons of good policy 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 the measures on security of supply.

As regards companies, there are also costs reductions resulting from the implementation of horizontal measures which apply to all the options. The revision aims at simplifying the regulatory framework and improving its effectiveness and efficiency thereby reducing the administrative costs. Annex 3 presents the cost for the horizontal measures that relate most directly to streamlining of processes and coordination of network as well as digitisation 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 €524.5-1,050m for the industry[174].

More specifically:

- The proposed streamlining procedures, including enhanced support, will yield useful cost savings for European pharmaceutical businesses, with estimated cost savings falling in the range of €412.5-825m over the next 15-years.

[173] A quantification of these costs and savings is presented in Annex 3.
[174] Methodological details underpinning the calculations are described in Annex 4.

- 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. Electronic submission will however deliver industry cost savings. These are estimated at €112m-€225m over 15 years.

For citizens/patients, there are many improvements foreseen in all areas of importance[175] but there are no obligations and therefore costs induced by the legislation.

9 HOW WILL ACTUAL IMPACTS BE MONITORED AND EVALUATED?

Indicators for the preferred option, in relation to the core objectives, with suggested data sources and proposed frequency of data collection are presented in table 15. The Commission will review the indicators periodically.

Much of the data collected by EMA are already collected today and published in its annual reports; the new data collected by EMA would result in only a minor additional burden. The burden on the Member States to provide data on the number of shortages, variations and authorised antimicrobials would also be minor, and even further reduced by digitisation. The Commission has access to the IQVIA data and data from the other sources are already being collected.

The development of medicines is a long process and the completion of clinical development plans can take up to 10-15 years. Regulatory protection periods of the preferred option exert their effect up to 11 years after marketing authorisation. For certain measures concerning incentives for innovation, affordability and access, a meaningful evaluation of the revised legislation can take place only 15 years from its application. The Commission will monitor though the indicators and assess the need for an earlier revision.

Table 15 Proposed list of monitoring and evaluation indicators

Specific objective	Monitoring indicators	Data source/frequency
Promote innovation, in particular for UMN	• Number of authorised medicines with new active substance • Number of authorised medicines addressing UMN • Number of authorised antimicrobials • Number of authorised novel antibiotics/transferable vouchers granted • Number of incentives granted for comparative trials • Use of pre-marketing regulatory support (scientific advice, PRIME) • Number of sandboxes used	• EMA data/annual • EMA/annual • EMA and NCAs/annual • EMA/annual • EMA/annual • EMA/annual • EMA/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 • Development of prices of medicines • Member States' pharmaceutical spending	• IQVIA data/biannual • Euripid database, IQVIA data, OECD data/biannual • Eurostat, OECD data/biannual
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 • Number of Member States where basket of medicines (both innovative and established medicines) are launched • Number of market access incentives granted • Number of withdrawal of medicines reported </> 1 year in advance • Number of withdrawals for which, as a result of the	• IQVIA data/biannual • IQVIA data/biannual • EMA and NCAs/annual

[175] The legislation aims at improving the flow of cutting-edge treatments for conditions for which there are no effective treatments 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 support environmental goals. Measures on security of supply will improve access to medicines.

	notification, measures could be identified to mitigate, prevent or alleviate a critical impact on the health system or on patients of the withdrawal • Total number of shortages • Number of shortages reported </> 6 months in advance, specifying number of critical shortages • Number, root cause and duration of critical shortages and identification of measures that mitigated, prevented or alleviated impact on the shortage • Number of NCAs automatically sharing information with the EMA platform and number of NCAs manually submitting information with the EMA platform	• EMA and NCAs/annual • EMA and NCAs/annual • EMA and NCAs/annual • EMA and NCAs/annual • EMA
Reduce the environmental impact of the pharmaceutical product lifecycle	• Presence of medicines residues in the environment • Consumption of antimicrobials • GHG emissions of EU-based pharmaceutical manufacturers	• Information Platform for Chemical Monitoring that includes data on occurrence of pharmaceuticals in the environment • ECDC annual report on antimicrobial consumption • Eurostat/annually
Reduce the regulatory burden and provide a flexible regulatory framework	• Number of variations • Number of meeting of EMA scientific committees and their working parties • Number of early dialogues/ scientific advice including other public authorities than medicine authorities • Number of scientific advice given to SMEs and academia	• EMA, CMDh and NCAs/annually • EMA/annually • EMA/annually • EMA/annually