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COMMISSION STAFF WORKING DOCUMENT

IMPACT ASSESSMENT REPORT

Impact Assessment Report

Accompanying the document

Proposal for a revision of

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 and 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

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GLOSSARY

<i>Term or acronym</i>	<i>Meaning or definition</i>
Accessibility	A medicine becomes accessible to patients once it has been authorised, is being marketed, and can be reimbursed in a Member State.
Affordability	Relates to payments to be made by patients (out of pocket on healthcare or through co-payments) which can be described as affordability at micro level and to the sustainability of public funding of the healthcare sector raised through social security contributions or taxes (affordability at macro level).
AMR	Antimicrobial resistance.
API	Active Pharmaceutical Ingredient.
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).
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	Highest 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.
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.
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.
TEV	Transferable exclusivity voucher
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/EC¹ and Regulation (EC) No 726/2004² (“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 a pivotal part of the pharmaceutical legislation. It governs the granting of marketing authorisations for medicines for human use by defining conditions and procedures to enter and remain on the market. A fundamental principle is that a marketing authorisation is granted only to medicines with a positive benefit-risk balance after assessment of their quality, safety and efficacy.

The most recent comprehensive revision took place in 2004 while targeted revisions on post-authorisation monitoring (pharmacovigilance)³ and on falsified medicines⁴ 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. Science and technology have evolved at a rapid pace. However, there continues to be unmet medical need⁵, 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 also a greater awareness of the environmental impact of medicines. More recently, the COVID-19 pandemic has stress tested the framework. It has had to deliver authorisation of vaccines in very short timeframes and maintain business continuity.

This impact assessment (IA) analyses policy options designed to address shortcomings highlighted in the evaluation⁶ of the general pharmaceutical legislation, taking into account the lessons learnt from the COVID-19 pandemic. It was conducted in a ‘back-to-back’ exercise. The revision is part of the implementation of the Pharmaceutical strategy for Europe⁷ and aims to:

1. Promote innovation, in particular for unmet medical needs, while reducing regulatory burden and the environmental footprint of medicines;
2. Ensure access to innovative and to 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;
3. Create a balanced and competitive system that keeps medicines affordable for health systems while rewarding innovation.

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 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.

⁴ 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.

⁵ Possible criteria to define unmet medical need are described in Annex 6.

⁶ Annex 5.

⁷ [COM\(2020\) 761 final](#).

1.1 Political context

Since the 2004 revision of the general pharmaceutical legislation, certain aspects relating to medicines such as affordability, shortages, or medicine residues in the environment have increasingly become an issue and therefore moved up the political agenda. This is evidenced by recent Council conclusions⁸ and resolutions of the European Parliament⁹.

In 2020 – as a response to the COVID-19 pandemic – the EU announced its ambition to build a European Health Union¹⁰ to better protect EU citizens, to equip the EU and its Member States to better prevent and address future pandemics and to improve the resilience of EU's health systems. The Pharmaceutical strategy for Europe – adopted in November 2020 – is an important building block of the European Health Union. This strategy is more than a response to the COVID-19 pandemic. It is a holistic answer to the current challenges of pharmaceutical policy and includes this revision of the general pharmaceutical legislation and the ongoing revision of the legislation on medicines for children and rare diseases¹¹. The legislative proposals will be presented as a package to ensure the coherence between the initiatives.

Several other ongoing initiatives and activities are relevant. The **research and development stage** for medicines is supported by Horizon Europe¹² – a key funding programme for EU research and innovation – as well as the Innovative Health Initiative, co-funded by Horizon Europe, to promote innovation of medicines. The Mission on Cancer¹³, under Horizon Europe, together with Europe's Beating Cancer Plan¹⁴ will allow to better support development of medicines in this area and promote innovation of medicines. The budget for health research under Horizon Europe amounts to €8 246m¹⁵; additional health research is funded by national programmes. In the EU, private investment in research and development 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 period¹⁶.

The European Health Data Space¹⁷ – the first specific data space to emerge from the European strategy for data¹⁸ – will provide a common framework across Member States for the access to high-quality real world health data. The data that will become accessible are expected to allow progress in research and development of medicines and provide new tools in pharmacovigilance. The revision's aim to better accommodate digital tools also fits the ambitions of 'Shaping Europe's Digital

⁸ 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).

⁹ European Parliament resolution of 2 March 2017 on EU options for improving access to medicine (2016/2057(INI)) https://www.europarl.europa.eu/doceo/document/TA-8-2017-0061_EN.html. Shortages of medicines, 2020/2071(INI).

¹⁰ COM(2020) 724 final, available at https://ec.europa.eu/info/strategy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_en.

¹¹ 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.

¹² 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.

¹³ EU Mission: Cancer, available at [EU Mission: Cancer | European Commission \(europa.eu\)](https://ec.europa.eu/mission-cancer/)

¹⁴ COM/2021/44 final.

¹⁵ European Commission, Directorate-General for Research and Innovation, *Horizon Europe, budget: Horizon Europe - the most ambitious EU research & innovation programme ever*, Publications Office, 2021, <https://data.europa.eu/doi/10.2777/202859>.

¹⁶ Analytical report, indicator RI-8, Annex 10.

¹⁷ COM(2022) 197 final.

¹⁸ COM(2020) 66 final.

Future¹⁹ and the digital transition. The Clinical Trials Regulation²⁰, applicable since January 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 crises²¹ to ensure access to medicines in such crisis. The EMA fees legislation²² is currently under revision. The fees support EMA and national competent authorities and contribute to the sustainability of the EU regulatory system.

The pending revision of the EU legislations on blood, tissues and cells (BTC)²³ is relevant as some substances of human origin are starting materials for medicinal products. Coherence between the two revisions is key to ensure clarity as to which legislation applies to some BTC based therapies.

The European One Health Action Plan against Antimicrobial Resistance (AMR)²⁴ aims to reduce AMR and develop alternative treatments or prevent diseases otherwise treated with antimicrobials. The revision of the general pharmaceutical legislation would contribute to the implementation of this action plan and to addressing **environmental challenges**. Under the European Green Deal²⁵, initiatives such as the EU Action Plan “Towards a Zero Pollution for Air, Water and Soil”²⁶, the revision of the Urban Waste Water Treatment Directive²⁷ and the revision of the list of surface and groundwater pollutants²⁸ under the Water Framework Directive²⁹ to include some medicines, have been launched to protect the environment and public health. Moreover, the EU Strategic Approach to Pharmaceuticals in the Environment³⁰ lists measures to address challenges from medicine residues.

The Intellectual Property Action Plan under the Industrial Strategy³¹ includes the modernisation of the system of supplementary protection certificates (SPC) in the form of a “Unitary SPC”³². SPCs extend patent rights and hence impact the effect of regulatory protection periods provided by the pharmaceutical legislation and therefore patient **access to medicines**. Member States’ decisions on pricing and reimbursement of medicines also influence access. The new Health Technology

¹⁹ COM(2020) 67 final.

²⁰ 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.

²¹ [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.

²² 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.

²³ 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.

²⁴ A European One Health Action Plan against Antimicrobial Resistance (AMR) (June 2017).

²⁵ COM (2019) 640 final.

²⁶ COM/2021/400 final

²⁷ Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment, OJ L 135, 30.5.1991, p. 40.

²⁸ [Integrated water management – revised lists of surface and groundwater pollutants \(europa.eu\)](#).

²⁹ 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

³⁰ COM(2019) 128 final.

³¹ COM(2021) 350 final.

³² [Medicinal & plant protection products – singles procedure for the granting of SPCs](#)

Assessment (HTA) Regulation³³ will engage national HTA bodies in joint clinical assessment which will 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.

Finally, this initiative supports the United Nations' Sustainable Development Goals (SDGs)³⁴ 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

The general pharmaceutical legislation regulates the authorisation, manufacturing, distribution and monitoring of medicines. It also provides regulatory protection periods to reward innovative medicines³⁵. The legislation is based on cooperation and division of responsibilities between the EU and Member States. It provides for different pathways for an authorisation at EU and at Member State level.³⁶ Member States are moreover responsible for the authorisation of manufacturers and wholesale distributors and they conduct inspections of companies. 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 frameworks. Of particular importance are the complementary, *specialised* legislation for medicines for rare diseases, medicines for children and advanced therapy medicines. The general legislation applies to these specialised medicines, while the specialised frameworks provide additional measures to address specific characteristics of those medicines. The ongoing revision of the legislation on medicines for rare diseases and medicines for children are coherent with the revision of the general pharmaceutical legislation in its aims to address unmet medical needs and improve patient access to medicines; a description of the coherence between the initiatives can be found in Annex 6.

The authorisation and conduct of clinical trials supporting marketing authorisation applications fall under the Clinical Trial Regulation. Moreover, medicines may use BTC as starting materials or integrate medical devices and refer to in-vitro diagnostics. For access, intellectual property frameworks (patents and SPCs) as well as the HTA Regulation and the 'Transparency' Directive³⁷ play a role. A description of the pharmaceutical ecosystem and legislative landscape can be found in Annex 8 together with an overview of the lifecycle of a medicine in Annex 9.

³³ 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.

³⁴ [Home - United Nations Sustainable Development](#)

³⁵ These regulatory protection periods are described in section 6.1 and in the evaluation SWD, section 3.3, Annex 5.

³⁶ 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.

³⁷ 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.

2 PROBLEM DEFINITION

2.1 What are the problems?

The evaluation of the general pharmaceutical legislation showed that the legislation continues to contribute and 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 all objectives of the 2004 revision. The objective to ensure quality, safety and efficacy of medicines was achieved to the largest extent, while that to ensure patient access to medicines in all Member States was achieved only to a limited extent. As to ensuring the competitive functioning of the internal market and attractiveness in a global context, the legislation has performed to a moderate extent. In general, 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 pharmaceutical 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 exist, e.g. the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

Medical needs of patients are not sufficiently met

The evaluation showed that the legislation has been less relevant to ensure development and authorisation of medicines addressing unmet medical needs, including novel antimicrobials.

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 needs³⁸. However, there continue to be diseases with no or only few treatment options, e.g. neurodegenerative diseases such as Alzheimer's disease. These unmet medical needs affect millions of EU citizens³⁹. In the public consultation⁴⁰, all stakeholders found that the legislation moderately promotes the development of medicines for unmet medical needs, with industry having the most positive view in that regard.

An important area of unmet medical needs are 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 1.5 billion euro every year in healthcare costs and productivity losses⁴¹.

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 such as strategic decisions by companies whether and when to launch a product in a given Member State and national pricing and reimbursement policies.

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,

³⁸ Analytical report, indicator RI-9, Annex 10.

³⁹ 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 (alzheimereurope.org).

⁴⁰ https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Evaluation-and-revision-of-the-general-pharmaceutical-legislation/public-consultation_en.

⁴¹ A European One Health Action Plan against Antimicrobial Resistance (AMR) (June 2017).

primarily generic medicines, were authorised through mutual recognition and decentralised procedures in the same period⁴². However, patient access to medicines varies considerably across the EU⁴³. The number of EU countries in which CAPs are launched has been steadily decreasing⁴⁴. Substantial differences have been reported in terms of time to entry on the market⁴⁵.

Most medicines are – after authorisation – subject to national pricing and reimbursement decisions and, in selected cases, also HTA. The evidence requirements for these decisions (on relative or cost effectiveness) are different than for the authorisation of medicines, which is based on a positive benefit-risk balance and supported by the data submitted, as per the requirements set by the general pharmaceutical legislation. 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.

Evidence⁴⁶ 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, like Romania, had fewer than 50 of these available⁴⁷. The time to patient access is also significantly longer for most of these latter countries, at 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.

Most of the nationally authorised medicines are generic medicines⁴⁸. These medicines – and biosimilar medicines – can be marketed only after the expiry of regulatory and other intellectual property protection periods. Low volume markets still experience limited access to generics.

Stakeholders agree that there is still room for improvement in terms of access. The legislation is seen to have underperformed by most responders in the targeted survey, except industry.

Affordability of medicines is a challenge for health systems

Innovative medicines are often costly. Medicine prices vary significantly between Member States. The desk research suggests for example an almost 11-fold difference between interferone-beta list prices in Germany (€1451.17) and Croatia (€132.77)⁴⁹. For a sample of medicines, the same study showed that list prices were the highest in Germany and the cheapest in many different EU countries but never in the poorest ones like Bulgaria or Romania⁵⁰. The medicines analysed were unaffordable for many EU health care systems or citizens. Pharmaceutical budgets also put pressure on health

⁴² Analytical report, indicator ACC-1, Annex 10.

⁴³ Technopolis Evaluation study report, figure 10, 2022.

⁴⁴ 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>

⁴⁵ Bergmann et al., 2016, Ferrario (2016). Access to innovative oncology medicines in Europe. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 27(2), 353-356. <https://doi.org/10.1093/ANNONC/MDV547>

⁴⁶ Data from European Federation of Pharmaceutical Industries (EFPIA) and Associations and IQVIA.

⁴⁷ Newton et al. (2021). EFPIA Patients W.A.I.T. Indicator 2020 Survey.

⁴⁸ 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.

⁴⁹ Such list prices do not include the confidential rebates (if they exist) or ‘price freezes’ and may therefore not correspond to the actual price.

⁵⁰ Zaprutko T, Kopciuch D, Kus K, et al. Affordability of medicines in the European Union. *PLoS One*. 2017;12(2):e0172753.

systems. Medicines in the hospital account for over 20-30% of hospital expenditures and are growing⁵¹.

Against this backdrop, generic and biosimilar entry and competition can be an important factor to achieve lower prices, broadening patients' access and alleviating healthcare costs⁵². In the EU, the share of generics in total medicinal products sales revenue modestly increased (from 13% to 16%) between 2002-2020⁵³. An analysis shows that the EU is on a similar trend as other comparable markets (Japan and USA). However, the evaluation suggests that further efforts can be made to fully exploit the savings generated by generic and biosimilar competition; though measures in this regard are primarily outside the scope of the general pharmaceutical legislation.

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 2019⁵⁴. There are a number of root causes. This includes 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, ultimately are putting patients at risk of sub-optimal care and health systems at risk of higher healthcare costs⁵⁵.

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

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 least effective in addressing issues related to security of supply and medicine shortages.

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, e.g. the expansion of the number of EMA scientific committees and their interactions⁵⁶. New types of medicines (e.g. personalised medicines), approaches and processes, which may raise questions about whether they meet the medicinal product scope or definitions and whether they fully fit within the legislation, can find themselves subject to unintended barriers to innovation, development, production or marketing authorisation. Products combining medicines with technologies regulated

⁵¹ European Commission, State of health in the EU: companion report 2019 (ISBN 978-92-76-10194-9)

⁵² IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

⁵³ Evaluation SWD, section 4.1.1.4, Annex 5.

⁵⁴ 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.

⁵⁵ 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>.

⁵⁶ COM(2021) 497 final.

under other frameworks (e.g. medical devices with artificial intelligence) or products using new platform technologies⁵⁷ 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.

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

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. National competent authorities pointed to a very complex governance system for EU telematics.

An assessment of the current authorisation system⁵⁸ 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 fee incentives exist for SMEs⁵⁹.

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, particularly in relation to antimicrobial resistance, to human health. Residues of medicines may enter the environment during their manufacturing, use by patients and disposal, with the largest source being the use⁶⁰. 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 sources⁶¹. Traces have also been found in drinking water. Residues of medicines in the environment is a global problem⁶². The current requirement for an environmental risk assessment (ERA) accompanying the application for marketing authorisation has been found to include some weaknesses as regards compliance and the content and scope of the ERA.

In the targeted consultations, the stakeholders (industry, civil society and public authorities) ranked reducing the environmental footprint 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.

⁵⁷ 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.

⁵⁸ COM(2021) 497 final.

⁵⁹ Commission Regulation (EC) No 2049/2005 provides for specific support for SMEs, including an SME Office in the EMA and fee reductions and deferrals. Further fee incentives for SMEs are provided in the Rules for implementation of the EMA fee regulation (Council Regulation (EC) No 297/95) and in the EMA pharmacovigilance fee regulation (Regulation (EU) No 658/2014).

⁶⁰ COM(2019) 128 final.

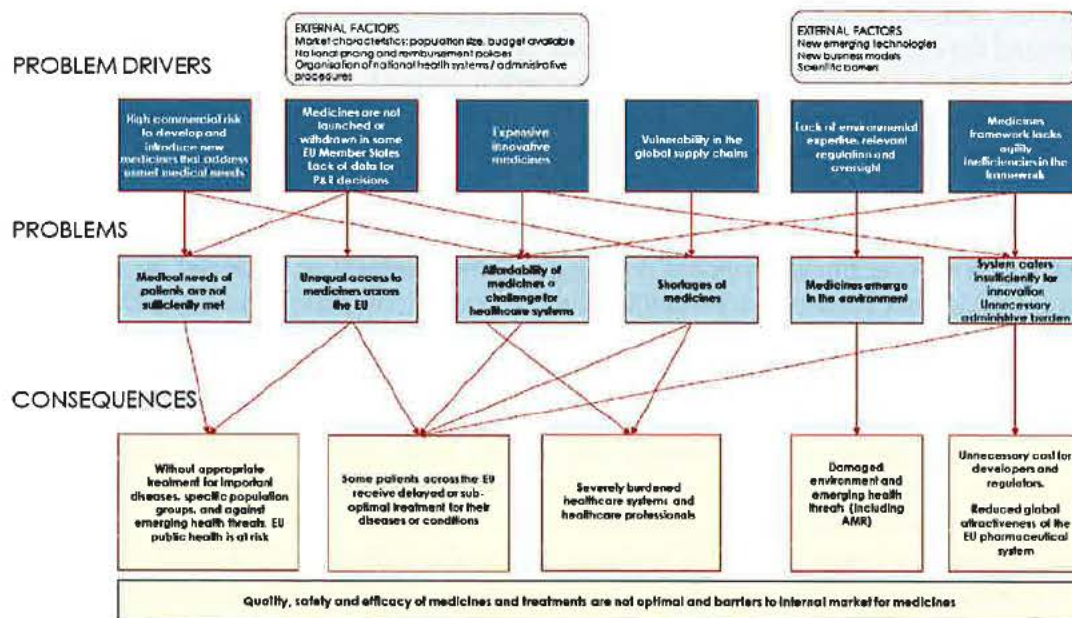
⁶¹ Analytical report, indicator E-1, Annex 10.

⁶² Idem.

2.2 What are the problem drivers?

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

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



Despite the fast-paced advances in science and technology, for some diseases, **scientific barriers** exist to develop medicines to treat or cure diseases such as Alzheimer's disease. These scientific barriers are an external factor outside of the scope of the general pharmaceutical legislation.

While the EU has a world-leading, research-intensive pharmaceutical industry⁶³, the rising costs and complexity of medicines research is affecting pipelines, forcing companies to invest more heavily in R&D, while also increasing the price of many new treatments⁶⁴. This has increased the **commercial risk of developing and introducing new medicines** addressing unmet medical need.

For antimicrobials, there is a weak global pipeline of major new classes of antimicrobials because of evident and growing market failures, with an evident gap between the typical cost and scale of the scientific challenge involved in developing new antimicrobials and the typical income and profit that can be derived from sales of these products as healthcare systems want to keep new antimicrobials in reserve or limit their use.

A key problem driver is that authorised **medicines are not launched in all Member States or subsequently withdrawn**. External factors, such as market size, purchasing power, national pricing and reimbursement policies and tax rates⁶⁵ impact the companies' strategies in that regard.

Pharmaceutical expenditure is largely subsidised by national health systems in order to ensure the adequate provision of medicines to all their respective citizens. In this context, Member States adopt measures to regulate the prices of medicines and the conditions of their public funding based on their

⁶³ The Pharmaceutical Industry in Figures, Key Data 2021 (EFPIA, 2021).

⁶⁴ 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>.

⁶⁵ Zaprutko T, Kopciuch D, Kus K, et al. Affordability of medicines in the European Union. *PLoS One*. 2017;12(2):e0172753.

exclusive competence in this field (Article 168 TFEU). Such measures influence the prescription and utilisation of medicines in each Member State. Such measures affect the capacity of pharmaceutical companies to sell their products in domestic markets. Industry stakeholders highlight delays in national pricing and reimbursement decisions, contributing to postponing the entry of medicines after the granting of a (central) marketing authorisation. However, **pricing and reimbursement decisions can be delayed by lack of relevant data**. Data requirements for marketing authorisation for medicines and for decision making by HTA bodies, payers and health professionals are different and hence those data generated for marketing authorisation purposes are not always sufficient to demonstrate the added therapeutic benefit during the reimbursement process for new medicines especially if they are expensive, leading potentially to delay of access^{66,67,68}.

New, highly **innovative medicines** may place pressure on public budgets due to their prices. The prices are influenced by factors such as research costs incurred (also for unsuccessful development of medicine), return on investments, national pricing and reimbursement policies and tax rates⁶⁹; of these factors research costs incurred are partially influenced by the pharmaceutical legislation and its documentation/evidence requirements. However, there is a lack of transparency on R&D costs or public contributions to these costs. While R&D costs are not relevant for the assessment of a medicine's benefit-risk balance, information on such costs are relevant for the downstream actors.

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 implementation of provisions related to continuity of supply of medicines, such as the notification requirements and obligation to ensure appropriate and continued supply, varies across Member States, e.g. Italy requires notification of shortages 4 months in advance while Romania requires them at least 6 months in advance⁷⁰.

The **lack of available environmental expertise, relevant regulation and oversight** currently influences the effects medicines use may cause for the environment. 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 form⁷¹. However, different policy instruments are available - beyond the general pharmaceutical legislation - to reduce the environmental footprint of the industry and environmental residues.

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 these 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

⁶⁶ Evidence gaps for drugs and medical devices at market entry in Europe and potential solutions - KCE (fgov.be).

⁶⁷ Bloem LT, Mantel-Teeuwisse AK, Leufkens HGM, De Bruin ML, Klungel OH, Hoekman J. Postauthorization Changes to Specific Obligations of Conditionally Authorized Medicines in the European Union: A Retrospective Cohort Study. *Clin Pharmacol Ther.* 2019;105(2):426-35.

⁶⁸ Banzi R, Gerardi C, Bertele V, Garattini S. Conditional approval of medicines by the EMA. *BMJ.* 2017;357:j2062.

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, 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>.

⁷¹ COM(2019) 128 final.

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, such as electronic product information, which 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. More medicines are expected to be authorised; for centrally authorised medicines this might increase to 40-60 medicines containing new active substances per year⁷², however these medicines will not necessarily address unmet medical needs to a greater extent than today. For example, recently approved antibiotics and the clinical pipeline are insufficient to tackle the increasing emergence and spread of antimicrobial resistance⁷³ and 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 Centre⁷⁴. 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 may continue to be inaccessible at affordable prices. However, many complementary actions outside this legislation have to be taken to address these problems⁷⁵.

Since new scientific and technological developments will continue and may even accelerate, some problems may exacerbate if the legislation is not future-proofed. Current work-arounds will become bottlenecks, especially for complex products. Borderlines between product categories may be more blurred and hence determination of applicable legal frameworks as well as their interaction may become complex, leading to longer development or authorisation processes for innovative medicines and thus a longer time to reach patients. Some of these innovative products may remain unregulated.

If the efficiency of the regulatory system is not improved and administrative burden not reduced, e.g. by digitisation, valuable resource might not be available to facilitate development and to assess 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. 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.

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

⁷² Described in the baseline in section 5.2.

⁷³ Antimicrobial products in clinical development for priority pathogens (April, 2021), available at <https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antibacterial-products-in-clinical-development-for-priority-pathogens>.

⁷⁴ [The Megatrends Hub | Knowledge for policy \(europa.eu\)](https://ec.europa.eu/eurostat/tgm/table.do?tab=table&init=1&language=en&plugin=1)

⁷⁵ E.g. best practice exchange between Member States on pricing, payment and procurement policies.

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.

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 takes advantage of 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 shortages⁷⁶. A harmonised approach at EU level also provides greater potential for incentives for development in the area of unmet needs.

The legislation respects Member States' exclusive competence in the provision of health services, including pricing and reimbursement policies and decisions as well as prescription of medicines.

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, reduced administrative burden and reduced duplication of work⁷⁷.

This revision is expected to bring benefits by addressing unmet medical needs and contributing to reducing the unequal access to medicines across the EU. At the same time, simplification and streamlining of requirements and processes are expected to reduce administrative burden for companies and medicines authorities and hence improve the efficiency of the regulatory system. These benefits and cost-savings can be achieved only by EU action. However, external factors such as national pricing and reimbursement decision and company decisions to launch medicines have great impact on access. Furthermore, the scientific and technological developments as well as company decisions influence the achievement of the objective to address unmet medical need.

⁷⁶ 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>

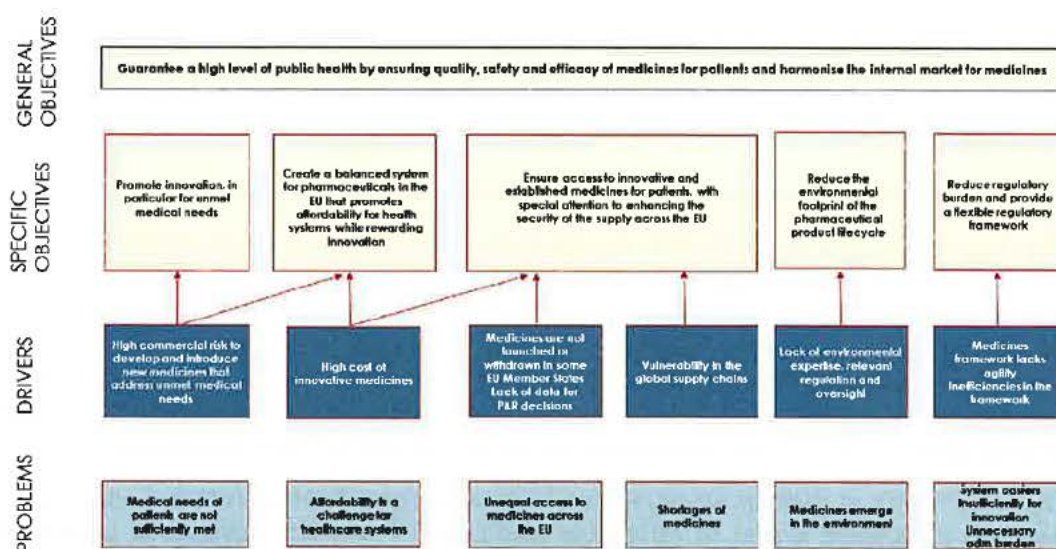
⁷⁷ Evaluation SWD, section 4.2, see Annex 5.

4 OBJECTIVES: WHAT IS TO BE ACHIEVED?

4.1 Introduction

This chapter 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 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). It will enable major biomedical research advances and ensure a pipeline of innovative new medicines for use across the EU. It will also support pharmaceutical R&D and strengthen the competitiveness of the research-based EU pharmaceutical sectors.

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

This objective aims to enable competition, to promote affordability of medicines for healthcare 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.

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, with an additional focus on preventing and addressing shortages of medicines.

4. Reduce the environmental footprint of the pharmaceutical product lifecycle

This objective aims to enhance environmental sustainability of pharmaceuticals through minimising medicine residues in the environment from their production, use, and disposal. This would entail a robust assessment of environmental risks of medicines as well as promoting 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 quality, safety, and efficacy of medicines. Digital by default, leveraging digital technology and the use of electronic product information could support this objective.

Objectives 1, 2 and 5 work in synergy for promotion of 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 environmental footprint are likely to increase the administrative burden. Trade-offs have also to be considered for measures under objective 3 to address the risk of shortages with the objective to reduce 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 Green Deal and Digital agenda and with the right of access to preventive health care and the right to benefit from medical treatment set out in the EU Charter of fundamental rights.

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 were made.

The current system provides incentives⁷⁸ for innovation in terms of data (8 years) and market (2 years) protection to give time to developers to recoup their investment by delaying the entry of generic or biosimilar medicines. These are without prejudice to intellectual property protection and specific rewards and market exclusivity for orphan and paediatric indications. The evaluation found that the harmonised incentives of the current regulatory system had contributed to the growing numbers of applications for new and innovative medicines received by the EMA.

⁷⁸ This is explained in the Evaluation (Annex 5) in chapter 3.2

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

There are no special incentives or obligations for the development of new antimicrobials or prudent use of existing ones, neither for conducting comparative clinical trials.

At present, there are no incentives or obligations on MAHs to place their products on the markets that, on their own, do not offer a sufficient business case.

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 currently has two provisions on continuity of supply of medicines. The first places an obligation on MAHs to notify competent authorities 2 months in advance if they expect a temporary or permanent withdrawal of an authorised medicine from an EU market. The second obliges MAHs and wholesalers to ensure appropriate and continued supplies of authorised medicines, however without effective means to enforce the obligations.

The ERA is the main mechanism within the current legislation for addressing environmental sustainability of pharmaceuticals. It is required for all new MA applications and covers the environmental risks of the use, storage and disposal of pharmaceuticals. No measures currently exist within the general pharmaceutical legislation to supervise the effect of manufacturing. While it provides data on the amount and impact of medicine residues released into the environment and possible risk minimisation measures, some gaps exist with regard to timely enforcement.

5.1.1 Projections

If no changes are made to the current situation, the following projections can be made for the next 10-20 years. Given the long-run nature of medicines development cycles, we can assume historical growth rates, an almost doubling in the numbers of innovative medicines in the last 15 years, will continue to hold in the medium term. As 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.⁷⁹ Rich pipelines translate to more medicine authorisations and market launches, 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.

Within the overall positive outlook for innovation, research efficiency declines, it costs more money and failures to develop a new medicine⁸⁰. Investments in R&D are driven by commercial interest rather than public health needs, leaving important unmet medical needs unaddressed. There is a particularly dry pipeline for antimicrobials⁸¹. According to WHO, drug-resistant diseases already cause at least 700 000 deaths globally a year, including 230 000 deaths from multidrug-resistant tuberculosis, a figure that could increase to 10 million deaths globally per year by 2050 under the most alarming scenario if no action is taken.

Regarding access to medicines, a recurring IQVIA survey⁸² 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. The average delay between market authorisation and patient access can vary by a factor greater than x7 across EU, from as little

⁷⁹ 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022.

⁸⁰ *idem*

⁸¹ Of the 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.

⁸² EFPIA Patients W.A.I.T. Indicator 2021 Survey, available at <https://www.efpia.eu/media/636821/efpia-patients-wait-indicator-final.pdf>

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 increasing⁸³. 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.

If no changes are made to current requirements, the effect of the ERA would remain limited to manage environmental risks.

5.2 Description of the policy options

In order to respond to the specific objectives, we considered more than 70 potential policy measures. They stem from the analysis carried out as part of the evaluation of the legislation, from the numerous consultations on this revision, from support studies and from political commitments of the Commission. The high number of measures reflect the scope of the legislation and the fact that a series of responses are needed along a complex value chain⁸⁴.

We grouped the policy measures in 3 policy options (A, B and C), which represent alternative ways of reaching the general and specific objectives and the grouping was driven by certain underlying principles. Alternative groupings are also conceivable. To support the legislators in giving the best policy response, we conducted a thorough multi-criteria impact analysis for each policy measure, based on data, literature review and stakeholder feedback. This is detailed in Annex 11.

Beyond the policy measures outlined in each of the options, a set of 16 common measures were identified as well. These could be equally implemented regardless of which policy option is selected. These 'horizontal' measures are intended to reduce regulatory burden and provide a flexible regulatory framework. Detailed impact analysis of the horizontal measures is covered in Annex 11.

However, the impact assessment report focuses mainly on the 'pivotal' measures and the 'pivotal horizontal measures' (main horizontal measures). These pivotal measures were selected on the basis of the magnitude of their impacts and their political importance. These pivotal measures will be complemented by other technical measures, which contribute to achieving the specific objectives. A detailed analysis of the latter is provided in the Annex 11⁸⁵. **Table 1** shows how the pivotal measures map on to the specific objectives.

⁸³ 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>

⁸⁴ 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.

⁸⁵ 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 objectives

Objective	Baseline	Option A	Option B	Option C
Promote innovation, in particular for unmet medical needs	8 years DP +2 years MP No special incentives for the development of antimicrobials	8 years DP +2 years MP Special incentive: +1 year DP for medicines that address UMN +6 months DP to include comparative trials Transferable exclusivity vouchers for antimicrobial products	Standard protection for all originators: 6 years DP +2 years MP Special incentive: + 2 years DP for originators that address UMN. Pay or play model for antimicrobial products	6 years standard DP + 2 years (or 1) DP if all EU markets +2 years MP Special incentive: +1 year DP for medicines that address UMN + 6 months DP for comparative trials Transferable exclusivity vouchers for antimicrobial products
Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation	Not applicable	No provision	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	Require transparency on public contribution to R&D costs in relation to clinical trials included in the MA application
Ensure access to innovative and established medicines for patients with special attention to enhancing security of supply across the EU	Currently no obligation or incentive to launch in a particular or group of MS	Additional protection period if centrally authorised product is placed on market in all MS 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)	Last 2 years (or 1) of DP only granted 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 footprint 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 ERA requirements, including the assessment of the environmental risk of manufacturing	Strengthen the ERA requirements, including the assessment of the environmental risk of manufacturing, and conditions of use for medicines Include AMR aspects in GMPs
Reduce regulatory burden, and provide a flexible regulatory framework	Not applicable	Horizontal measures	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). 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 **antimicrobials** through transferable exclusivity vouchers (transfer the right to extend the regulatory protection period to another product marketed by the same or another company). This is a measure supported widely by industry as a way to underpin the substantial R&D costs of bringing new classes of antimicrobials to the market⁸⁶. This will be supported by measures on prudent use and 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 sustainability 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.

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.

It introduces a modulated system of incentives, with a reduction in the current standard regulatory protection periods. The new standard protection 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. Furthermore, all MA applicants will be required to publicly disclose any relevant public funding received (R&D transparency).

Option B also encourages the development of **antimicrobials** 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.

⁸⁶ Previously explored in the Joint Action on Antimicrobial Resistance and Healthcare Associated Infections.

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 regulatory protection, and generics are allowed to enter the market.

Measures on **security of supply** encourage EU coordination for exchange of information and use existing guidelines and systems, such as the EU medicines verification system⁸⁷ to track supply, and measures to increase manufacturers' responsibilities to ensure supply. The notification period for withdrawals remains identical to the baseline and MAHs are obliged to offer their MA for transfer to another MAH in case of withdrawals from the market.

The **ERA requirements** remain the same with no legislative change but complemented by stronger overall responsibilities of MAHs vis-a-vis suppliers. Moreover, it proposes improving oversight of sites through modification of provisions on inspections and a mandatory joint audit scheme for Member State 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 in the EMA scientific advice beyond crisis-related medicines, and measures to future-proof the regulatory system by reviewing the scope and definition of products that need to be accommodated under the general pharmaceutical legislation and simplifying/clarifying the regulatory framework for certain categories of medicines (e.g. borderline products). 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.

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). 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, with some exemptions to this condition.⁸⁸ The additional regulatory protection is not intended to compensate the cost of EU-wide market-launch (which would be disproportionate to the relative low cost of launching the product) but is rather a tool to accelerate the market launch and **therefore access**. On the other hand, if a company fails to comply with the market launch, there will be earlier generic competition and increased **affordability for health systems**⁸⁹. Moreover, originator medicines addressing an UMN would receive an additional 1 year of data protection.

⁸⁷ 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.

⁸⁸ E.g. if it is demonstrated that a MS does not wish to be supplied

⁸⁹ 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.

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 but the total regulatory protection period is capped at the available maximum of the baseline, which is a significant 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 variation⁹⁰ 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, all other elements being kept.

The next chapters 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 standard 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
Transferable exclusivity vouchers for antimicrobial products

To incentivise development of new **antimicrobials**, 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.

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 legislation⁹¹. 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** and conditions of use for medicines are strengthened. As in option B, this option also foresees the assessment of the environmental risk of manufacturing in the ERA as part of the marketing authorisation. It would also strengthen conditions of use of medicines on a case by case basis to limit the environmental impact without affecting the 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**⁹², 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. Moreover, this option foresees stronger oversight of manufacturing supply chains through changes to inspections,

⁹⁰ During the evaluation several stakeholders from patients' groups and academia argued that incentives are overly generous within the EU.

⁹¹ 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.

⁹² See Annex 11 for details.

enhanced Member State cooperation (joint audits) and increased EMA coordination. Measures to promote competition listed in Option B are retained. The changes to the scope, definitions and classification advice with regard to medicines would be similar to option B. However, this option 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.

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 objective “to reduce regulatory burden and provide 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 same site. A more efficient repeat use procedure⁹³ 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 could potentially reduce the administrative costs uncured 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 evaluation⁹⁴ 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 not 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 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 children⁹⁵ 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

⁹³ See glossary.

⁹⁴ See Annex 5. The evaluation showed that national competent authorities highlighted 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.

⁹⁵ SWD(2020) 163 final.

authorities for integrated medicines development and post-authorisation monitoring, pricing and reimbursement.

6 WHAT ARE THE IMPACTS OF THE POLICY OPTIONS?

6.1 Scope of the impacts

The general pharmaceutical legislation defines conditions and procedures for medicines to enter and remain on the EU market. In addition, the legislation rewards innovators through the **regulatory data and market protection (RP)**. RP protects data on the safety and efficacy of the product generated for the purpose of marketing authorisation. It guarantees that during the protection period no abbreviated marketing authorisation may be granted referring to the originator's regulatory data. This protects innovators from generic or biosimilar competition⁹⁶ for 10 or 11⁹⁷ years after authorisation. In international comparison, the EU is considered generous (see **Table 2**).

Table 2 Basic regulatory protection periods for medicines globally⁹⁸

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

However, RP is not the only legal construct that protects from generic/biosimilar competition. Medicines are also protected by patents (20 years from patent filing), SPCs (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). 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, demonstrated by **Figure 3** on a representative sample of 200 medicines.

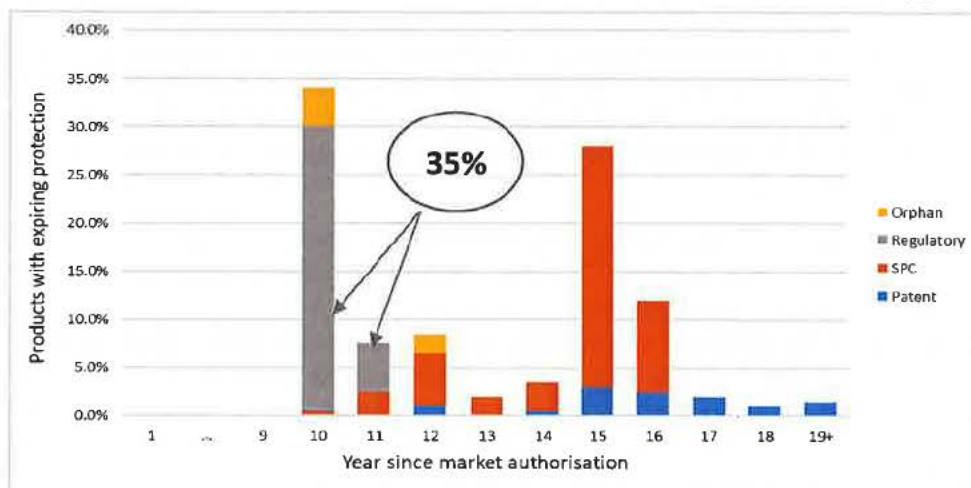
The RP is the last layer of protection to expire for 35% of the medicines, which have some unique characteristics. The lack of SPC protection means that it took at least 15 years from patenting to authorisation of these products, some extreme long development times. Moreover, RP protected products are less successful commercially than SPC protected ones (€158m vs. €358m average peak annual sales), and also the protection period is either 10 or 11 years, as opposed to SPC where most products are protected for maximum 15 years (or 15.5 if paediatric studies were carried out too). Consequently, changes to the **RP would concern only around 1/3 (i.e. 35%) of the newly approved medicines**, which have a 23% share among all originator medicine sales in the EU.

⁹⁶ 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.

⁹⁷ An extra year is granted for an additional indication with significant clinical benefit. Historically around 1 in 8 medicines qualify for that.

⁹⁸ Data collection by Technopolis Group, 2022

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

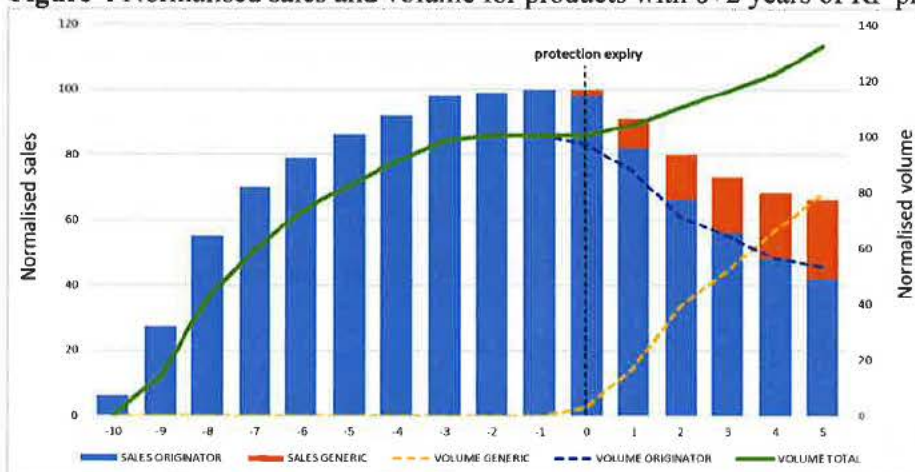


6.2 Economic impacts

6.2.1 Baseline

We provide a conceptual model to explain the impacts of the changes in the RP, including on different stakeholders. The model is based on the commercial lifecycle of a representative innovative medicine, an analogue, for which RP is the ultimate protection. To create this analogue, historical data⁹⁹ 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.

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



The SPC evaluation¹⁰⁰ 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,

⁹⁹ 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.

¹⁰⁰ SWD(2020) 292 final.

leading to quick erosion of the price and the innovator's premium. On the other hand, biological medicines, medicines for rare diseases and low revenue products are less likely to be contested, resulting in slower price erosion, or even maintaining a monopoly position. To account for this variability, the model took a cross-section of RP protected medicines, even including some medicines that was not contested by generics after protection expiry. The model represents well real-life at systemic level, however individual medicines might show a much steeper erosion, or the opposite, a constant high sales after expiry.

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 discounts¹⁰¹. The volume of generic medicines steeply increases, partly because some users substitute the originator medicine with generics and partly because the total volume rises with increased affordability. For healthcare systems, the price drop following generic competition means cost savings. In our analogue, the price drop is 50% on average at year +5. The lower price extends eligibility and more patients and from more Member States can have access to the medicine either in its original or generic form. Even with the 32% more patients served at year +5, health systems pay 34% less than at peak sales in year -1.

To account for the impacts of modifying the 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 in different scenarios.

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.

For **originator** and **generic industry** the key measure of impact is **the profit** that they can realise from their business operations.

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

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

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

6.2.2 Economic impacts of key policy measures

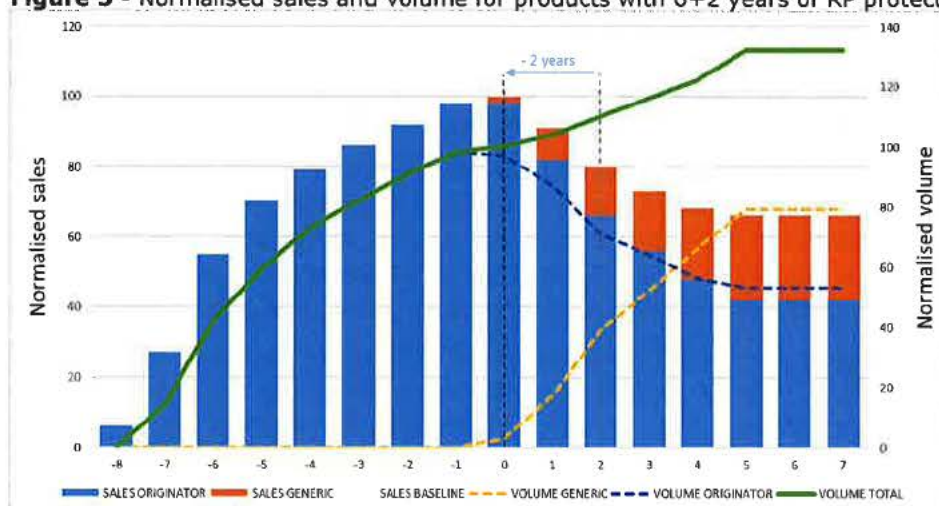
6.2.2.1 Decreasing standard regulatory protection (Option B)

To model for a regulatory protection of 6+2 years instead of the 8+2 years in baseline, we removed from our analogue the original year -1 and -2, enabling earlier generic competition. To keep the same 16 years of observation period, we have added year +6 and +7 in the model, which we assumed to be equal to year +5¹⁰² (**Figure 5**).

¹⁰¹ The evaluation (Annex 5) found that originator products can maintain a 30% premium over their generic competitors

¹⁰² More on the assumptions in Annex 4

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



At systemic level, due to other existing protections, such as SPC, patent and orphan exclusivity this measure would only be applicable for 30%¹⁰³ of all new medicines. Moreover, Option B would exempt medicines addressing UMN and medicines with no return on investment from the measure (as they can maintain the baseline protection), resulting in 20-25% of new medicines affected by the measure, or 8-13 medicines annually. Using the average peak sales of €160m for RP medicines (see in section 6.1), **Table 3** summarises the impacts at product and systemic level.

Table 3 – changes between baseline and RP 6+2 per stakeholder

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

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

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

¹⁰³ Some of the RP protected medicines are eligible for SPC protection between year 8 and 10 from MA, this is discounted, hence not 35% but only 30% of the RP protected medicines would be affected.

additional benefit would be a higher proportion of UMN among newly approved medicines¹⁰⁴, due to the relative higher reward.

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

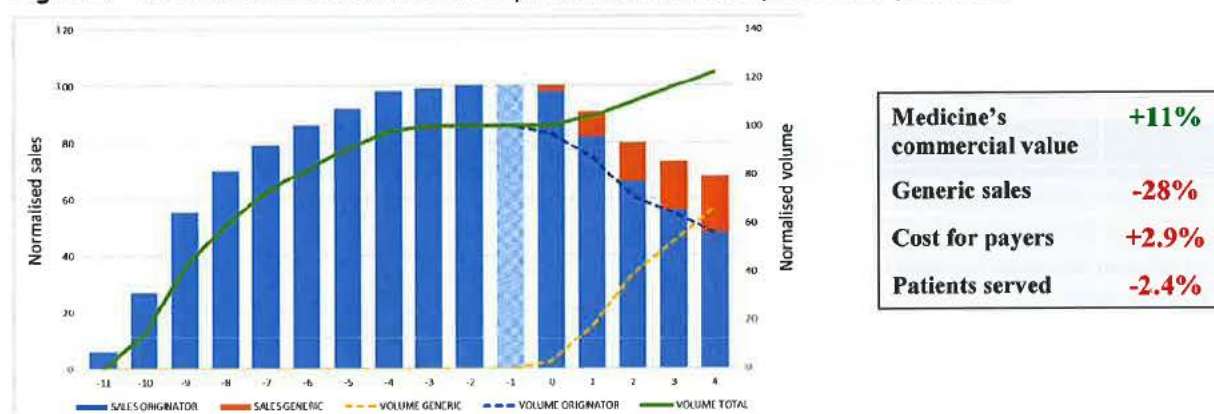
Apart from the imbalanced impact, the measure would have additional costs. With a lower reward, some developer will decide not to enter the EU market, or delay entry and seek return on other markets first. Moreover, an estimated €510-830 m will be lost for innovation¹⁰⁵, equal to the development cost of 8-12 new medicines over 15 years, or more incremental innovation (new indication of existing products, improved formulation or combination) that could benefit patients.

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

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

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

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



In this case, an additional protected year¹⁰⁶ is added at peak sales, extending the protection. The originator captures 14% increase of its protected and thus most profitable sales. The benefits are offset to some extent by losing one year of contested sales, still resulting in an overall 11% increase of the product's commercial value.

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

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

¹⁰⁴ As a result of decreasing non-UMN medicines

¹⁰⁵ 20% of lost protected sales, the typical R&D rate of revenue for originator companies.

¹⁰⁶ Impacts can be proportionated if the extension is longer or shorter than a year

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

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

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

The cost of this incentive is shared among generic industry, health payers and patients. With 2-4 such incentives annually, the generic industry would lose €77-154m a year and the health payers would need to pay €109-218m more. Accounting for the unserved patients too, the **public cost would rise to €163-326m**. The consultations showed that both public authorities and patients support modulating the RP periods around factors such as UMN. Industry on the other hand said that if incentives were limited to UMN only, that would disregard the reality of science and incremental innovation and also would introduce uncertainty.

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

Similar to the previous incentive, this measure could benefit RP protected medicines and some medicines for rare diseases. Around **40% of all new medicines would be eligible**. Conducting comparative trials should be feasible for many medicines, but not for some, especially UMN medicines¹⁰⁷. Also, if the cost of the comparative trial is too high as opposed to the reward, companies will decide to decline the incentive. The Paediatric Regulation offers a similar incentive for paediatric trials, and it works efficiently. We expect that half of the RP products could benefit from it, or **8-10 medicines annually**.

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

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

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

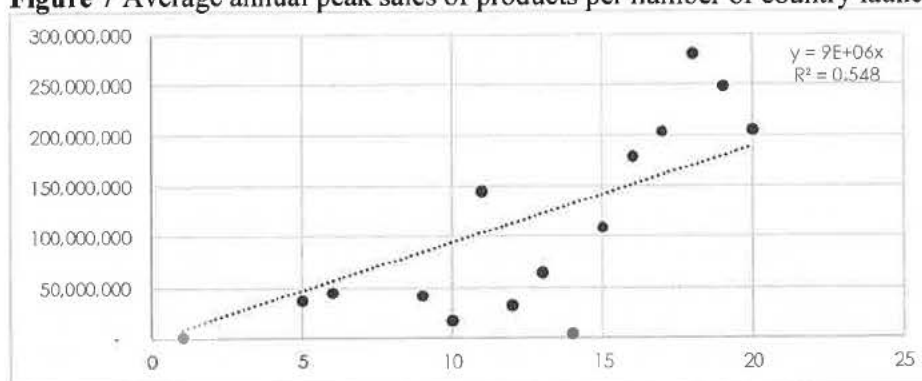
¹⁰⁷ In case of UMN, there are no satisfactory therapeutic options. Consequently a new therapy would have no comparator.

6.2.2.3 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. Option A offers a +6 months RP extension incentive for medicines launched in all EU markets within 5 years of market authorisation. Option B instead requires companies to launch their product in the majority of all EU countries within 5 years, otherwise they lose their regulatory protection and generics are allowed to the market. On the other hand, Option C links the market launch with the standard RP period as modulation. It requires market launch in all EU MS¹⁰⁸ and within 2 years of authorisation as a conditionality to parts of the protection period. Non-complying medicines would lose the 2 years conditional part of their RP (or 1 year in the case of the variation of Option C).

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

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



Based on the size of the incentive (or potential loss in option B and C), the compliance is estimated as the percentage of medicines fulfilling the market launch requirements. From this, the costs or savings to the public have been calculated (**Table 4**). For option A, we used the same model as for the special incentive for comparative trials, but expecting that only the higher sales medicines would comply, a higher average peak sales was used in the model (detailed in Annex 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 6.2.2.1). Again, the average peak-sales value was adjusted, assuming that the low-sales medicines will be the ones not complying.

¹⁰⁸ Except those not willing to be served.

Table 4 – 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)	+5.5% commercial value	€390-520m public cost
Option B -5 years, if not in majority of MS	75% (11-13 medicines) But not all markets	-20-60% commercial value	€270-360m gain from non-complying medicines
Option C -2 years, if not in all EU	66% (10-12 medicines)	-22% commercial value	€360-440m gain from non-complying medicines

The access measures benefit society, above all patients. These benefits are elaborated in depth within the social impacts section (6.3). 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 5 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.

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

6.2.2.4 AMR addressing measures

Antibiotic development is not attractive commercially because new antibiotics are kept on the shelf and only used as a last resort, to delay or avoid the evolution of resistant bacteria. The lack of use translates to low sales and a broken business model, which can only be tackled by public intervention. Pull incentives¹⁰⁹ reward successfully developed medicines, either by creating markets for them, or by giving a prize to the developer. There are several models considered at EU level, some of them under the realm of research and crisis preparedness policies, such as the subscription model (guaranteed revenue delinked from volume) and the innovation partnership (funding for research + guaranteed purchase of the product). These models require commitment and direct funding contributions from the Member States. There are other models discussed below, that can be implemented through the general pharmaceutical legislation.

Pay or play model (Option B)

In this model, a company co-finance the innovation and either holds an antimicrobial in its portfolio or it pays to a fund that is destined to finance the development of novel antimicrobials. The analysis found that a pay or play model would impose additional costs on EU pharmaceutical businesses. Undoubtedly the increased fees on other therapeutic areas will be passed on health systems (insurers and/or patients) through higher prices¹¹⁰ and while a minority may look to avoid a levy by developing antimicrobials or acquire businesses with an antimicrobial in the portfolio, the majority would be likely view the surcharge as an unavoidable additional cost to be factored into their wider pricing policies. In addition, the fund would generate only limited amount of money therefore only

¹⁰⁹ As opposed to push incentives that provide funding for research and development

¹¹⁰ (<https://academic.oup.com/cid/article/71/8/1994/5736365?login=true>).

partial return of investment and/or limited number of rewards can be ensured. The results of this model could be seen only after several years (when the fund collects enough capital). Finally, other therapeutic areas that also suffer lack of investment may need/request to be included, making the scheme unsustainable.

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

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

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

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

According to EFPIA¹¹¹, the value of such voucher in the EU should be between €280 and €440 million per product, based on assumptions around a “fair European share”, a proportionate contribution to product development that would benefit the global population.

Cost and benefit of transferable exclusivity vouchers

To understand the impacts of such 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 generic/biosimilar competitors. It results in a faster erosion of price and originator’s sales, therefore an additional year of protection has a higher value for the originator, and has a higher cost for the other stakeholders. We have examined over a 10-year period the highest selling RP protected medicines, and identified the champions for each year¹¹². The average peak annual sales of these champions is € 545 m, this was used in our model. Table 5 summarises the changes caused by the voucher to the various stakeholders.

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

Stakeholder	change	change %
Originator protected sales	+€545 m	+14%
Generic sales	-€164 m	-23%
Cost to public payer	+€283 m	+4.7%

¹¹¹ Representative of innovative industry: [A new EU pull incentive to address Anti-microbial Resistance \(AMR\) Recommendations from EFPIA](https://www.efpia.eu/media/636464/a-new-eu-pull-incentive-to-address-anti-microbial-resistance-amr.pdf), available at <https://www.efpia.eu/media/636464/a-new-eu-pull-incentive-to-address-anti-microbial-resistance-amr.pdf>.

¹¹² More details on data and inputs to the model in Annex 4

Patients served (normalised volume)		-3.8%
Patient + payer monetised gain/loss	-€441 m	-7.3%

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

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

Sharing the value of the voucher between buyer and seller

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

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

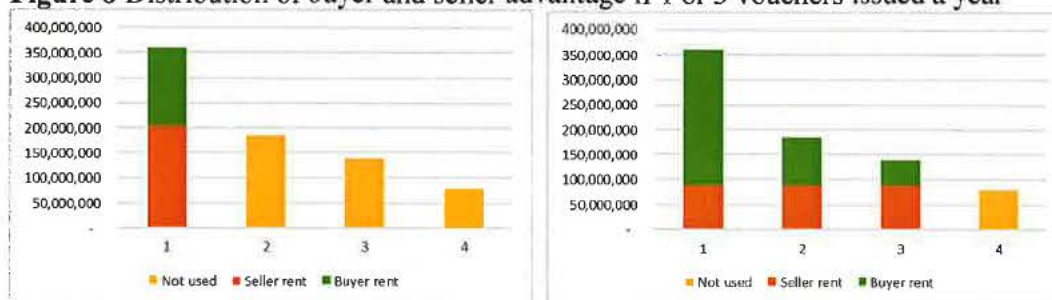


Table 6 – share of value among buyer, seller and the public

1 voucher		3 vouchers		Voucher 1	Voucher 2	Voucher 3	Total
Seller rent	€205 m	Seller rent	€89 m	€89 m	€89 m	€89 m	€267 m
Buyer rent	€154 m	Buyer rent	€270 m	€97 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	€147 m	€109 m	€539 m
Cost to public incl. unserved patients	€441 m	Cost to public incl. unserved patients	€441 m	€228 m	€228 m	€170 m	€839 m

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

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

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

Table 7 - cost for the public payer to reward the developer with 1€

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

If it were possible to add safeguards, ensuring that 90% of the value of the voucher is captured by the seller (developer), the ratio of the award and the cost would significantly improve. In this case, it would cost €87 m to the health payers to give a €100 m reward, but this payer cost does not account for the unserved patients' loss¹¹³.

Regardless of the cost calculation method, the public has to pay more than 1€ for each euro awarded to the developer. However, it would be a feasible way to pool sizeable resources and incentivise antibiotic development, which so far have proven ineffective with other incentives. These costs should be reflected taking into the current €1,5bn in health care costs and productivity losses from AMR¹¹⁴ 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 (6.3).

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

6.2.2.5 Horizontal measures¹¹⁵

The proposed horizontal measures are intended to deliver wide-ranging improvements in terms of efficiency and effectiveness of the EU pharmaceutical regulatory system. They complement each of the policy options (A, B, C) and fully respond to the 'digital by default' principle via the promotion of an increased digitalisation. The horizontal measures are expected to generate net benefit of €0.10bn a year and a €1,5bn over 15 years, shared among businesses and authorities (Annex 3).

Table 8 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.

¹¹³ Unserved patients refer to those patients that were not served due to the delayed entry of generics, ie. the lost volume

¹¹⁴ [201020 EUJAMRAI policy-brief WP7 appropriate-use-of-antibiotics-one-health-perspective.pdf \(eu-jamrai.eu\)](#)

¹¹⁵ Detailed analysis of the measures are in Annex 11.

Table 8 - Qualitative assessment of the benefits of pivotal horizontal measures, by key stakeholder group

	Business	EMA	NCA	SMEs	Health Systems	Environment
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	M
#7 Electronic submission of applications	H	H	M	H	L	M
Enhanced support and regulatory flexibility						
#8 Optimise regulatory support to SMEs and non-commercial 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 coherent vis-a-vis horizontal measures. Reducing regulatory burden (e.g. through elimination of the renewal procedure and digitisation) can be considered as common ground both for industry and public authorities. Healthcare professionals and patients support the introduction of electronic product information (a measure also supported by industry), however they also found it important to keep paper package leaflets in certain cases to ensure that patients without access to computers/internet can be sufficiently informed. Member States are also supportive of electronic product information but call for the application of the measure in a way that respects the different national levels of 'digital readiness'.

6.2.3 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 could negatively impact the generic and biosimilar industry as it would further delay their access to the market. Measures on security of supply retain the current requirements hence they would bring no additional burden.

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

payers against a more robust assessment by medicine regulators and a better evidence base for HTAs and payers.

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

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 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 the studied medicines and their comparators.

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

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.

6.2.4 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 is expected that developers would adjust / increase prices to counter the loss or otherwise rebalance their portfolios towards those market segments with greater commercial potential. The threat to EU-based originators will be offset to some degree by giving a boost to EU's generic industries, broadening their portfolios and potentially creating a prime-mover advantage in global markets. Similarly, developers of products addressing UMN will be exempt from the negative impacts of the measure.

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

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

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

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

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 chapter 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. They may either be required to operate in markets where they cannot generate a sufficient ROI or bear the consequences of the lost regulatory protection. The MAH will also have to provide additional information to regulators to demonstrate their compliance with obligations. This implies increased administrative costs. These obligations will also increase the costs to MAHs for interacting with regulatory agencies and HTA bodies in the Member States.

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.

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 or distribution channels in such markets.

6.2.5 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.

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: Incentives providing longer data protection periods in general (whether to promote innovation or market access across all Member States) would carry additional cost to national health systems and payers by potentially delaying generic entry and increasing the period for premium pricing. On the other hand, the special incentive for comparative trials would lead to a more straightforward and robust assessment by regulators and a better evidence base for HTAs and payers.

There may also be additional administrative burden for the public authorities involved in the assessment of UMN criteria and verification of product market supply to determine whether a MAH is eligible for longer data protection. Similarly, an increase in notification period for withdrawals and 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 quicker time period. It is observed that national pricing and reimbursement decisions for new medicines often take longer than the legally maximum of 180 days.¹¹⁶ 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 may strengthen pricing and reimbursement agencies' negotiating position with MAHs.

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

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

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

¹¹⁶ The Directive 89/105/CEE sets a maximum period of 180 days. For compliance issues see e.g. SWD(2012) 29 final.

Functioning of the internal market: The increase in the number of new innovative medicines owing to incentives provided and the increase in access to medicines through the market launch measure will improve patient coverage and functioning of the internal market. Transferable vouchers introduce an element of unpredictability for the start date of the competition.

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

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

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

6.3 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. Among the specific objectives of this revision, the one on **access** is the most important and directly impacting patients. Analysis of historical data¹¹⁷ reveals that access to newly authorised medicines in the EU is unequal and even among citizens having access to a medicine, there is a large variation in time to access. Moreover, medicines whose last layer of protection is SPC are more accessible than RP protected ones (Figure 9.)

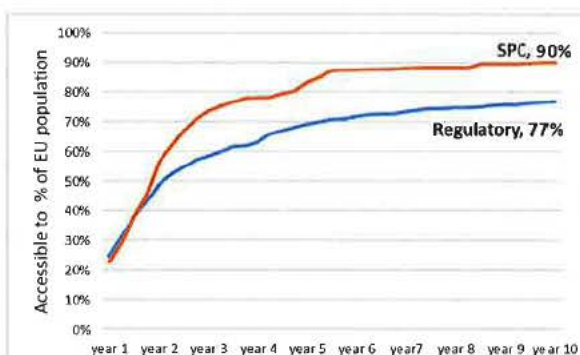
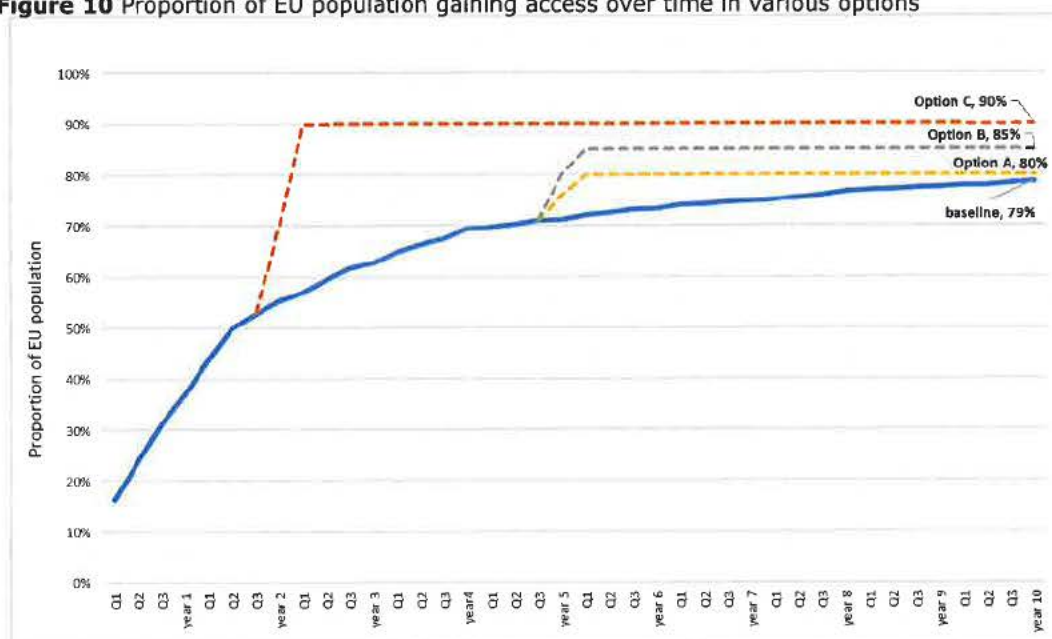


Figure 9 Avg product accessibility to EU population over time, by protection type

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

¹¹⁷ See Annex 4 (analytical methods and methodology) and Annex 5 (evaluation SWD)

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



As discussed in section 6.2.2.3, each option has an assumed compliance rate and together with the required threshold (all vs. majority of EU markets) we could model when and what percentage of the EU population can gain access to the average RP protected medicine (see also section 6.2.2.3).

In this respect, Option C outperforms all options, by providing access on average to 80% of EU population over the 10 years protected period, 15% higher than in the baseline. Also options A and B offer a higher access than the baseline (67,6% and 70.2% respectively). In other words, in Option A 11 million, in Option B 22 million and in Option C 67 million more EU citizens would have access to a typical RP protected medicinal product, should they need it¹¹⁸ compared to the baseline.

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

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

The transferable exclusivity voucher in Option A and C would help develop new antibiotics. While those novel antibiotics need to be used selectively, i.e. as a last-line therapeutic instrument (to avoid bacteria developing resistance against them), they serve as an 'insurance' scheme for the EU and global population. The growing threat of antimicrobial resistance means that routine hospital

¹¹⁸ 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.

procedures such as a hip replacement or a caesarean section can turn fatal, or a small injury during a holiday trip can end with an amputated limb. So far these events are sporadic within the EU, but can develop into a dangerous public health emergency in the future. New antibiotics on the shelf can protect citizens from such a crisis and the cost of inaction may be much higher than any of the models considered. The use of transferable exclusivity voucher to address this challenge will be after all a matter of political choice.

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

6.4 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. A common measure across the policy options is the more prudent prescription rules for antimicrobials, which should result in fewer antibiotics entering the environment. Apart from that, Option A is not different to the baseline. Option B increases the requirements for the environmental risk assessment (ERA), by including the assessment of the environmental risk of manufacturing too as part of the marketing authorisation process. Option C goes beyond this level, it 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.

The impact of these measures should be less residues (sex hormones, genotoxic substances, antimicrobials) in the environment and less disruptions to the ecosystem and human health. Option C has the highest likely impact, followed by B and A. In the consultations, stakeholders have pointed out that the introduction of new rules at an EU level has been known to be a trigger for other regions, leveraging EU actions. There is variable stakeholder support to the extent of strengthening of the ERA which ranges from support for it to cover all stages of pharmaceutical manufacturing, from raw materials to end-product (public authorities and patients) to views considering existing measures (controls, benchmarking on the manufacturing and disposal of products in the environment) stringent enough, (industry).

7 HOW DO THE OPTIONS COMPARE?

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

The comparison has focussed on the pivotal elements as these are likely to contribute the most significant impacts and will allow clear differentiation between the options. The horizontal measures, common across the three options, together with the pivotal elements 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 9**. The complete analysis of all the elements of the options is provided in Annex 11.

Table 9 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 footprint of the pharmaceutical product lifecycle	0	+	++	+++
Reduce regulatory burden and provide a flexible regulatory framework	0	+++	++	++
Effectiveness: other impacts				
Economic impacts (businesses, public authorities)	0	+	+	++
Social impacts (patients, public health and safety)	0	++	+	+++
Environmental impacts	0	+	++	+++
Efficiency				
Administrative and compliance costs	0	++	++	+
Savings and benefits	0	+	++	+++
Coherence	0	+	++	++
Legal and political feasibility	0	+	-	++
EU added value	0	++	++	+++
Proportionality	0	+	+	++
Overall	0	+	+	+++

7.1 Effectiveness

Innovation

Options A and C both offer the same incentives for innovation, in particular for UMN and AMR. Overall, Option A is slightly more generous towards innovators, as in this option incentives can be freely cumulated, whereas in Option C the maximum period of RP is capped. Option B keeps the baseline protection period for UMN medicines, whereas for other RP protected originator medicines there will be a 22% loss in commercial value, resulting in €510-830 m less funds for innovation annually. Option B's pay or play model is considered less effective than the transferable exclusivity voucher of Option A and C in stimulating AMR related innovation.

Affordability

In terms of affordability, the general pharmaceutical legislation has a limited role, 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.

With these limitations, Option B offers the most effective measure in terms of affordability, offering €0.9-1.4 billion direct cost reduction for health payers with the reduced RP period (6+2 years). This reduction of 0.4%-0.6% of the EU pharmaceutical expenditure would heavily impact 20-25%¹¹⁹ of the new medicines (they would lose 22% of the commercial value) while other, often more profitable medicines would be unaffected. Due to this imbalance, option B scores lower in legal and political feasibility. Options A and C keep the baseline protection period. The R&D transparency requirements in option B and C are supposed to indirectly contribute to affordability too, better equipping national bodies for price negotiations.

The market launch obligations in options B and C would result in cost savings to the public as non-complying medicines would lose a part of their protection period. In option A, the market launch incentive would come with an extra €390-520m cost to the public. Options A and C offer additional incentives for UMN, and for the TEV, which come with additional costs. This is a trade-off between innovation and affordability. Options A and C also offer an incentive for comparative trials, however the cost of that incentive may be offset by savings to the health systems by more informed pricing and reimbursement decisions, with an expected overall neutral/positive impact on affordability. However, this could not be quantified. Option B does not offer incentives, and it is overall the strongest option for affordability, at the cost of lower revenues for a subset of innovators. Option C is more affordable than Option A, because the incentives are capped, and because it enforces market launch by an obligation rather than an incentive.

Access

All measures 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, if a company fails to comply with the market launch obligation, it will lose part of its regulatory protection, meaning earlier generic competition and more affordable prices. In options B and C, the public wins in either case: more access if companies comply, or more affordable medicines 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 EU in B).

Shortages

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. Stakeholder feedbacks from industry suggest that these costs are tolerable for them.

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

¹¹⁹ 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.

than the baseline. Option C offers the highest safeguards against uncontrolled release of pharmaceutical residues 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. As with the shortages, there is a trade-off among environment protecting measures and administrative burden.

Regulatory burden

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 reporting, where options C and B score worse than option A. However, this difference compared to the positive impacts from the horizontal measures is minor.

Other impacts

Chapter 6 analyses in depth the economic, social and environmental impacts of the different policy options, and the most favoured option depends on the perspective. For originator companies, Option A offers the most benefits, whereas for the generic industry, Option B would be the preferred one. From a patient/public health perspective, Option C is the most advantageous by far, and that option represents a fair compromise between originator and generic industry, along with public authorities and payers.

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 chapter 6. The data in tables are always compared to the baseline.

Improving access to medicines measures

Table 10 Cost-benefit table of access measures

	Option A +6 months	Option B Lost protection after 5y	Option C 2y protection lost after 2y
Population with access	+10m	+22m	+66m
Expected compliance	50% (6-8 medicines)	75% (11-13 medicines)	66% (10-12 medicines)
Reward/loss for companies	+5.5% commercial value	-20-60% commercial value	-22% commercial value
Cost/benefit for public	€390-520m cost	€270-360 m gain	€360-440 m gain
Cost/benefit for originator	+€770-1020m protected sales	-€480-640m protected sales	-€640-800m protected sales
Cost/benefit for generics	-€180-250m sales	+€120-150m sales	+€150-190m sales

Table 10 provides an overview of the different access measures considered. Option A provides a marginal benefit at a very high cost for patients. Options B and C¹²⁰ use obligations and conditional rewards to encourage product launch on commercially less attractive markets too. The model is

¹²⁰ A variation in Option C is presented in section 8.1., which results in different distribution of costs and benefits

sensitive to the compliance rate. If in Options B and C the compliance rate is lower, the access will be lower too, but the public cost savings increase through earlier entry of generics thus the public gains either way. **Option C both offers the highest additional EU population with access, and the highest level of cost savings.** This is thanks to the earlier deadline to comply (within 2 years from authorisation) and to the highest bar (full EU access).

Incentives

Table 11 Cost-benefit table of incentives

	Cost/benefit for originators	Cost/benefit for public payer and patients	Cost/benefit for generic industry
+1 year extension of RP for medicines addressing UMN	+ €320-640m protected sales (2-4 medicines)	+ €163-326m cost + higher proportion of UMN among new medicines	- €77-154m sales loss
+6 months extension of RP for conducting comparative clinical trials	+ €640-800m protected sales +€240-500m cost (8-10 medicines)	+ €326-408m cost + faster access and cost saving thanks to improved reimbursement decisions	- €154-192m sales loss
Transferable exclusivity voucher	+€545m protected sales (1 voucher)	+€441m cost + 1 new antibiotic	- €164m sales loss

Incentives in **Table 11** only appear in Options A and C, and not in option B. Chapter 6 found that for each proposed incentive the social and economic benefits outweigh the costs. The UMN incentive will deliver more medicines addressing disease with high public health burden. The comparative trials incentive compensates companies for the extra cost of the trials, meanwhile allowing faster and better reimbursement decisions and ultimately cost savings to health systems. The transferable exclusivity voucher rewards new antibiotics, expanding the toolbox to fight the growing threat of AMR. The cost for health systems would be €930-1175m for the three incentives. This is equivalent to 0.4-0.5% of the EU pharmaceutical expenditure.

Affordability

There is one measure with significant monetary impact on affordability, the reduction of the standard regulatory protection in Option B, which has been analysed in section 6.2.2.1. This measure would result in a direct (cash) cost reduction of -€0.9-1.4 billion, or 0.4-0.6% of the EU pharmaceutical expenditure and cause 28% drop in protected sales for 8-13 medicines¹²¹ (altogether €2.5-4.1 billion lost protected revenue for originators).

Horizontal and other measures

In Annex 3, our analysis concluded that the horizontal measures are expected to generate around €300m savings annually regardless of the selected option, shared among businesses and authorities. Additional administrative cost resulting from measures on R&D transparency, shortages and environment would offset a maximum of 10% of these savings (maximum €30m additional cost). Option A is exempted from these extra costs, however it does not either deliver on certain specific objectives, therefore Option C is the most cost-effective, followed by Option B and A.

In summary, Option C offers the most cost-effective solution to achieve the specific objectives. In view of the findings in the effectiveness and efficiency analysis, Option C is put forward as the preferred option.

¹²¹ The other 30-40 medicines authorised annually would be unaffected

7.3 Coherence

Options B and C are consistent with the EU Strategic approach to pharmaceuticals in the environment. All policy options are coherent with the EU Action Plan on Antimicrobial Resistance¹²². All three options contribute to SDG 3 (“health and well-being”), SDG 9 (“innovation and infrastructure”) and SDG 10 (“reduced inequalities”) ¹²³ (Chapter 1).

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 (section 5.3.4). 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.

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. 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 this chapter 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 policies at Member State level (e.g. for pricing and reimbursement). There is also a level of uncertainty owing to the limitations and assumptions involved in assessing and quantifying the likely impacts of the options provided.

¹²² 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

¹²³ Sustainable development in the European Union, overview of progress towards the SDGs in an EU context, 2022 edition, Eurostat (2022)

8 PREFERRED OPTION

The impact assessment of the three policy options indicates that policy option C is the strongest option to effectively address all the objectives of the revision of the general pharmaceutical legislation in an efficient and consistent manner. It 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 footprint 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.

8.1 Costs and benefits of the preferred option

Table 12 reviews the most significant costs and benefits from the pivotal measures, and also includes the variation to Option C described in section 5.3.3.1. 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 “price” for compliance, thus we assumed that fewer medicines would meet the requirement (50% vs. 66% in the default). The variation is presented in two blue rows in the table, presenting the impacts of both the 1 year reduction for all RP medicines, and the 1 year conditional protection. The variation allows the legislator to consider the impacts on the various stakeholder groups by “moving the cursor”.

Table 12 Cost-benefit table of incentives in Option C compared to baseline

	Cost/benefit for public payer and patients	Cost/benefit for originators	Cost/benefit for generic industry
Default Option C – 6+2+2 2 year conditional protection for all EU launch in 2 years	€360-440 m gain ¹²⁴ Access for +15%	-€640-800m protected sales (4-5 non-complying MP)	+€150-190m sales
Variation 6+1+2 (component A) - 1 year reduction of baseline protection	€0.7-1.1 b gain ¹²⁵ Innovation loss	-€1.4-2.1 b protected sales	+€350-500m sales
Variation 6+1+2 (component B) – 1 year conditional protection for all EU launch	€270-360 m gain ¹²⁶ Access for +8%	-€480-640m protected sales (6-8 non-complying MP)	+€120-150m sales
+1 year extension of RP for medicines addressing UMN	+ €163-326m cost + higher proportion of UMN among new medicines	+ €320-640m protected sales (2-4 medicines)	- €77-154m sales
+6 months extension of RP for conducting comparative clinical trials	+ €326-408m cost + faster access and cost saving thanks to improved reimbursement decisions	+ €640-800m protected sales +€240-500m cost (8-10 medicines)	- €154-192m sales
Default Option C 6+2+2 - Total monetary balance	+ €129-294m cost Access + 15%	+€80-140m protected sales	- €81-156m sales
Option C Variation 6+1+2 – Total monetary balance	€481-726m gain Access + 8%	-€1160-1800m protected sales	+€239-304m sales

¹²⁴ The public gain results from the non-complying medicines, that lose 2 years protection

¹²⁵ The public gain results from the 1 year general RP reduction compared to baseline (component A of the variation)

¹²⁶ The public gain results from the non-complying medicines, that lose 1 year protection (component B of the variation).

Transferable exclusivity voucher ¹²⁷	+€441m cost + 1 new antibiotic	+€545m protected sales (1 voucher)	- €164m sales
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The transferable exclusivity voucher is a special case. We therefore present it separately from the other incentives and did not make it part of the total monetary balance.

In the default Option C, the higher market access is achieved without extra cost to the public, even some gains are expected from the 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, overall resulting in a saving for health systems. 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.

The variation of option C would change the final balance and 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, without turning the public monetary balance into negative. In the variation, all the costs of the positive social impacts would be borne by 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.

The drawbacks of the variation is that it puts the cost only on a subset of innovator companies, e.g. high-sales, SPC protected medicines would be unaffected. The shorter conditional period means a smaller loss, 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 represent a trade-off among more access and more affordability, and the final choice shall depend on the political priority.

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 systems. The new measures to promote access across all Member States, requiring companies to launch their products on all EU markets, coupled with heavy impacts in case of non-compliance will be the first EU-level legislative measure to address the long-standing inequalities in **access and will increase access to innovative medicines**. The additional incentive for addressing UMN will lead to more medicines with high public health benefit. Transferable vouchers would give access to additional antimicrobials and reduce EU deaths due to AMR, and also ensure a better preparedness against the increasing threat of resistant bacteria. **Security of supply** measures will improve access of both critical and non-critical medicines, which will significantly benefit patients and healthcare services. Citizens will also benefit from strengthened and more holistic environmental risk assessments applied to medicines.

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.)¹²⁸. Along with the measures facilitating generic entry right after protection expiry (C.1.4.,

¹²⁷ We present the transferable exclusivity voucher separately, as it only affects a very few individual companies

¹²⁸ The codes in brackets refer to the codes of the measures in Annex 11 for easier identification

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).

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 manufacturing process specification from the legislation's scope will address potential regulatory gaps (without changing the overall scope) due to changes in the manufacturing of medicines e.g. low-volume products, bedside-manufactured or single batch personalised medicines that do not involve an industrial manufacturing process¹²⁹ (C.3.3.). Pathways 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, introduction of the legal basis for electronic product information will bring advances to readability for patients and opportunities for healthcare professionals to communicate information more effectively (Horizontal 6).

Industry

For the originator industry, the modulation of the regulatory protection will bring **no change in the duration of the protection**, as long as they comply with the **condition of launch in all EU-markets within 2 years from authorisation**. 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 €320-640m additional protected revenue 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 €640-800m extra protected revenue, but also with €240-500m 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 new 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 €77m - €154m revenue per year for generic companies, and €154m - €192m for comparative trials. They would also have increased costs from the obligation to include smaller markets in their own mutual recognition procedure (or decentralised procedure) applications (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.).

¹²⁹ 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 EUR 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.

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 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.

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 sustainability 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 advice 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 administrations¹³⁰. 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 regulators¹³¹. The envisaged reduction in the number of notifiable variations could potentially reduce the administrative costs uncured 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.

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.

¹³⁰ A quantification of these costs is presented in Annex 3.

¹³¹ 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.

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 baseline¹³².

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 governance but also in part to create the financial headroom to introduce new legislative actions and procedures that will inevitably bring additional costs in pursuit of additional social benefits. As a case in point, the strengthening of the environmental risk assessment within the overall assessment process (e.g. in consideration of manufacturing and supply chain issues) will add costs, compared with the current situation, as will the inclusion of environmental issues within post-market authorisation monitoring and the measures on security of supply.

As regards companies, there are also costs reductions resulting from the implementation of horizontal measures. 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 €1.2bn-€2.4bn for the industry¹³³.

More specifically:

- The proposed streamlining procedures will yield useful cost savings for European pharmaceutical businesses, with estimated cost savings falling in the range of €1.0-2.1b over the next 15-years.
- The proposed digitalisation measures will provide relatively modest financial savings to industry, given the primary focus is on the integration of regulatory systems and platforms across the EU and support for the re-use of data. 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 importance¹³⁴ 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 13. The Commission will review the indicators periodically.

¹³² A quantification of these costs and savings is presented in Annex 3

¹³³ Methodological details underpinning the calculations are described in Annex 5.

¹³⁴ The legislation aims at improving the flow of cutting-edge treatments available for conditions for which there are no effective treatment options currently (UMN), reversing the decline in investment in antimicrobial research and encircling the issues driving AMR, incentivising access in all Member States, a broader repurposing, and the generic and biosimilar entry. A more robust ERA will also support environmental goals. Measures on security of supply will moreover improve access to medicines.

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 13 Proposed list of monitoring and evaluation indicators

Specific objective	Monitoring indicators	Data source/frequency
Promote innovation, in particular for UMN	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Market share of generic and biosimilar medicines • Development of prices of medicines • Member States' pharmaceutical spending 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 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 	<ul style="list-style-type: none"> • IQVIA data/biannual • IQVIA data/biannual • EMA and NCAs/annual • EMA and NCAs/annual • EMA and NCAs/annual • EMA and NCAs/annual • EMA and NCAs/annual • EMA

	information with the EMA platform and number of NCAs manually submitting information with the EMA platform	
Reduce the environmental footprint of the pharmaceutical product lifecycle	<ul style="list-style-type: none"> • Presence of medicines residues in the environment • Consumption of antimicrobials • GHG emissions of EU-based pharmaceutical manufacturers 	<ul style="list-style-type: none"> • Watch list of substances for Union-wide monitoring in the field of water policy • EDCD annual report on antimicrobial consumption • Eurostat/annually
Reduce the regulatory burden and provide a flexible regulatory framework	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • EMA, CMDh and NCAs/annually • EMA/annually • EMA/annually • EMA/annually

ANNEX I: PROCEDURAL INFORMATION

– *Lead DG, Decide reference and Work Programme reference.*

The Directorate General for Health and Food Safety (DG SANTE) is the lead DG on the initiative for the Pharmaceutical Strategy for Europe.

The initiative is in the European Commission's Work Programme for 2022, COM(2021)645 final, under the heading "Promoting our European Way of Life". The initiative has received the validation in the Agenda Planning on 25 March 2021 (reference PLAN/2021/10601) and the Inception Impact Assessment was published on 7 April 2021.

– *Organisation and timing.*

An inter-service steering group (ISSG) for the implementation of the Pharmaceutical Strategy for Europe was established on 22 January 2021. At meetings on 19 March 2021, 14 July 2021, 9 December 2021, 14 March 2022 and 13 June 2022, the ISSG specifically discussed matters relating to the evaluation and impact assessment of the general pharmaceutical legislation to ensure that they met the necessary standards for quality, impartiality and usefulness, see table A.1. The ISSG was also invited to the inception meeting with the contractor on 14 July 2021.

In addition to these meetings, written consultations of the ISSG on draft key documents took place.

Along with the Secretariat-General and Legal Service, the following Commission services took part in the ISSG: DG Health and Food Safety (SANTE) DG Employment (EMPL); DG Communications Networks, Content and Technology (CONNECT); DG Internal Market, Industry, Entrepreneurship and SMEs (GROW); DG for Research and Innovation (RTD); Joint Research Centre (JRC); DG Trade (TRADE), DG International Partnerships (INTPA); DG Eurostat – European statistics (ESTAT); DG Environment (ENV); DG Energy (ENER); DG Economical and Financial Affairs (ECFIN); DG Competition (COMP), DG Climate Action (CLIMA) and DG European Health Emergency Preparedness and Response Authority (HERA).

Table A.1: Inter-Service Steering Group meetings on the revision of the General Pharmaceutical Legislation

Dates	Topics for discussion
19 March 2021	Presentation of the draft terms of reference for the evaluation and impact assessment studies for the revision.
14 July 2021	Discussion on the state of play of the revision and on the draft inception report for evaluation and impact assessment study.
9 December 2021	Discussion on the state of play of the revision.
14 March 2022	Presentation of state of play of the revision, draft policy options and draft final evaluation study report.
13 June 2022	Discussion on draft Commission impact assessment report.

– *Consultation of the Regulatory Scrutiny Board.*

The file benefitted from an upstream meeting with the Regulatory Scrutiny Board (RSB) on 26 January 2022. A first version of this Impact Assessment Report – with the Evaluation Report annexed – was submitted to the RSB on 22 June 2022, the meeting took place on 19 July and the RSB written report was received on xx 2022. The Board concluded that xxx.

– *Evidence used together with sources and any issues regarding its quality*

The impact assessment and the accompanying evaluation have been built on:

- Evaluation of general pharmaceutical legislation (for the impact assessment)
- Participatory workshops bringing stakeholders together to inform respectively the evaluation and the impact assessment (see Annex 2: Stakeholder Consultation)
- In a back-to-back exercise, two studies were commissioned to a consortium led by Technopolis Group; an evaluation study and an impact assessment study. These studies are not publicly available and are annexed to this impact assessment as Annexes 12 and 13.

Extensive stakeholder consultations were organised, with input gathered through a public consultation, targeted surveys, an interview programme and workshops, for more information, see Annex 2: Stakeholder Consultation.

Evidence on costs were particularly difficult to gather. Public authorities and pharmaceutical industry provided very little information.

ANNEX 2: STAKEHOLDER CONSULTATION (SYNOPSIS REPORT)

1. Introduction

This report provides an overview of the stakeholder consultation activities carried out as part of the ‘back-to-back’ evaluation and impact assessment for the revision of the general pharmaceutical legislation (Directive 2001/83/EC and Regulation (EC) No 726/2004). A single consultation strategy was prepared for this exercise, including consultation activities looking backward and forward. It aimed to collect inputs and perspectives of all stakeholder groups both on the evaluation of the legislation and on potential future policy options.

Information was collected through consultations that took place between 30 March 2021 and 25 April 2022 and consisted of: feedback on the Commission combined evaluation roadmap/inception impact assessment (30 March-27 April 2021); Commission online public consultation (PC) (28 September-21 December 2021); targeted stakeholder surveys (survey) (16 November 2021-14 January 2022); interviews (2 December 2021-31 January 2022); a validation workshop on the evaluation findings (workshop 1), on 19 January 2022; and a validation workshop on the impact assessment findings (workshop 2), on 25 April 2022.

The following key stakeholder groups were identified as priority groups in the consultation strategy for the evaluation and revision of the legislation: Citizens; Organisations representing patients, consumers and civil society active in public health and social issues (CSOs); Healthcare professionals and healthcare providers; Researchers, academia and learned societies (academics); Environmental organisations; The pharmaceutical industry and their representatives.

As part of the internal policy work process supporting the revision, the Commission collaborated with the European Medicines Agency (EMA) and the National Medicines Authorities. Both actors play a pivotal role in the implementation of the pharmaceutical legislation. The Commission also worked with Member States, EEA countries (Iceland, Liechtenstein and Norway) and public authorities in the framework of the Pharmaceutical Committee¹³⁵. Other national authorities were consulted to receive the point of view of payers or pricing and reimbursement (P&R) bodies in the meetings of the national authorities on Pricing, Reimbursement and Public Healthcare payers. The results of the consultation activities conducted for the Pharmaceutical strategy for Europe¹³⁶ were also considered as valuable inputs to the revision.

¹³⁵ [Pharmaceutical Committee, Veterinary Pharmaceutical Committee and Expert groups \(europa.eu\)](#)

¹³⁶ [Pharmaceuticals – safe and affordable medicines \(new EU strategy\) \(europa.eu\)](#)

2. Methodology of the consultation activities

a) *Feedback mechanism on Commission combined evaluation roadmap/inception impact assessment*

The roadmap was published on the Commission *Have your Say*¹³⁷ website. 173 responses¹³⁸ were submitted by eleven types of stakeholders from 25 different countries. The largest number of submissions came from Belgium (34%), France (12%), Germany (8%) and the United States (7%). The large majority of submissions came from individual businesses (26%), CSOs (25,5%) and business associations (22,5%). All 173 entries were analysed in Excel and Word, recording the main topics, sub-topics and the type of stakeholder. No duplicates were found, but one campaign was identified from developers of innovative medicines.

b) *Public consultation (PC)*

The PC was published on the Commission *Have your Say*¹³⁹ website. There were 478 responses¹⁴⁰. Most of the answers were submitted by respondents from Germany (18.2%), Belgium (16.7%), and France (9.2%). Contributions from non-EU countries mainly came from the United States (23%), United Kingdom (15%) and Switzerland (9%). With respect to the type of stakeholder groups, most respondents were from the pharmaceutical industry (28.4%), followed by patient or consumer organisations (13.8%), healthcare provider organisation (9.8%) and healthcare professionals (7.9%). 158 respondents (33.1%) attached 183 separate position documents and 19 (4%) did not provide any response to closed questions. The questionnaire was structured into two main sections, backward-looking questions (Questions 1 and 2) exploring how the legislation performed and which issues should be addressed by the revision of the legislation and forward-looking questions (Questions 3 to 15) addressing possible solutions to the problems identified. Closed questions were quantitatively analysed using Excel and STATA, while open questions were manually checked and opinions and themes were summarised for each stakeholder group. Campaigns were identified using combination of statistical analysis and manual checking in Excel.

Summary of campaigns:

Campaign 1 (Nuclear medicine practitioners – 23 answers) – main message: to adapt the legislation to facilitate production and marketing authorisation of radiopharmaceuticals and to simplify regulations for dispensing of radioactive medicinal products.

Campaign 2 (Wholesalers – 16 answers) – main message: to identify the causes of medicines shortages and address them; to revise the wholesale distribution licensing system and the distinction between pharmaceutical full-line wholesalers and other wholesalers; to recognise the role of pharmaceutical full-line wholesalers to address shortages and strengthen supply.

¹³⁷ [Revision of the EU general pharmaceuticals legislation \(europa.eu\)](#)

¹³⁸ The full set of contributions received are published on the Commission website and can be found here: [Revision of the EU general pharmaceuticals legislation \(europa.eu\)](#).

¹³⁹ [Revision of the EU general pharmaceuticals legislation \(europa.eu\)](#)

¹⁴⁰ The full set of contributions received are published on the Commission and a report summarising the stakeholders' replies to the PC can also be found at: [Revision of the EU general pharmaceuticals legislation \(europa.eu\)](#)

Campaign 3 (Innovative pharmaceutical industry – 12 answers) – main message: to consider the importance of a future-proof, predictable and stable legal framework and the importance of maintaining a good level of reimbursement and of regulatory protection periods.

Campaign 4 (Generic companies – 11 answers) – main message: to give incentives and facilitate the uptake of off-patent products, such as creating new regulatory pathways for value added medicines innovation.

Campaign 5 (Rare disease patient associations – 10 answers) – main message: to have better genetic testing for approval of oncology therapies; to ensure equal access to medicines and consider local capacity perspectives (i.e. hospital pharmacies); to use real-world evidence to generate information on access, patient needs and response to treatments.

Campaign 6 (Microbiome-based product developers – 10 answers) – main message: To integrate microbiome science in the legislation, including standards, methods and definitions.

c) Targeted stakeholder surveys (survey)

Surveys tailored for each stakeholder group were developed and implemented in the form of online questionnaires using the survey tool ‘Survey Monkey’. It consisted of both closed (scored from 1 to 5) and open questions. Invitations to complete the survey were sent to 220 participants across all stakeholder groups. 90 of these organisations were asked to further disseminate the invitation through their networks. In total, 440 responses were received and 209 remained after cleaning and checking exercises. Representation amongst the different groups was not as anticipated with industry particularly over-represented (55.1%) and CSOs underrepresented (5.8%). Inputs were received from public authorities (26.4%), academic (8.2%) and health services (4.8%). Organisations from Western Europe (45.5%) mainly answered but contributions also came from Southern (19.7%), Eastern (16.3%) and Northern Europe (12.5%) and from non-EEA countries (6.3%). Data was downloaded and quantitatively analysed in STATA. Open-ended questions were analysed qualitatively in Excel. Eight campaigns were identified using a combination of statistical analysis and manual checking in Excel, but only three of them were considered for further analysis because they received more than ten responses.

Summary of campaigns:

Campaign 1 (Industry associations, parallel traders – 20 answers) – main message: support supply obligation for the marketing authorisation holder (MAH) at EU level to enable better competition of on-patent medicines, current legislation does not ensure sufficient stocks to enable a competitive parallel trade market to deliver on affordability; support increased move towards central authorisation for all medicines.

Campaign 2 (generic companies – 16 answers) – main message: burdensome regulatory requirements and inconsistency with other legal frameworks (medical device regulation, transparency directive...); support regulatory flexibility to accelerate access and avoid shortages; support stimulating the uptake of off-patent medicines and better dialogue between P&R authorities to improve access.

Campaign 3 (industry associations, wholesalers – 14 answers) – main message: current squeezes on margin/ remuneration for distribution endangers access to all medicines; support the regulatory flexibility applied during COVID-19 and the implementation of ‘Green lanes’.

d) Interviews

Semi-structured interviews of about one and an half hour were organised remotely via Zoom or Teams. They were based on an interview guide and individual questions were tailored to each interviewee. The guide had two parts covering the evaluation criteria and later discussing the problem analysis, possible policy measures and their comparison. A total of 138 individuals across all the identified stakeholder groups were interviewed including 57 representatives of the industry, 45 health service providers, 20 representatives of civil society organisations, 10 representatives of the public authorities and 6 academics. Summary notes were imported into Nvivo and coded thematically according to the objectives of the ongoing revision and abstracts were exported for synthesis into the reports.

e) Validation workshops

Two online stakeholder workshops were conducted with participants from all stakeholder groups. Both workshops followed the same structure: half-day event hosted via Zoom, with a plenary presentation and interactive polls, breakout sessions and plenary presentation of the breakout discussions. Ahead of the workshop, participants were able to choose two preferred breakout sessions and invitations included a discussion paper for contextualising the emerging findings. For both workshops, over 80% of participants were retained at the final plenary.

Validation workshop 1 on the evaluation findings

Out of the 246 invitations sent, 208 participants joined the workshop. The industry was the most represented group (86), followed by public authorities (61), civil society organisations (53), academics (23) and healthcare services (23). Five breakout rooms were created and grouped about 50 participants covering the five stakeholder groups: 1. Safeguarding Public Health; 2. Europe's regulatory Attractiveness; 3. Accommodating advances in science and technology; 4. Ensuring access to medicines; 5. Functioning of the EU market for medicines.

Validation workshop 2 on the impact assessment findings

Out of the 339 invitations sent, 199 participants joined the workshop. Public authorities was the most represented group (82), followed by the industry (68), academics (17), civil society organisations (16), and healthcare services (11). Four breakout rooms were created and grouped about 50 participants covering the five stakeholder groups: 1. Enabling innovation including for UMN; 2. Ensuring Access to Affordable Medicines for Patients; 3. Enhancing the security of supply of medicines and addressing shortages; 4. Reducing the regulatory burden and providing a flexible regulatory framework.

3. Overview of responses

A summary of the main themes and views provided by each stakeholder group in during the consultation activities is presented below. With regards to the numerous consultation activities conducted, which covered simultaneously the evaluation and the impact assessment, it seemed natural to present the results according to topics and sub-topics.

a) Evaluation

Effectiveness

Overall, the stakeholders were positive about the effectiveness of the legislation and its revision in meeting its objectives, i.e. safeguarding public health in Europe and supporting innovation of new medicines, providing an attractive and robust authorisation system for medicines and ensuring quality and safety of medicines. The interviews also stressed the positive impact of the centralised procedure to achieve the objectives of the legislation. On innovation, the legislation delivers a good framework for biosimilar medicines and the PRIME scheme¹⁴¹ has supported access to innovative products.

In some areas, the legislation was less effective; interviews with public authorities and healthcare professionals highlighted shortcomings in terms of ensuring access to medicines as reimbursement remains a Member State responsibility. Workshop 1 also identified the issue of access, affordability and innovation as areas where gaps remain to be addressed in the legislation. On access, several participants noted the lack of continuity in processes from marketing authorisation to patient access, with some products gaining marketing authorisation but not moving forward fast enough with the Member States' reimbursement decision. It was also suggested by some participants that regulatory protection can affect access by maintaining high prices for innovative medicines. In the scored questions of the survey, stakeholders indicated areas where the legislation has been effective to a lesser extent: *enabling access to affordable medicines for patients and health systems* (assessed as "moderate" by 33% CSOs, 15% public authorities and 24% academia), *minimising inefficiencies and administrative burden of regulatory procedures* (assessed as 'small' by 30% industry and health services, 16% public authorities¹⁴²), *enhancing security of supply of medicines and address shortages* (assessed as 'small' by 24% industry, 42% CSOs, 16% public authorities and 23% health services), *ensuring a competitive EU market for medicines* (assessed as 'moderate' by 24% industry, 8% CSOs and 35% public authorities), *reducing the environmental footprint of medicines* (assessed as 'very small' by 16% industry, 25% CSOs, 20% public authorities).

In their answers to open questions to the PC, academics expressed concerns on the evidence requirements for certain innovative cancer medicines. HTA bodies, healthcare payer organisations and a regional authority were also concerned about quantification of benefits based on early efficacy assessment for their cost-effectiveness assessment. In the context of the functioning of the EU market, patient or consumer organisations, healthcare payers and generic/biosimilar companies indicated that the legislation did not facilitate generic entry sufficiently; a campaign by the latter group was identified. However, chemical industry respondents and innovative medicine companies opposed this position. Industry associations also shared the view that the current incentives of the legislation promote the development of traditional product types (e.g. small molecules), while members of the public authorities and CSOs noted the need for more incentives for medicines for rare diseases and new antimicrobials. Another issue raised in the PC and the interviews was the lack of flexibility to accommodate scientific advances, such as advanced therapy medicines (ATMPs) and real-world data; a view that was shared by academic, patient or consumer organisations, healthcare professionals and industry respondents.

¹⁴¹ For details regarding the Priority Medicines Scheme, see [EMA's website on PRIME](#)

¹⁴² For targeted surveys not all questions were asked to all stakeholders, e.g. this question was only answered by industry, public authorities and health services.

Finally, during workshop 1 the environmental impact of pharmaceuticals and the environmental risk assessment (ERA) was debated. CSOs opposed industry stakeholders and shared concerns over the low priority of ERA in marketing authorisation decisions. The workshop also raised issues over genetically modified organisms (GMO) requirements, which do not fit with the legislation; complex innovative products lacking streamlined regulatory pathway; the lack of financial model for antimicrobials; the lack of incentives for repurposing and value-added medicines. Medicine shortages and security of supply were considered a high priority among participants and participants noted that lessons learned from the COVID-19 pandemic could prevent future shortages.

Efficiency

While 31% of the respondents to the survey indicated that the costs incurred by the legislation by all stakeholders impacted by it (industry and society including health systems and patients) were proportionate to its benefits to a moderate extent (46% industry, 8% CSOs, 15% public authorities, 18% academics and 30% health services), most stakeholders interviewed could not provide specific quantitative estimates of the costs and benefits associated with implementing the legislation. Interviews with industry stakeholders (41% of total interviews) noted the major drivers of costs were the additional data requirements related with the regulatory dossier and post-marketing authorisation requirements. Both innovative and generic medicine companies stated that abolition of the recurrent 5-year renewal cycle reduced regulatory burden. Yet, several pharmaceutical industry respondents in the PC and in workshop 1 explained the impact of duplicative processes causes costly regulatory burden, hinders innovation, in particular for SMEs, and causes delays across the life cycle of medicines. Despite the challenges to provide accurate monetary costs, a few industry respondents to the survey provided one-off adjustment costs, related to upgrading IT systems, as well as ongoing regulatory costs. Public authorities noted in interviews and in the open questions of the PC that they had increased workload and resources, including staff numbers, due to the revised legislation.

Relevance

Interviews, workshop 1 and results from the survey showed a general consensus that the objectives of the legislation are still relevant, but that the legislation should be amended to address new technological developments, to provide more clarity over unmet medical needs (UMN) and to ensure access to affordable products. In interviews, stakeholders provided further details on the areas the legislation needs to medicines. Academics and CSOs raised issues related to the lack of robust evidence to allow reimbursement, CSOs and public authorities were also looking for more equitable access to medicines, CSOs and healthcare professionals stressed the need for incentives to address antimicrobial resistance (AMR) (for novel antimicrobials and environmental impact of antibiotics); CSOs, public authorities and healthcare professionals were looking for more initiatives to ensure security of supplies. These results were echoed by the survey, where these topics were all ranked as least relevant in the current legislation. In the survey, 24% of respondents assessed the legislation as 'very' relevant to maintain the security of supply of medicines in the EU, 36% said it was 'moderately' relevant to maintain resilience and responsiveness of health systems during health crises. For industry interviewees, the legislation needs to be flexible to allow for technological developments and borderline products, and expertise in areas such as gene therapy, healthcare digitisation and use of real-world evidence is important to be built in regulatory agencies. This view was also noted by public authority interviewees, though it was highlighted that resources are needed to continue to expand capacity and expertise.

Coherence

All consultation activities indicated there was no major issues concerning the internal coherence of the legislation. However, it was highlighted that coherence with other specialised legislation and wider EU policies (such as ATMPs, medical devices, GDPR and Blood, Tissue and Cells - BTC)

could be improved. The lack of clarity of borderline products (e.g. medical devices containing medicines) was mentioned several times in interviews and in the PC by all stakeholders, noting that there is uncertainty over the legislation regulating the area of BTC and also concerns of excessive exclusivity given due to the interplay the legislation and the Orphan Regulation. The survey confirmed the same coherence problems but also highlighted the need to complement health-related legislations on GMOs (assessed as '*not at all*' coherent by 15% of stakeholders including 21% of industry and 5% of public authorities); to complement other EU legislations and policies on data protection (assessed as '*not at all*' coherent by 12% of stakeholders); on environmental requirements (assessed as '*slightly*' coherent by 12% of stakeholders including 12% of industry and 16% of public).

EU-added value

The EU-added value of the legislation was clearly supported among stakeholders interviewed compared to what can be achieved at the Member State level, in particular the benefit of the centralised authorisation procedure was noted as very valuable for small countries. This view was confirmed in workshop 1. The harmonisation of good manufacturing practices (GMP) and the regime of inspection was mentioned as another benefit of EU level action in workshop 1. Participants noted, however, the tensions to maintain requirements for high safety and efficacy of medicines and to improve the speed of authorisation. All stakeholder groups interviewed agreed that EU level action was important to tackle the COVID-19 pandemic in a quicker and more coordinated way. This view was supported, in the survey, to a large or a very large extent. Overall, stakeholders agreed that EU level action has improved Member States ability to put in place appropriate measures. The results of the survey indicated that, without EU level action, Member States would have had no more than a '*very small*' (16% of respondents including 20% industry, 25% CSOs, 13% public authorities and 10% health services) to '*small*' or '*moderate*' (24% of respondents including 26% industry, 33% CSOs, 18% public authorities and academics, 30% health services) ability to put in place appropriate measures.

b) Impact Assessment

The consultations indicated several areas of the legislation in which future policy measures may be needed. The following areas were discussed in details.

Incentives for innovation, including unmet medical needs and repurposing

The PC presented seven possible policy measures to support innovation, including for UMN and repurposing. In the open-ended questions to the PC as well as in the survey, there was no consensus across stakeholder groups on the most appropriate types of incentives and regulatory schemes to support innovation. Industry stakeholders called for a robust, stable and predictable intellectual property and regulatory protection system to support innovation but there were internal disagreements within this group. A campaign led by innovative medicine companies to maintain current level of incentives and exploring new types of push and pull incentives. Another campaign led by generic/biosimilar companies stated that extending data/market protection for any medicine will have a significant negative impact on affordability and competitiveness. These opposing views were also echoed during interviews. Several industry respondents to the PC and interviewed also expressed a wish to increasing the current 1-year data protection for over-the-counter (OTC) switches to 3 years. Regional public authorities noted that an assessment for better definition of '*innovative medicines*' is needed, with transparency of research and development (R&D) costs as

requirement for incentives, a view that was also supported by several CSOs in the PC. However, in interviews and workshop 2, industry stakeholders noted that transparency of R&D costs is not feasible as the methodology to calculate them would vary enormously and would contain sensitive information. Other regional public authorities stated that incentives for early market launch of generics and biosimilars could negatively impact medicine development and noted that strengthening the reward systems for innovative biotechnological medicines would be beneficial for UMN. Academics indicated a need for more incentives to engage universities, hospitals and other non-profit organisations to work in areas of low commercial interest.

The possibility to incentivise the provision of comparative data at the marketing authorisation stage was discussed in workshop 2. There was no consensus on whether there is a need or not for the provision of comparative data, with some noting that this data is already being provided where possible and also that, for some products, this would not be feasible (e.g. ATMPs).

There was broad agreement among stakeholders for the need to define UMN in a clear and transparent way including a multi-stakeholder approach to ensure consistency across different regulatory frameworks and along the medicine life cycle. The PC indicated the most important criteria to define UMN were the '*absence of satisfactory treatment authorised in the EU*' (scored as very important by 63% of all respondents) and the '*seriousness of a disease*' (scored as very important by 50% of all respondents). Similar positions were shared in workshop 2 with industry stakeholders emphasising that the lack of a definition of UMN could lead to legal unpredictability and impact investment decisions. In the survey, CSOs and academics rated as favourable the option to '*reduce the regulatory protection period for new products that do not address an UMN*', while for industry, the most important measures were additional regulatory protection for repurposing and codification of the PRIME scheme. The majority of stakeholders, but the industry, were supportive of a measure to permit breaking of regulatory protection under exceptional circumstances and the simplification of the obligations for not-for-profit/non-commercial entities to become marketing authorisation holders (MAH). According to the industry this is because regulatory protection is crucial to incentivise the significant investment needed to develop medicines. Other concerns among workshop participants were raised about '*indication slicing*' to meet UMN and the inefficiency of the regulatory protection system due to the patent protection and supplementary protection certificates. In the PC, there was strong consensus across all stakeholder groups that '*early scientific support and faster review/authorisation of a new promising medicine for an UMN*' was a very important (50% of all answers)/ important measure (25% of all answers), and more so for SMEs. However, public authorities and healthcare professionals highlighted that expedited regulatory frameworks should include robust pharmacovigilance and post-marketing authorisation studies to address uncertainties, proposing that sanctions should be in place in case of non-compliance. During the interviews, public authorities confirmed the view that expedited authorisation is important but also cautioned that it should not compromise safety and efficacy of medicines. The PC also showed overall positive views across stakeholder groups on repurposing. Healthcare provider organisations and public authorities noted in the PC and in the interviews more efforts could be done to collect evidence of off-label use and using real-world evidence to identify repurposing studies. CSOs and learned societies suggested in interviews and the PC the creation of a database for repurposed medicine. Most respondents also supported the provision of financial rewards or incentives to stimulate repurposing, in particular for SMEs. Yet, HTA bodies cautioned in the PC that more regulatory or intellectual property protection would not have a positive result for patients, and fair pricing mechanisms should be used instead. This aspect was supported by several health service stakeholders in interviews. Despite this, industry stakeholders and especially generic and biosimilar companies interviewed noted that the current protection of the commercial value of repurposing efforts is a key limiting factor to progress in this area. Several interviewees noted that public

investment could also play a role in repurposing as the research is often led by academics, hospital and other publicly funded institutions.

Antimicrobial resistance (AMR)

The survey presented ten possible policy measures to address AMR with the highest ranking measure being the *'introduction of a "pay or play" model'* mostly supported by CSOs and opposed by the industry as being unfair for companies with no expertise in AMR. The second highest ranking measure was *'additional market protection period for companies that hold MA for a novel antimicrobial'* mostly supported by the industry. However, there was low inter-stakeholder agreement for both measures. In the open-ended questions of the PC, there was similarly no clear consensus of opinions across stakeholder groups regarding the best types of regulatory incentives for the development of new antimicrobials. Several CSOs, public authorities, healthcare professionals and citizens cited small milestone rewards or longer data protection periods and novel incentives as potential positive measures facilitate development. Feedback from workshop 2 indicated stakeholders had mixed views on TEV. While large industry and SMEs see TEVs as an effective approach to meet the scale of the investment needed for sustainable R&D, the generic industry raised concerns about the high level of investment needed and the potential increase costs for the health system by delaying generic entry. Healthcare payers supported this last point. Interviews with public authorities highlighted that market exclusivity will not solve the problem, as the sale volumes will remain too low to incentivise the required investment. Instead, they favoured direct financial incentives (e.g. market entry rewards). CSOs concurred that companies would profit from the TEV but recognised the system could be fine-tuned to meet the needs of the public.

Future-proofing: adapted, agile and predictable regulatory framework for novel products

In the PC, there was a consensus among stakeholders that *'creating adaptive regulatory frameworks for certain novel types of medicines or low volume products (hospital preparations) in coherence with other legal frameworks'* and *'making use of the possibility for 'regulatory sandboxes' in legislation to pilot certain categories of novel products/technologies'* are the most important measures to consider to create an adapted, agile and predictable regulatory framework for novel medicines. Both measures were ranked as *'very important'* by respectively 43% and 34% of all respondents. These results were also supported in the survey and in interviews, where stakeholders highlighted that regulatory sandbox could increase innovation, competition, and speed to market for complex /cutting edge medicinal products. However, CSOs were concerned that regulatory sandboxes have the potential to lead to undesirable consequences such as *'carve-outs'* and a *'two-tiered'* regulatory framework.

The majority of stakeholder groups also rated as *'very important'* (43% of all answers) or *'important'* (19% of all answers) the measure to *'introduce an EU-wide centrally coordinated process for early dialogue and more coordination among clinical trial, marketing authorisation, health technology assessment bodies, P&R authorities and payers for integrated medicines development and post-authorisation monitoring'*. While this view was supported in the survey across all stakeholder groups but academics, it should be noted that in the PC, the industry expressed split views with 28% of them considering this measure as *'not important'* and 37% as *'very important'*. Workshop 2 highlighted that a centralised classification mechanism would need to involve close stakeholder engagement and have good balance between the competence and expertise of the advisory bodies responsible under each legal framework.

In the survey, out of the three possible policy measures explored to assess the future-proofing aspects of the legislation; the measure to *'adapt the regulatory framework for certain categories of*

novel products and technologies, including personalised medicines, medicines that contain or consist of a GMOs, platform technologies, or combined with artificial intelligence' scored consistently highest as having a positive or very positive impact by all stakeholders. The survey also proposed three policy measures related to scope and definitions of cell-based medicinal products. Overall, the measure *'adaptation of regulatory requirements for specific cell-based medicinal products (ATMPs) to facilitate production in the hospital setting while ensuring safety, quality and efficacy'* scored consistently highest as having a positive impact by stakeholders, except industry. The overall lowest ranked measure by the stakeholder groups was to *'provide a mechanism to exclude less complex cell-based medicinal products from the scope of the Pharmaceutical legislation and transfer to the BTC legislation'*. Workshop 2 highlighted that any changes to definitions require an integrated approach in consideration with other relevant legislations. Concerns were also raised about creating new classifications/categories for less-complex ATMPs and different regulatory routes for the different categories with the risk of causing confusion and jeopardise safety requirements for these products. Possible policy measures were also presented to harmonise requirements for GMOs Environmental Risk Assessment (ERA) where the measure to *'adapt a risk-based approach to determine when a specific ERA is required'* consistently scored highest. Interviews highlighted that this measure could increase the efficiency of authorisation of GMO-containing medicines and the competitiveness of the EU in this field.

Rewards and obligations related to improved access to medicines

In the PC, there was a shared view among all stakeholders that harmonisation of HTA and greater transparency on P&R is needed at the EU level to improve patient access to medicines. This view was confirmed during interviews and workshop 2. Stakeholders acknowledged that national policies on payment and reimbursement and reference price systems are outside the remit of the legislation and national competence. Among the eight measures explored to improve access in the PC, there was consensus among respondent on the least and most important measures to improve access. *'Maintain the current rules which provide no obligation to market medicines in all EU countries'* was scored as not important by 35% of the respondents, while *'introduce harmonised rules for multi-country packages of medicines'* scored as very important by 41% of all respondents with the strongest support coming from the industry (69%). Results from the survey confirm this view. The second highest rated measure was *'introduction of electronic product information (ePI)'* (scored very important by 27% of respondents). While the industry considered this measure as very important (47%), healthcare professionals, public authorities and citizens were relatively less supportive of this measure (13%). Workshop 2, dominated by industry stakeholders, also confirm this result. Participants explained that marketing authorisation could be complemented by ePI and multi-country packs to address the access issues related to national language requirements on leaflets and packaging. Healthcare professionals, CSOs and public authorities were concerned for citizens with no access to computers.

Regarding obligations to improve access, most consultation activities considered the *'requirement for companies to place – within a certain period after authorisation – a medicine on the market in the majority of Member States (including small markets)'* as a very important policy measure. Industry stakeholders were largely unsupportive of this measure and raised concerns about regulatory penalties to ensure medicine are available on the market. In their view, there are 'multifactorial' issues that may not be in their control, including differences in national regulatory requirements; speed of P&R negotiations; possibly of needing to conduct further research; and unforeseen manufacturing delays. These views were echoed in the interviews and the workshop 2. Results from the survey highlighted that the majority of stakeholders but industry were supportive of the *'requirement to MAH applying for mutual recognition procedure/decentralised procedure*

(MRP/DCP) to include small markets'. The workshop 2 also discussed the obligation to place a centrally authorised medicine on the market in the majority of EU Member States. In general, participants found that the obligation could bring benefits depending on its implementation. It was suggested that the obligation could focus on facilitating access to early generic entry in countries where the obligation is not being met.

In the PC, there was consensus across most stakeholders groups that there should be new incentives for swift market launch of medicines across the EU: CSOs and academic/research institutes were most in favour (37% and 33%), with industry split between 'slightly important' (27%, innovative pharmaceutical companies) and 'very important' (31%, wholesalers). Results from the PC also indicated the measure to 'allow early introduction of generics in case of delayed market launch of medicines across the EU while respecting intellectual property rights' was scored as 'very important' by 30% of stakeholders to improve patient access to medicines. Workshop 2 also explored incentivising product launch in all EU Member States but participants were broadly of the view that the incentive will not necessarily ensure access but it could provide a financial incentive to launch in smaller markets. In the PC, there was a shared view among academics, healthcare professionals and CSOs for the introduction of a 'solidarity pricing' whereby wealthy Member States contribute to create an 'EU based fund' to finance access to medicines.

Enhance the competitive functioning of the market to ensure affordable medicines

The survey explored measures to enhance the competitive functioning of the market, including measures to support early market entry for off-patent medicines, to facilitate market entry of generics/biosimilars and to address 'duplicates' of centrally authorised medicines. Overall, the measures 'certification procedures to include outcomes that could be used for multiple products to avoid duplicative assessment' and 'introduce new simpler regulatory pathway for generics and biosimilars to reduce assessment time by authorities' were the most consistently highly scored by all stakeholder groups. The measure to 'establish the legal basis for EMA committee to provide advice on interchangeability of specific biologics' was also highly scored by most stakeholder groups (29% of respondents assessed it as having a 'positive impact') but the industry. This group was split with 10% of respondents scoring the measure as 'strongly negative', 14% as having 'little or no impact' and 12% with 'strongly positive impact'.

The 'broadening of the scope of "Bolar exemption" beyond generics by allowing repurposing studies/comparative trials without infringing patent rights' was assessed as having a 'positive impact' by CSOs (25%), public authorities (31%) and academics (18%). The industry was relatively less supportive of this measure with 25% of respondents scoring it as having 'little or no impact' and only 11% of respondents viewing it as having 'strong positive impact'. Workshop 2, participants confirmed support for this measure in terms of broadening it to more actors and extending it to other purposes (e.g. repurposing studies or comparative studies). But there were mixed views about what aspects this measure should cover. The generic industry was supportive of extending the Bolar exemption. It was noted that the Bolar exemption needs to be considered along with the research exemption and that the activities exempted from patent infringement should be precisely defined. The generics industry noted that proposed changes do not cover all activities needed to get Day 1 launch.

One of the lowest ranked policy measure in the survey was 'introduce specific incentives for a limited number of first biosimilars for a shared market protection', in particular by industry and public authorities. In workshop 2, it was discussed that this incentive is unlikely to increase uptake in smaller populations. Concerns were raised about giving only one product priority as this would limit competition and thus increase prices of medicines. Moreover, workshop participants indicated

the bottleneck is the uptake rather than market entry of biosimilars. The industry shared in interviews concerns over the incompatibility of shared market protection with EU regulatory system because of patent linkage issues. While CSOs (49%), citizens (39%), academics (33%) and public authorities (22%) considered this measure as very important, 26% of the industry ranked it as *'not important'*. In interviews, innovative medicine companies indicated their concerns that increasing incentives for generic entry to the market could discourage innovation in EU.

Security and supply of medicines

The PC presented ten possible policy measures to ensure security of supply of medicines in the EU. Overall, stakeholders scored the measure *'companies to have shortage prevention plans'* (46%) and *'introduce a shortage monitoring system at EU level'* (43%) as very important. In contrast, *'maintaining the current rules'* (15%) and *'introducing penalties for non-compliance by companies with proposed new obligations'* (18%) were scored as the least important. CSOs (34%) and public authorities (30%) ranked as very important the requirement for companies to diversify their supply chains, while 34% of industry considered this as not important. 41% of stakeholders ranked as very important *'monitoring and reporting of medicines shortages coordinated at the EU level'* as another measure to ensure security of supply. This view was confirmed in the survey, where the highest ranked policy measure was the *'introduction of an EU information exchange on critical shortages based on national supply-demand monitoring data'*.

In workshop 2, stakeholders explained that diversification of the supply chain is challenging and not always feasible due to the difficulty to find alternative suppliers upstream in the supply chain. It was pointed out that having a more diverse and sustainable supply chain would likely increase the cost of medicines due to increased compliance costs.

On the possibility to increase shortage notification requirements for all medicines from 2 to 6 months, workshop participants suggested having a definition for critical shortage rather than increasing the notification period. The industry consistently supported this view in interviews and in the PC. In the workshop, concerns were also raised that earlier notification of potential shortages could lead to real shortages by triggering stockpiling and hoarding in Member States. In the PC and in interviews, several public authorities explained that the current notification requirements are appropriate, but compliance needs to be improved. According to academics a requirement for safety stocks should not result in significant price rises. In the survey, most stakeholders, but wholesalers and the developers, thought the measure to *'require MAH to notify authorities of impending shortages 6 months in advance'* would positively impact the security of supply. This split view was also confirmed in the PC.

The issue of stockpiling measures, requirements (or reserve requirements) for MAHs and wholesalers for critical medicines was discussed at the workshop. It was assessed by most participants as an effective approach to temporarily alleviate the effects of shortages. However, such measure would need to happen at the EU level in the form of unfinished product, and for critical medicines only. When considering EU-wide vs national level stockpiling, it was suggested that implementation at a national level would require an obligation for stock-sharing and special flexibility to facilitate easy movement of products between Member States. On the duration of stockpiling, there was a consensus that this could not be a permanent solution but only helpful for the first 2-3 weeks of shortages. Participants highlighted warehousing requirements for stockpiling would be challenging for certain types of products that need to be produced on site or cannot be stored for long periods of time (e.g. plasma-derived products or personalised medicines).

Quality and manufacturing

Several policy options were discussed in the consultation activities including harmonising a system of sanctions on GMP, increase sustainability performance in relation to AMR, ensure the legislation is adapted to regulate new manufacturing methods and, lastly, the modification of inspections regime and supply chain oversight. In the survey, only public authorities and industry stakeholders contributed to these aspects. Public authorities viewed all policies, on average, as having potential for positive or large positive impact. Industry stakeholders were in support of reinforcing Member States' GMP and good distribution practices (GDP) inspection capacity by setting up a joint audit scheme to reinforce and strengthen the quality of inspections; strengthening the role of the EMA in supporting the robust oversight of manufacturing sites and in the coordination of all inspections; and to adapt the terms of the legislation to accommodate new and emerging manufacturing methods. They were less in favour of introducing a harmonised system of sanctions related to GMP and GDP; of extending the scope of mandatory inspections to encompass supply chains; of increasing the responsibilities of MAH vis-a-vis the quality of the supply of APIs and raw materials and clarify responsibilities of business operators over the entire supply chain; of adapting GMP procedures to environmental and antimicrobials challenges. Interviews confirmed the support for the policies mentioned above, but also highlighted some tensions. National competent authorities noted the need for more resources to train inspectors (e.g. in the area of antimicrobial resistance) and to cope with an increased regime of inspections. Industry stakeholders noted that the system of sanctions and the increased regime of inspection and supply chain oversight would present barriers for SMEs. They also stressed the existence of other legislations regulating antimicrobials and thus on the risk for duplication. The PC confirmed the overall positive view on the need to adapt new manufacturing rules and methods. In open questions, CSOs, academics, health services and citizens highlighted the importance to increase the transparency of the supply chain through more oversight. Regional public authorities suggested to increase cooperation for supply chain monitoring within and outside the EU; to clarify the documentation necessary for active substances production; to promote EU manufacturing of essential vaccines and medicines. Both pharmaceutical industry and pharmaceuticals traders/wholesalers emphasised the need for more resources for GMP inspections in less regulated third countries to ensure a level playing field.

Environmental challenges

The PC showed general consensus on the importance of strengthening efforts to reduce the environmental impact of medicines, but opinions varied on the urgency and appropriate measures. Citizens were concerned about the pollution of waters, the environmental impact of packaging and disposal of medicines. Environmental organisations expressed that the ERA should be a requirement and part of the risk-benefit analysis for all medicines and through the whole life cycle of the product, including assessment for AMR. This position was also expressed during workshop 1, where CSOs opposed industry stakeholders and shared concerns over the low priority of ERA in marketing authorisation decisions. Several public authorities, healthcare professionals and CSOs suggested the inclusion of environmental impact in the decision-making criteria to award incentives to developers and reduce the environmental impact of medicines. Pharmaceutical industry noted in the PC and in interviews that most APIs do not have a significant risk for the environment and that ERA for off-patent medicines are duplicative and unnecessary. The chemicals industry noted that the current system for tendering does not reward environmentally sound manufacturing practices, and instead focus on low prices. In their view, environmental standards could benefit from more international regulatory alignment. Industry respondents suggested the creation of a fund for investment in greener manufacturing practices in the EU to help SMEs and improve security of supply. Several environmental organisations, healthcare professionals, civils society organisations and citizens noted

in the PC the need for clearer guidelines for procurement of medicines, which should include greener manufacturing practices, and more MAH responsibility over all supply chain actors.

Of the three possible policy measures presented in the survey, the option *‘to strengthen the environmental risk assessment (ERA) requirements and conditions of use for medicines’* was rated positively by most public authorities, healthcare professionals and CSOs, while the industry was divided with answers ranging from strong negative to strong positive impact. There was no consensus within academics on this option. The option *‘to introduce a requirement to include information on the environmental risk of manufacturing medicines, including supply chain actors, in ERA / application dossiers’* was mostly rated as negative by industry stakeholders while all other stakeholder groups viewed this option bringing a positive impact. The last option of the survey *‘to establish an advisory role for EMA with regard to ERA and green manufacturing aspects and quality of medicines’* was seen as having potential positive impact for all stakeholder groups, with only industry average response closer to *‘little to no impact’*.

Interviews with industry stakeholders noted that higher manufacturing standards to reduce environmental impact comes with associated costs. In this regard, EU companies should be supported to remain competitive with other regions. Public authorities also highlighted the double challenge to ensure environmental sustainability and to bring manufacturing back to Europe. This will require a multifactorial approach beyond the legislation. They also confirmed an overall support for strengthening the ERA as long as it does not impact access to patients. CSOs stressed the need for transparency over environmental impact of medicines and suggested to make use of the best practices already implemented across Member States. Workshop 2 confirmed the general view that there is a tension between the need to reduce regulatory burden while expanding environmental considerations. There was a general consensus that the legislation should be linked to environmental legislations. Participants raised several issues, e.g. inspectorates lacking adequate background or mandate over environmental matters, environmental parameters not fit for purpose for GMP and environmental risks related to manufacturing can be site specific and difficult to standardise.

COVID-19 lessons learnt

Participants of workshop 1 highlighted that medicine shortages and security of supply was a high priority and noted that lessons learned from the COVID-19 pandemic could prevent future shortages. Out of the four possible policy measures of the survey, the *‘possibility of introducing a codified system of rolling reviews for products addressing UMN’* did not gain stakeholders consensus, with industry and public authorities rating this option more favourable than health services and academics. In interviews, all stakeholders recognised that the rolling reviews were successful to address the pandemic. Some public authorities noted the benefit of more developer-regulator interaction but others also highlighted the unsustainability of that system for national authorities. CSOs and healthcare services also noted that if P&R authorities are not able to assess therapeutic value (due to lack of relevant data), the medicine will not reach patients. In the PC, this view was confirmed by academics, healthcare payers and CSOs respondents. Yet, several pharmaceutical industry respondents argued that real-world evidence can support data provision and rolling reviews can play an important role for certain products (e.g. plasma-derived medicinal products). Similar exchanges took place during workshop 1. Academics interviewed noted that the EMA pandemic taskforce was a key enabler in allowing coordinated response and CSOs, healthcare professionals and public authorities discussed the importance of the EU joint procurement of vaccines for speedy and efficient action for access. Industry stakeholders interviewed noted that the virtual audits and inspections could be implemented post-pandemic to save resources, and they highlighted the need for more alignment in clinical trials during pandemics to ensure speed and appropriate designs. It was also noted that the GMO exemption for COVID-19 vaccine could be applied to other areas,

such as low risk ATMPs. Public authorities also noted that transparency measures were implemented as a response to the pandemic, as well as strengthening of the network (national competent authorities, EMA and the Commission) through regular meetings, which brought positive outcomes.

The second measure of the survey, *'the possibility of allowing regulators to reject immature marketing authorisation applications'* (when data is insufficient to conduct full assessment to support a decision) was rated as having strong positive impact by public authorities, while industry rated it more negatively. The third measure *to establish an EU emergency use authorisation (EUA) of medicines* received an overall positive score by all stakeholders as currently, there is only national emergency authorisation. The last and similar measure, *'to establish an EUA that would still leave Member States to decide but it would be based on EU level scientific advice'* was also positively viewed by all stakeholder groups, except for academics who ranked it as having little or no impact. Neither the third, nor the fourth measure were discussed in the PC, apart from two pharmaceutical industry respondents expressing a positive view on an EU EUA.

ANNEX 3: WHO IS AFFECTED AND HOW?

1. Practical implications of the initiative

The proposed revisions have substantial positive implications for EU patients, companies and national health systems.

For **patients**, there are many improvements foreseen in all areas of importance: improving the flow of cutting-edge treatments available for conditions for which there are no effective treatment options currently (UMNs), reversing the decline in investment in antimicrobial research and encircling the issues driving AMR, incentivising access in all Member States, a broader repurposing, and the generic and biosimilar entry. A more robust ERA will also support environmental goals. Measures on security of supply will moreover improve access to medicines.

For **companies**, the proposed revisions sought to strike a balance between ensuring a strongly positive environment for research-intensive pharma industry to continue to develop its cutting-edge products within the EU and the need to ensure all EU member states and citizens have access to a broader array of treatment options. Therefore, the modulated incentive scheme provides attractive incentives for innovation and placing on the market. The future proofing of the regulatory framework will also embrace technological change. New obligations for shortages prevention and environmental standards will result in additional costs for businesses. However, simplification and long term benefits from digitalisation are likely to offset any new costs and result in earlier authorisations.

For **health systems**, public health budgets would also benefit from the modulated incentive scheme since more EU citizens will have access to treatments, which results in savings due to more effective treatment and reduced hospitalisations. They will also benefit from stronger competition and transparency measures around public funding for clinical trials. There would be additional societal benefits for families and carers too, in terms of both quality of life / independence and earning potential. Overall, the new incentives will come with costs for healthcare budgets but the public health benefits should outweigh those.

For **regulators**, the effects of the proposed changes would be overall positive especially due to various horizontal measures, which will allow to better coordinate, simplify and accelerate regulatory processes to the benefit of industry and launch new digitalisation programmes to improve the integration and efficiency of the regulatory system overall (as well as its interfaces with other regulatory systems

2. Summary of costs and benefits

Table I presents an overview of the estimated benefits for the pivotal measures under the preferred option, and Table II presents an overview of the main estimated costs associated with those measures.

Taken together, we estimate the **benefits should be in the order of €2.27bn a year and €34bn over 15 years**. We estimate the total **costs to be in the order of €2.17bn a year and €32.5bn over 15 years**. That would represent a net benefit of **€0.10bn a year and a €1,5bn over 15 years**.

This estimate is an **underestimate as there will be many indirect benefits for health systems and patients from improved access to new medicines for UMNs, new classes of antimicrobials and extended market access**. However, while we expect many tens of thousands of individual citizens

to benefit in some degree from these revisions, it has not been possible to establish quantify and monetise these many and various social impacts.

Benefits

For **patients**, the principal benefit would be access to new medicines. The measures proposed would provide access to new medicines to 67 million more (as compared to today) EU citizens, should they need them.

For **companies**, the principal direct benefits relate to the income for originators associated with additional flow of protected sales that will result from the various incentives foreseen (e.g. a year one extension to the overall period of regulatory data protection for medicines addressing an unmet medical need).

For **health systems**, the main indirect benefits relate to the lower prices for health payers associated with those medicinal products where MA holders do not place their product in all Members States and where, as a consequence, generic competition will emerge two or one years earlier.

There are also savings expected from the various horizontal measures, which will allow benefits for both companies and **regulators**. They will allow to better coordinate, simplify and accelerate regulatory processes to the benefit of industry and launch new digitalisation programmes to improve the integration and efficiency of the regulatory system overall (as well as its interfaces with other regulatory systems).

I. Overview of Benefits (total for all provisions) – Preferred Option		
<i>Description</i>	<i>Amount</i>	<i>Comments</i>
Direct benefits		
Medicines for unmet medical needs (UMNs)	An additional 2-3 new medicines annually relevant to UMNs (c. 40 new medicines over 15 years). This would result in originators securing an additional €320m-€640m protected sales annually (15 years: €4.8bn - €9.6bn). Overall additional income of on average €480m annually (€7.2bn over 15 years).	+12 months extension of RDP for innovation, particularly around unmet medical needs (UMNs) would result in a higher proportion of UMNs within all newly authorised medicines.
Novel antimicrobials	An additional 1 novel antimicrobial annually (c. 15 over 15 years). This would result in originators securing an additional €545m protected sales annually (15 years: €8.2bn).	The transferable voucher, if approved, would provide strong support for innovation in novel antimicrobials. The additional income may be secured by the developer of the novel antimicrobial where they use a voucher with another high value medicine in their portfolio or split between the developer of the antimicrobial and another originator that has purchased the (transferable) voucher. We have estimate the purchase value at €360m (assuming one voucher a year). With more breakthroughs a more vouchers the average sale price would fall.
Comparative trials	A small number of EMA medicines applications will be able to implement more robust trials and take advantage of the incentive (8-10 a year). This would result in originators securing an additional €640m-€800m protected sales annually (15 years: €4.2bn - €6.3bn). Overall additional income of on average €720m annually (€10.8bn over 15 years).	+6 months extension of RDP for medicines applications that include the findings of comparative trials.

I. Overview of Benefits (total for all provisions) – Preferred Option		
<i>Description</i>	<i>Amount</i>	<i>Comments</i>
Market access	<p>The great majority of new medicines will be able to comply with the market access conditions.</p> <p>10-12 medicines annually (150-180 over 15 years) may fail to meet the conditions, and in these cases the RDP will lapse at 6+2 years (not 6+2+2).</p> <p>For this sub-set of products where the RDP is the last line of defence, there will be a €210m-€270m gain each year (€3.1bn-€4.1bn over 15 years) to the EU health system, because of lower prices from earlier competition by generics.</p> <p>Overall additional income of on average €240m annually (€3.6bn over 15 years).</p>	+2 years protection conditional on launch in all EU markets in 2 years.
Indirect benefits		
Patients benefit from effective medicines (UMNs)	<p>Thousands of EU citizens will have access to treatments that help recover from or manage their debilitating conditions, improving their quality of life and life expectancy.</p> <p>There may also be indirect benefits / savings for health systems from more effective treatment and reduced hospitalisations.</p> <p>There would be benefits for families and carers too, in terms of both quality of life / independence and earning potential.</p>	It is not possible to quantify / monetise (indirect) patient benefits given the diversity of UMNs (certain neurological conditions, cancers, muscular dystrophy, etc.). These conditions may affect hundreds of citizens or millions in the case of Alzheimer.
Patients have access to new classes of antimicrobials that help to contain AMR	<p>It is estimated that each year about 670,000 infections occur, and that 33,000 Europeans die as a consequence of antibiotic-resistant bacteria. With the burden being highest in the elderly and infants.</p> <p>It is also estimated that AMR costs the EU €1.5bn per year in healthcare costs and productivity losses.</p> <p>Even a 1% improvement in our management of AMR could save several hundred lives annually and save health systems hundreds of millions too.</p>	It was not possible to quantify / monetise the (indirect) patient benefits that might result from new classes of antimicrobials.
Improved decision making for HTAs / Reimbursement bodies	More robust evidence from comparative trials should facilitate HTA decision making, leading to improved reimbursement decisions and faster decisions / access where medicines are approved for reimbursement.	It was not possible to quantify / monetise the (indirect) HTA and patient benefits that might result from the greater use of more robust trials.
All EU member states (inc smaller countries) have improved access to new medicines	<p>On average, new medicines will be available to patients in 22-25 markets compared with the current situation (12-15), reaching 80% of the population compared with the current situation (c. 65%).</p> <p>The access to all new medicines in 5-10 additional markets will mean that hundreds of thousands of EU citizens will have better treatment options, with accompanying improvements in health equality and possibly public health.</p>	It was not possible to quantify / monetise the (indirect) patient benefits that might result from the systematic extension of market access
Improved management of shortages	<p>Most EU countries report increasing numbers of medicine shortages, with the great majority having recorded shortages for 200 or more medicines in the year.</p> <p>Fewer shortages may benefit tens of thousands of patients, with access to the more appropriate medicines.</p> <p>According to the Pharmaceutical Group of the EU, eliminating shortages might save healthcare systems 5-10% of their pharmacy-related staff costs as well as time wasted by frontline staff.</p>	<p>Fewer shortages would mean more patients have access to the medicines they need.</p> <p>Healthcare systems would see cost savings from avoiding time wasted deciding / finding appropriate alternative medicines.</p>
Improved environmental performance of pharma industry	<p>This may make a positive difference to 40-50 new medicines a year (600-750 in 15 years).</p> <p>This should result in a reduction in the intrinsic environmental risks of a proportion of medicines, a lowering of the levels of active ingredients getting into the environment through excretion and a lowering of the level and number of accidental releases to the environment by manufacturers (mostly non-EU).</p>	New medicines would be subject to a more rigorous assessment, which should feed forward to more informed selection of APIs, encourage green pharma and select for higher standards across global supply chains.
Administrative cost savings related to the 'one in, one out' approach*		
Streamlining, acceleration of processes and coordination of network	<p>Originators should realise savings in the range €15m-€30m annually (€225m-€450m over 15 years).</p> <p>Generics companies should secure additional income of €55m-€100m annually (€825m-€1,650m over 15 years).</p> <p>European and national regulators should see savings in the range €33.5m-€67m annually (€502.5m-€1005m over 15 years).</p> <p>Overall savings should represent on average €155m annually (€2.33bn over 15 years).</p>	<p>Originators will benefit from various simplification and governance enhancements producing administrative cost savings. Generics companies will benefit from administrative savings, faster procedures and earlier market entry.</p> <p>European and national regulators should see a reduction in</p>

I. Overview of Benefits (total for all provisions) – Preferred Option		
Description	Amount	Comments
		duplication of effort across committees and among regulators, producing savings in enforcement costs
Digitalisation	Digitalisation savings for businesses in the range €7.5m-€15m annually (€112.5m-€225m over 15 years). Digitalisation savings for regulators in the range €67m-€3.5m annually (€1,005m-€2,010m over 15 years). Overall savings of on average €112m annually (€1.67bn over 15 years)	The various digital initiatives proposed will save time and administrative costs for businesses and deliver substantial efficiencies / reductions in enforcement costs for regulators.
Adaptations to new concepts and support SMEs and non-commercial organisations	Enhancement savings for businesses in the range €7.5m-€15m annually (€112.5m-€225m over 15 years). Enhancement indirect benefits for businesses in the range €5m-€10m annually (€75m-€150m over 15 years). Enhancement savings for regulators in the range €1.75m-€3.5m annually (€26.25m-€52.5m over 15 years). Overall savings of on average €21m annually (€321mn over 15 years).	Industry - and SMEs in particular - should benefit from better and more dynamic advice avoiding queries on applications (delay) and rework to the same (cost); regulators should benefit from more mature applications that can be assessed more easily and quickly. There may be some limited indirect benefits, whereby faster assessments, on average, may facilitate at least some new medicines being approved for sale earlier and some generics entering the market earlier.

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

Costs

For patients, the principal costs (indirect) will relate to reduced access to treatments associated with the additional delays in generic entry for new medicines that have benefitted from extensions.

The principal costs for industry comprise around €425m in costs associated with the implementation of market access conditions and more stringent assessment and reporting on shortages and environmental risks.

The principal costs for health systems relate to the additional period in which they will need to pay a premium price for medicines benefiting from any extensions to the period of regulatory data protection.

For regulators, would bear some costs relating to the design and implementation of the wide-ranging proposals for streamlining and digitalisation.

II. Overview of costs – Preferred option							
		Citizens/Consumers		Businesses		Administrations	
		One-off	Recurrent	One-off	Recurrent	One-off	Recurrent
UMNs	Direct adjustment costs						
	Direct administrative costs						
	Direct regulatory fees and charges						

II. Overview of costs – Preferred option							
		Citizens/Consumers		Businesses		Administrations	
		One-off	Recurrent	One-off	Recurrent	One-off	Recurrent
	Direct enforcement costs						
	Indirect costs				Lost income for generics €77m-€154m a year (ave €115m) €1.15bn-€2.3bn over 15 years (ave €1.7bn)		Additional costs for payers €163m-€326m a year (ave €245m) €2.45bn-€4.9bn over 15 years (ave €3.67bn)
AMR	Direct adjustment costs						
	Direct administrative costs						
	Direct regulatory fees and charges						
	Direct enforcement costs						
	Indirect costs		Costs for 'unserved' patients €158m a year €2.37bn over 15 years				Additional costs for payers €283m a year €4.2bn over 15 years
Comparative trials	Direct adjustment costs						
	Direct administrative costs						
	Direct regulatory fees and charges						
	Direct enforcement costs						
	Indirect costs				Lost income for generics €154m-€192m a year (ave €173m) €2.3bn-€2.9bn over 15 years (ave €2.6bn)		Additional costs for payers €326m-€408m a year (ave €367m) €4.9bn-€6.1bn over 15 years (ave €5.5bn)
Market access	Direct adjustment costs						
	Direct administrative costs						
	Direct regulatory fees and charges						
	Direct enforcement costs						
	Indirect costs				Lost income for originators		

II. Overview of costs – Preferred option							
		Citizens/Consumers		Businesses		Administrations	
		One-off	Recurrent	One-off	Recurrent	One-off	Recurrent
					€352m-€422m a year (ave €387m) €5.3bn-€6.3bn over 15 years (ave €5.8bn)		
Shortages	Direct adjustment costs						
	Direct administrative costs				Additional costs for originators €10m-€20m a year (ave €15m) €150m-€300m over 15 years (ave €225m)		
	Direct regulatory fees and charges						
	Direct enforcement costs						Additional costs for regulators €10m-€20m a year (ave €15m) €150m-€300m over 15 years (ave €225m)
	Indirect costs						
Environment	Direct adjustment costs						
	Direct administrative costs				Additional costs for industry €20m-€25m a year (ave €22.5m) €300m-€375m over 15 years (ave €337.5m)		
	Direct regulatory fees and charges						
	Direct enforcement costs						Additional costs for regulators €20m-€25m a year (ave €22.5m) €300m-€375m over 15 years (ave €337.5m)
	Indirect costs						
Streamlining	Direct adjustment costs						

II. Overview of costs – Preferred option							
		Citizens/Consumers		Businesses		Administrations	
		One-off	Recurrent	One-off	Recurrent	One-off	Recurrent
	Direct administrative costs						
	Direct regulatory fees and charges						
	Direct enforcement costs					Additional one-off costs for regulators €16.8m-€33.6m (ave €25.2m)	Additional costs for regulators €33.5m-€67.5m a year (ave €50.5m) €502.5m-€1012.5m over 15 years (ave €757.5m)
	Indirect costs						
Digitalisation	Direct adjustment costs						
	Direct administrative costs						
	Direct regulatory fees and charges						
	Direct enforcement costs					Additional one-off costs for regulators €120m-€350m (ave €235m)	Additional costs for regulators €24m-€70m a year (ave €47m) €360m-€1050m over 15 years (ave €705m)
	Indirect costs						
Enhanced support	Direct adjustment costs						
	Direct administrative costs						
	Direct regulatory fees and charges						
	Direct enforcement costs						Additional costs for regulators €4.8m-€7.2m a year (ave €6m) €72m-€108m over 15 years (ave €90m)
	Indirect costs				Additional costs for industry €1.6m-€2.4m a year (ave €2m) €24m-€36m		

II. Overview of costs – Preferred option							
		Citizens/Consumers		Businesses		Administrations	
		One-off	Recurrent	One-off	Recurrent	One-off	Recurrent
					over 15 years (ave €30m)		
Costs related to the 'one in, one out' approach							
Total	Direct adjustment costs						
	Indirect costs		Costs for 'unserved' patients €158m a year €2.37bn over 15 years		Indirect costs to businesses €290.5m / yr €4.36bn / 15 yrs		
	Administrative costs (for offsetting)				Administrative costs to businesses €424.7m / yr €6.37bn / 15 yrs		

(1) Estimates (gross values) to be provided with respect to the baseline; (2) costs are provided for each identifiable action/obligation of the preferred option otherwise for all retained options when no preferred option is specified; (3) If relevant and available, please present information on costs according to the standard typology of costs (adjustment costs, administrative costs, regulatory charges, enforcement costs, indirect costs;). (4) Administrative costs for offsetting as explained in Tool #58 and #59 of the 'better regulation' toolbox. The total adjustment costs should equal the sum of the adjustment costs presented in the upper part of the table (whenever they are quantifiable and/or can be monetised). Measures taken with a view to compensate adjustment costs to the greatest extent possible are presented in the section of the impact assessment report presenting the preferred option.

3. Relevant sustainable development goals

III. Overview of relevant Sustainable Development Goals – Preferred Option(s)		
Relevant SDG	Expected progress towards the Goal	Comments
SDG 3: Good Health and Well-Being for people Highly relevant	<p>The revision will help futureproof the legislation, continuing to safeguard public health.</p> <p>The revisions will increase the proportion of new medicines that address unmet medical needs (UMN), thereby creating the potential for millions of people across the EU and internationally to access effective treatments for their debilitating conditions.</p> <p>The revisions will introduce new incentives for innovative with the potential to tackle disease resistant pathogens and contribute to managing antimicrobials resistance (AMR).</p>	<p>The expected progress towards SDG 3 and SDG 9 are closely interlinked and complementary.</p> <p>By improving the innovation capacity of the EU pharmaceutical industry, the revision will contribute to improve the access to all treatment for all Europeans and therefore to ensure good health and well-being to European citizens.</p>
SDG 9: Industry, Innovation, and Infrastructure. Highly relevant	<p>The revision sought to simultaneously support the EU pharmaceutical industry and patients. The introduction of substantial additional incentives for major medicines innovations in the areas of UMN, AMRs and other therapeutic areas where there is an evident social need and a demonstrable market failure (e.g. difficult / costly science and small, volatile markets).</p> <p>The revision should strengthen the EU industry's global competitiveness in those areas most directly related to UMN.</p> <p>The revisions is expected to lead to a refocus of the R&D industry on European territory</p>	<p>The revision will support progress towards SDG 9 by creating a future-proof environment supporting the pharmaceutical industry.</p> <p>Measures addressing the inefficiencies of the</p>

III. Overview of relevant Sustainable Development Goals – Preferred Option(s)		
Relevant SDG	Expected progress towards the Goal	Comments
	<p>attracted by streamlined and harmonised regulatory environments. Thus, the revision should also contribute to the strengthening of EU's attractiveness as a place for carrying out medicines research globally, through the implementation of new incentives for innovation, new definitions, various streamlining and digitalisation measures.</p> <p>The revision is expected to strengthen the EU generic industry's competitiveness by incentivising the industry stakeholder to retain their manufacturing capacity within the EU.</p> <p>The support ensured to the overall pharmaceutical industry and the related impact is expected to be extended to SMEs as well. However measures such as the transferable vouchers may provide a good opportunity for small biotech firms working on novel antimicrobials to secure substantial additional funding for research through the sale of vouchers or the raising of new finance or acquisition. The proposals to make the regulatory and scientific advice more dynamic and interactive is likely to be valuable to SMEs.</p>	<p>regulatory system such as the streamlining of administrative and regulatory activities; the adaptation to innovation and digitalisation will largely contribute to enhance support of the industry.</p> <p>Those measures are expected to ease innovation and day-to-day activities for all industry stakeholders, all along the lifecycle of medicines.</p>
SDG 10: Reduced Inequalities Relevant	<p>The revision will support improvements in health equality through improved market access, increasing the number and speed at which new medicines are launched on the great majority of EU markets.</p> <p>The revision will also support improvements in the management of medicines shortages across the EU, thus helping to contain the upward trend in shortages and increasing the likelihood that patients receive the most suitable medicines. Finally, the increase in the proportion of medicines addressing unmet medical needs will provide those patients with treatment options where that is not the case currently.</p> <p>Moreover, it should be noted that:</p> <ul style="list-style-type: none"> - The revision of general pharmaceutical legislation aligns with the pharmaceutical strategy for Europe, which emphasises the need to ensure access to safe, high quality and effective medicines as a key element of social well-being, including for persons from disadvantaged, vulnerable groups, such as people with disabilities, people with a minority ethnic or racial background and older people. - The revision of the general pharmaceutical legislation aligns with the revision of the orphan and paediatric legislation focusing on reducing health inequalities for these specific population. 	<p>Progresses towards SDG 10 echoed the ones of SDG 3.</p> <p>Measures such as innovation in the areas of UMN, AMR and the improvement of market access conditions are expected to contribute to the reduction of inequalities within the entire European population.</p>

ANNEX 4: ANALYTICAL METHODS

Methodology and models for the Impact Assessment

1. Data sources

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

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

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

Comparative legal analysis: we explored pharmaceutical legislation of third country jurisdictions in areas where a revision was proposed in the EU. These were based on desk research complemented as needed by targeted interviews with national experts. The following seven countries were selected: USA, Canada, Australia, South Korea, China, Japan, Israel – covering a mix of major developed global markets and smaller ones where regulatory innovation was expected. We have used a standard country report template as data gathering and reporting tool. Sources for those reports included legal research on the third country legal systems but also literature review both in English and respective national languages on the workability and outcome of these legal systems and interviews with relevant actors in these countries (i.e. competent authorities and experts).

Country reports were completed by national experts with good understandings of the national context and relevant language skills. The preparation of country reports involved the creation of a guidance document to the country report; a webinar with national experts to discuss aim, context and methodology; interview with regulatory authorities; quality assurance to ensure comparative analysis of indicators, which were based on the objectives of the review of the legislation, such as incentives innovation and future proofing of the legislation.

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

Competent Authorities for a bespoke European Commission study by Technopolis Group. The results of this are available in a separate Analytical report.

Case studies: seven areas were identified where a deeper analysis of a particular problem would be beneficial to support the impact assessment. These aimed at exploring the nature and evolution of the problem and link those to the proposed policy elements and their potential impacts. The analytical approach relied on document review, secondary data analysis and key stakeholder interviews. Selected case studies were: 1. Incentives for developing new antimicrobials. 2. Agile and adaptive regulatory systems. 3. Regulatory support for SMEs. 4. Improved access to medicines. 5. Generic competition and affordable medicines. 6. Regulatory barriers for emerging manufacturing technologies. 7. Criteria for unmet medical needs.

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

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

2. Identifying and selecting significant impact types

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

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

This screening identified 10 of the 35 impact types as being of most significance for this impact assessment and therefore a deeper assessment was appropriate for the following key impact types:

- Conduct of business
- Administrative costs on businesses
- Position of SMEs
- Sectoral competitiveness and trade

- Functioning of the internal market and competition
- Innovation and research
- Public authorities
- Resilience and technological sovereignty
- Public health & safety and health systems
- Sustainable consumption and production

3. *Multi-criteria analysis*

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

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

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

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

4. *Modelling changes in regulatory data and market protection system*

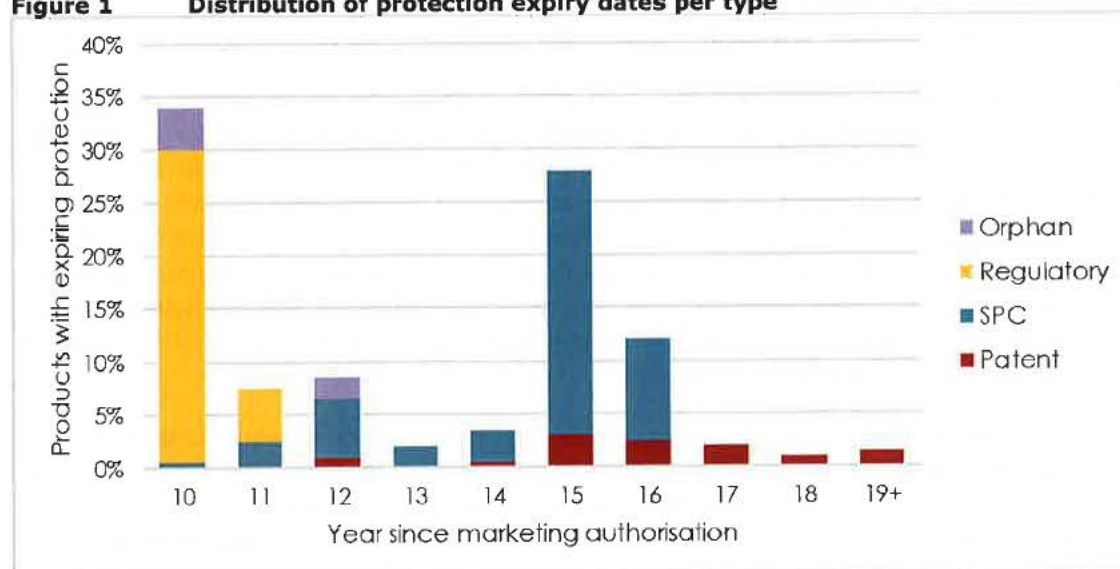
a. *Protection types and length in a sample of medicines*

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

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

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

Figure 1 Distribution of protection expiry dates per type



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

Table 1 Share and average peak sales of products under different protection types

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

b. Developing an 'analogue' representing an innovative medicinal product lifecycle

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

The first part included 20 products¹⁴³ (involving 2 biologic molecule) that have RDP expiry dates between 2016-2021 and for these annual sales were calculated over a 10-year period pre-expiry. The second part included 16 products¹⁴⁴ (involving 1 biologic molecule) that have RDP expiry dates between 2014-2016 and for these products annual sales were calculated over 5 years post expiry, along with annual sales data for their generic competitors. Note that 2 products were not contested after RDP expiry but included in the cohort to allow for observing systemic effects. For example, the RDP period for the biologic Cetuximab expired in 2014 and no biosimilar entered the market to date.

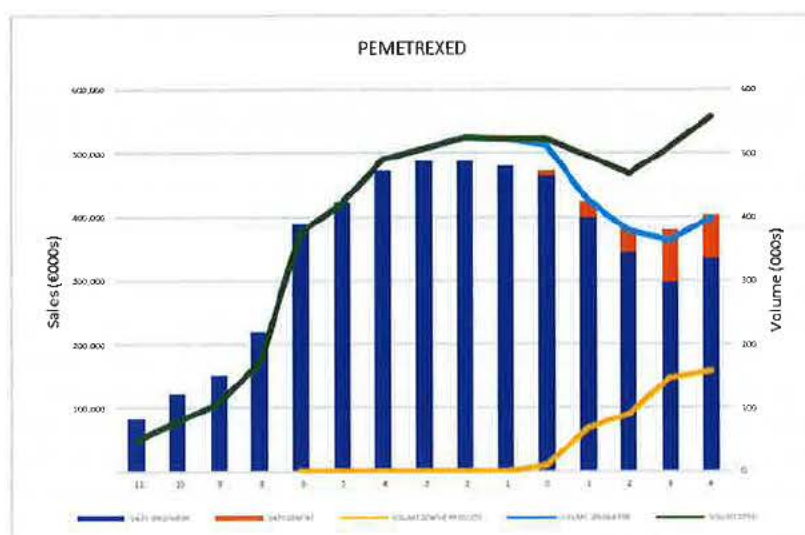
There is significant variation of the sales revenue-volume graphs across individual products, in some cases rapid generics entry erode the market value of the originator product, in other cases the originator maintains their market share, dependent on the level of sales generated by the originator. For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

Figure 2 Sales and volume data for two products from the 2014-16 cohort



¹⁴³ Products included: AGOMELATINE, AMLODIPINE!HYDROCHLOROTHIAZIDE!OLMESARTAN MEDOXOMIL, AMLODIPINE!HYDROCHLOROTHIAZIDE!VALSARTAN, AMLODIPINE!OLMESARTAN MEDOXOMIL, ANAGRELIDE, AZACITIDINE, CABAZITAXEL, CLEVIDIPINE, CLOFARABINE, DRONEDARONE, FEBUXOSTAT, GEFITINIB, MIFAMURTIDE, NELARABINE, PALIPERIDONE, PRASUGREL, ROFLUMILAST, SILODOSIN, ULIPRISTAL ACETATE, VELAGLUCERASE ALFA

¹⁴⁴ Products included: ALENDRONIC ACID!COLECALCIFEROL, ANAGRELIDE, CEFDITOREN PIVOXIL, CETUXIMAB, CLOFARABINE, DULOXETINE, EPLERENONE, FULVESTRANT, HYDROCHLOROTHIAZIDE!OLMESARTAN MEDOXOMIL, METFORMIN!PIOGLITAZONE, PEMETREXED, PREGABALIN, RASAGILINE, TIMOLOL!TRAVOPROST, TREPROSTINIL, ZONISAMIDE



We noted that very few biologics were found to be in the cohort for our analysis, however the biologics pipeline is growing (especially antibody modality, see Analytical report Table IEC1.3 and recent IQVIA report on biosimilar competition in Europe¹⁴⁵) and expected to make a larger share of future product baskets. Biologics and biosimilars may have unique market dynamics because of differences in related development timeline and cost-profile. A comparative analysis of medicinal products launched between 1996-2014 shows that biologics are introduced faster and in more countries than non-biologic medicinal products¹⁴⁶ as it may be more profitable for developers compared to small-molecules. Switching from originator to biosimilars may also have different considerations, and recently launched biosimilars achieved over 50% uptake in their market within two years.⁴ Examples of blockbusters (e.g. Humira, Herceptin and Enbrel) show that biologics are often protected by SPCs beyond RP expiry and biosimilars enter soon after expiry. In the RPRDP expiry and biosimilars enter soon after expiry. In the RDP cohort, we noted however another blockbuster example Xolair (Omalizumab) where RPRDP as the last measure of protection expired in 2015 yet no biosimilar entry has taken place. While there is no current SPC on the product, there is a formulation patent until 2024 in force that may be constraining. In summary, it is unclear In summary, it is not clear what share new biosimilars will have in future RPRDP product cohorts where policy elements under considerations will be of effect. reduced regulatory protection period would be of effect. If the share of biologics substantially increases, it is likely that the general product sales/volumes model employed below will be less predictive. here will be less predictive.

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

Table 2 Normalised sales, volume and price for products with RP as last measure of protection

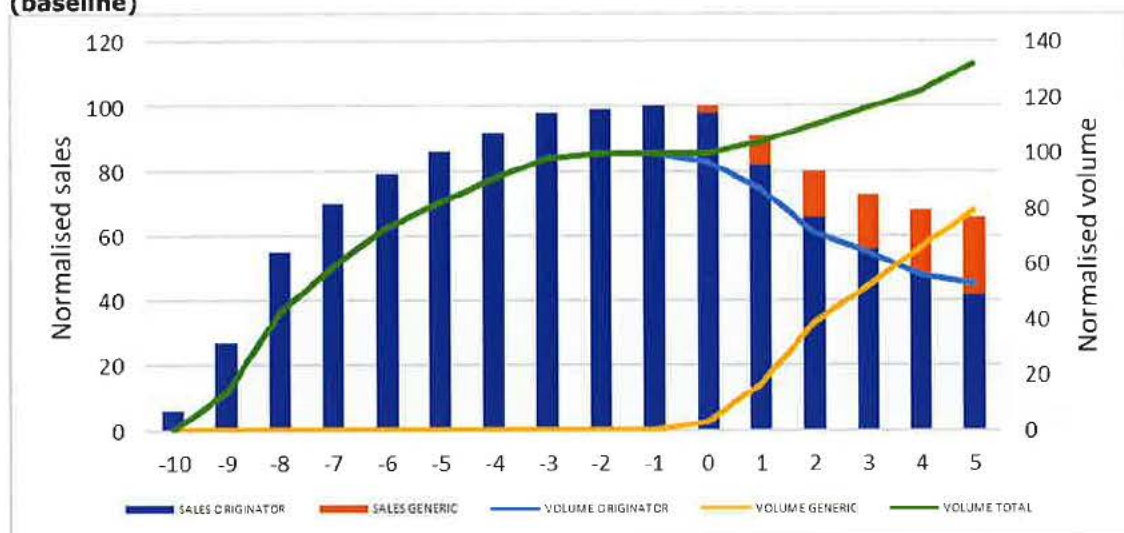
Year from expiry	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5
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¹⁴⁵ The Impact of Biosimilar Competition in Europe (2021) IQVIA. Available at: <https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/iqvia-impact-on-biosimilar-competition.pdf>

¹⁴⁶ Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018) Copenhagen Economics. Available at: <https://data.europa.eu/doi/10.2873/886648>

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

Figure 3 Normalised sales and volume for products with 8+2 years of RP protection (baseline)



It is evident from the graph that sales revenue and volume grow year-on-year over the 10-year RP period as (i) the product is taken up by the health system and make it accessible to increasingly more patients; and (ii) product is launched in increasingly more member states. It should be noted that health systems may require a number of years before the product becomes accepted by health professionals and routinely prescribed. However, these effects are expected to reach a plateau within a couple of years of introducing the product in a market, and indeed the figure shows that by Y-3 sales figures are close to peaking. The last year before expiry therefore accounts for 14% of total pre-expiry sales; while the final two years account for 28% of total pre-expiry sales.

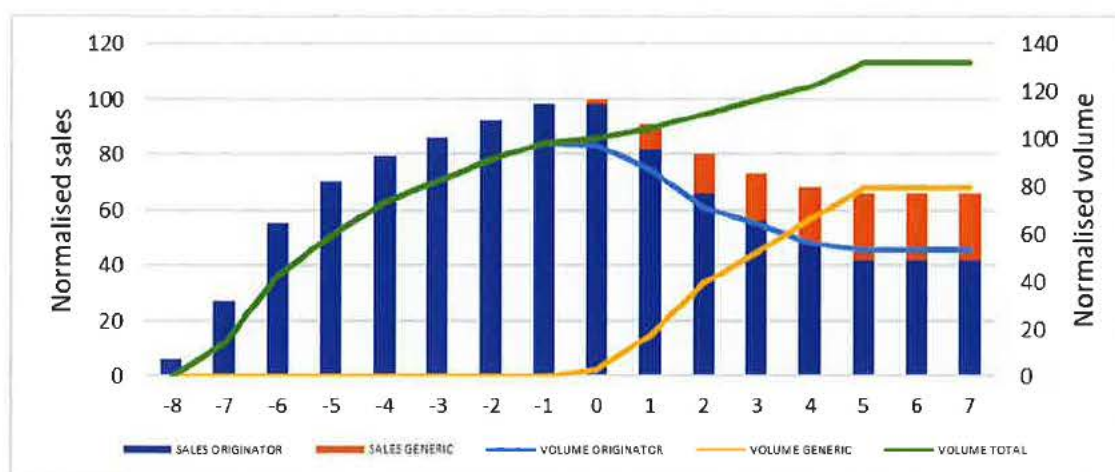
The baseline is the current standard regulatory protection (for all medicinal products) of 8 years of data exclusivity plus extra 2 years of market protection, and in cases of additional indication with significant benefit +1 year of market protection.

c. Modelling the economic impact of decreasing regulatory protection

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

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

Figure 4 Normalised volume and sales data for products with 6+2 years of RP period



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

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

We know that pharmaceutical industry is one of the most R&D intensive sector and they reinvest a large share of their revenue into innovation for new products and technologies. This share is 20% on average globally¹⁴⁷ and we can assume that the revenue loss will translate to a loss of innovation budget and thus a loss of development of new innovative products and/or incremental (i.e. cheaper) product innovation (e.g. for combination products or new formulations).

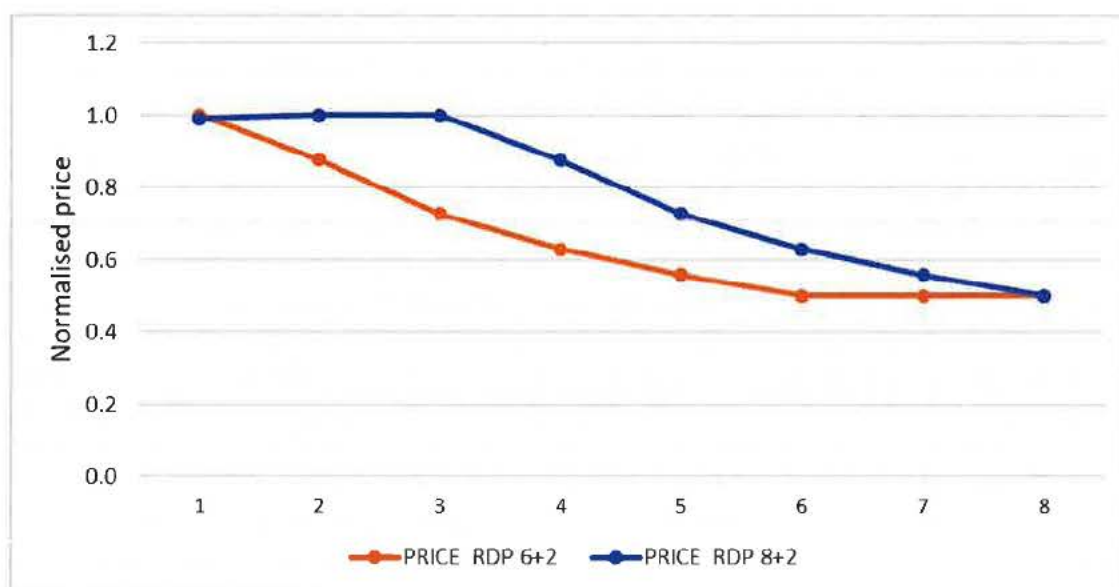
¹⁴⁷ See <https://www.drugdiscoverytrends.com/pharmas-top-20-rd-spenders-in-2021/>

- Generic companies' start to benefit from sales two years earlier compared to baseline, and thus reach equilibrium level two years earlier. These two extra years of equilibrium generic sales of +48 (normalised units), equal to an additional 56% sales, compared to baseline situation.
- Healthcare payers pay less overall due to a decrease in the average price they need to pay for a standard unit of the product. If we look at the annualised average price healthcare payers pay (calculated by dividing total sales and total volume in each year of the final 8 years of the product lifetime) in the different RDP regimes, we note that, as expected, the average price drops faster to the equilibrium value in the case of the new standard RDP regime (see Figure 5 below). If we consider the 'peak' volume sold of the originator product pre-expiry under the baseline situation and use the average price in each year under the different RDP regimes to calculate post-expiry adjusted sales, we can assess the total savings healthcare payers would make in the RDP 6+2 regime given equal volumes purchased. In the baseline RDP 8+2 regime, the total adjusted lifetime sales would be 1141 (normalised units) and in the new RDP 6+2 regime it would be 1042 (normalised units). Thus in the RDP 6+2 regime healthcare payers would pay -99 (normalised units) less, which is -9% less when considering the lifetime sales of the product.

In the real situation, however, healthcare payers may not realise this nominal saving but choose to purchase more units of the medicine at a lower price for the healthcare system and expand coverage of patients. This can be considered that payers 'reinvest' part of the savings in the same market and increase purchase of generic products at higher volumes for the benefit of the patient. We can thus calculate the total real sales of originator plus generics product volumes, which can be used to monetise patient benefit. Under the baseline situation, total sales value over the product lifetime is 1190 (normalised units), while under the RDP 6+2 regime it is 1123 (normalised units), equating to -67 (normalised units) or -6% saving to healthcare payers. Note, however, when considering total healthcare systems spending in the EU, pharmaceutical expenditure represents less than 20% of the total health spending (see Analytical report Figure AFF-3, OECD Health Statistics) so savings at the healthcare system level is marginal.

- Patients benefit due to the increased volume of the medicine sold after RDP expiry (2 years earlier) which then reach more patients creating higher level of health benefits. In the model, the total volume increases as soon as generic products enter the market and volume of generic products surpasses that of the originator product by year 4 after generic entry. In the new standard RDP 6+2 regime the total volume sold increases by +64 (normalised units) or 5% over the product lifetime above the baseline of 1343 (normalised units) under the RDP 8+2 regime. However, the extra volume of products available to patients manifest itself in the transition period between expiry and reaching the equilibrium value.

Figure 5 Normalised price of medicines over the final 8 years of the product lifetime



Monetising the systemic effects: Using the model in this study where only static effects are considered, we saw the normalised consequences for various stakeholders originating from a typical product where the last measure of protection to expire is RDP. We can convert the normalised units to monetary value by equating the peak sales of 100 (normalised units) to the average peak sales calculated for the basket of RDP products of approximately €160m per year. Note that per product level change should be considered as nominal since the actual individual product sales have a wide range around this average. At a systemic level, for a basket of products over years, however, the calculated values are expected to have predictive power.

Therefore, we need to assume the number of products per year to be affected by this policy measure. In the coming 15 years, we estimate that on average 40-50 new active substances will be authorised by EMA in each year (see Figure RI-9.1 and pipeline data in Analytical report and recent report¹⁴⁸). From the current level of 30-40, we expect the baseline to evolve to 50-60 by the end of the period. As discussed, 30% of new authorised products are expected to be affected, however, products that address UMN or medicines with no return on investment (Option B) will not have reduced RDP period. Overall, we estimate 20-25% of new medicines or 8-13 products will be affected annually by the measure.

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

Table 4 Changes calculated between baseline and RDP 6+2 per stakeholder group

Stakeholder	Product level change	% change	Annual systemic change (8-13 medicines)	Systemic change over 15 years
Originator protected sales	-€320m	-28%	-€2.5-4.1 billion (lost innovation budget: -€0.5bn-0.8bn)	-€38-62 billion (lost innovation budget: -€7.6bn-12.4bn)

¹⁴⁸ Global Trends in R&D, IQVIA Institute for Human Data Science, 2022. Available at: <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-trends-in-r-and-d-2022/iqvia-institute-global-trends-in-randd-to-2021.pdf>

Originator contested sales	+€134m			
Originator medicine's commercial value		-22%		
Generic sales	+€77m	+56%	+€0.6-1 billion	+€9-15 billion
Cost to public payer	-€107m	-6%	-€0.9-1.4 billion	-€0.9-1.4 billion
Patients served		+5%		
Patients + payer monetised gain/loss	+178m	+9%	+€1.4-2.3 billion	+€21-34.5 billion

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

Caveats to the model used:

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

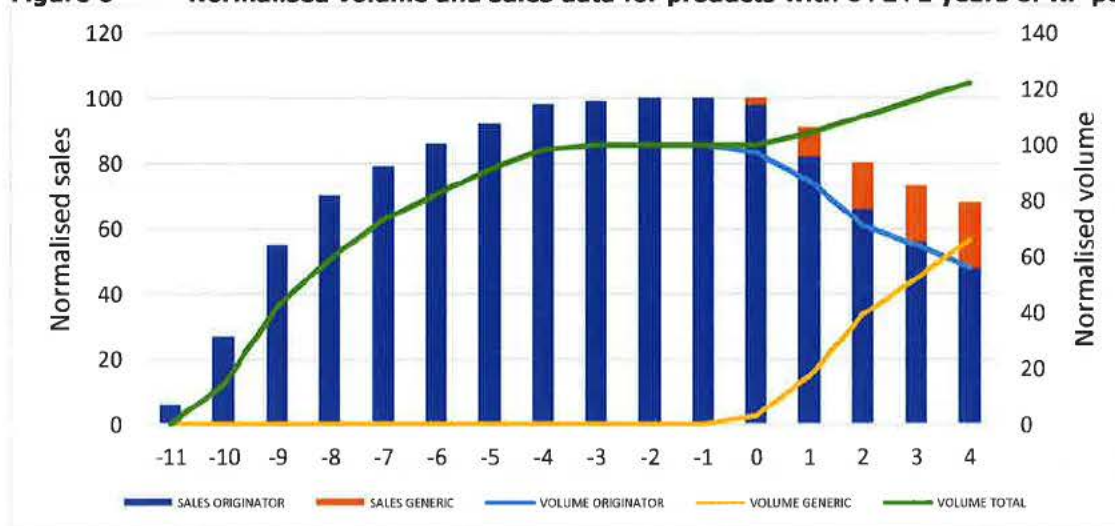
Opportunity cost: We present data at current euro level without inflation or cost of capital / commercial risk accounted for. This latter is a factor for commercial actors where monetary gains and losses are normally discounted in business calculations and may change decisions related to product developments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

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

d. Modelling the economic impact of special incentives through increasing regulatory protection

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

Figure 6 Normalised volume and sales data for products with 6+2+1 years of RP period



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

- Originator companies increase pre-expiry sales due to additional year of monopoly sales by 58 (normalised units) or 5% of lifetime sales
- Generic companies' start to benefit from sales one year later, and thus generic sales are reduced by 24 (normalised units) which is equal to a reduction of 28% sales, compared to baseline
- Healthcare payers pay more overall due to an increase in the average price they need to pay for a standard unit of the product. We consider again the 'peak' volume sold of the originator product pre-expiry in baseline and use the average price in each year under the different RP regimes to calculate sales. The total cost for healthcare payers is thus 49RDP regimes to calculate sales. The total cost for healthcare payers is thus -50 (normalised units) over the product lifetime compared to baseline
- Patients lose -32 (normalised units) in decreased volumes of the medicine over the lifetime of the product compared to baseline

We summarise the change calculated for each stakeholder group below:

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

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

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

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

Table 5 Changes calculated for 1-year extension of RDP protection per stakeholder group

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

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

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

Similar to the previous incentive, this measure could benefit RDP-protected products and some orphan medicines. Around 40% of all new medicines would be eligible. Conducting comparative trials should be feasible for many medicines, but not for some, especially UMN medicines¹⁴⁹. Also, if the cost of the comparative trial is too high as opposed to the reward, companies will decide to decline the incentive. We expect that half of the RDP products could benefit from it, or 8-10 medicines annually. Of course, higher sales medicines would have a higher compensation, regardless the cost of the trial.

It should be noted that this data is expected to generate new knowledge for better decision making at an earlier time point and thus represent additional fixed cost compared to baseline. We assume the additional costs of conducting comparative trial with standard of care amount to €10m on average.¹⁵⁰

¹⁴⁹ As per the definition of UMN, there are no satisfactory therapeutic options. Consequently, a new therapy would have no comparator.

¹⁵⁰ Moore et al (2020) in a review of 101 new FDA medicines (225 individual clinical trials), found the median cost of an individual clinical trial was around \$19m (range = \$12m-\$33m). They found the Phase 3 development costs almost

Therefore the incentive could attract developers to factor in comparative trial design in their clinical study programme. There is no information on how stakeholders (including developers and regulators) would respond to statistically insignificant or negative outcome emerging from the comparative effectiveness arm of the study.

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

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

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

5. Monetising the systemic effects of measures to improve market access

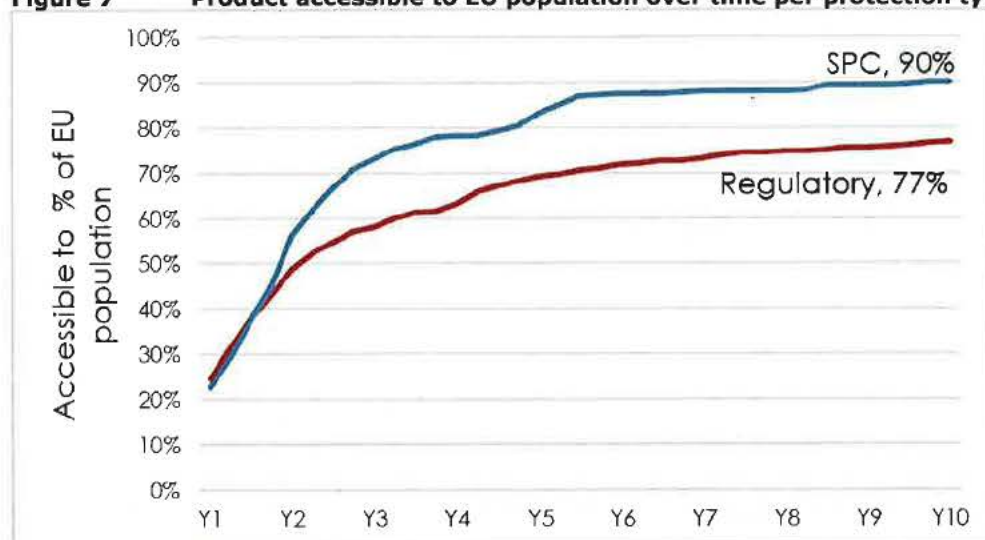
The baseline is that there is no obligation or incentive to launch a product in a particular member state. Indeed, products authorised only reach up to 15 Member States (MS) out of the maximum possible 27 (Kyle, 2019) and on average 49% EMA-approved medicines are reimbursed in an EU country (Access case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

We analysed products with protection expiry between 2016-2024 and recorded positive sales of originator products. For each molecule and each Member State, the first quarter in which meaningful non-zero sales occurred for at least two quarters. This is to eliminate cases where there may be one quarter of sales and then the product is not sold again in that Member State for several years. To follow the evolution of market access over 10 years, the sample was restricted to only those products that are authorised between Q1 2010 and Q4 2011. We have also created a larger sample of products between Q1 2010 and Q4 2014. The patterns for the first seven years in the two samples were very similar. We analysed access as a function of the number of Member States in which each product was available and the corresponding percentage of the EU population that was covered for each

doubled with second trial. (Albeit the single biggest cost driver is the number of patients). More et al identified 62 (27.5%) of the total set of 225 clinical trials had a comparison group rather than a placebo or uncontrolled trial.

product. Taking a simple average across all products gives a representative time series for all RDP products and a separate representative time series for all patent/SPC products. This analysis shows that those products that are SPC-protected are accessible to a higher share of the EU population than those that are RDP-protected.

Figure 7 Product accessible to EU population over time per protection type

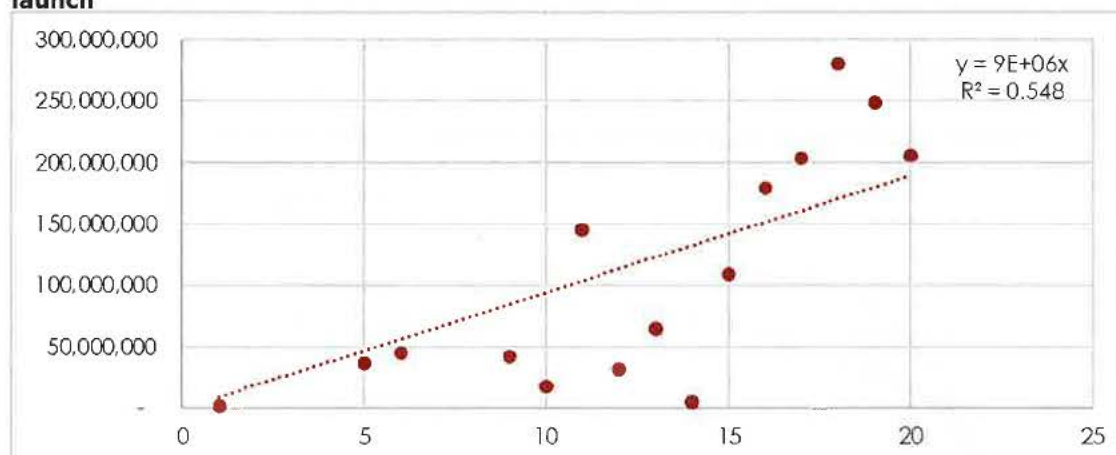


Deeper analysis point to higher coverage of products with higher sales and that larger member states with higher GDP tend to have a higher share of the products on their market. For example, there are 69 and 68 of the 78 products launched in Germany and Italy/Spain.

Table 7 Distribution of 78 products with RDP expiry 2016-2024 launched in member states

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

Figure 8 Average annual peak sales of products with RDP expiry 2016-2024 per country launch



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

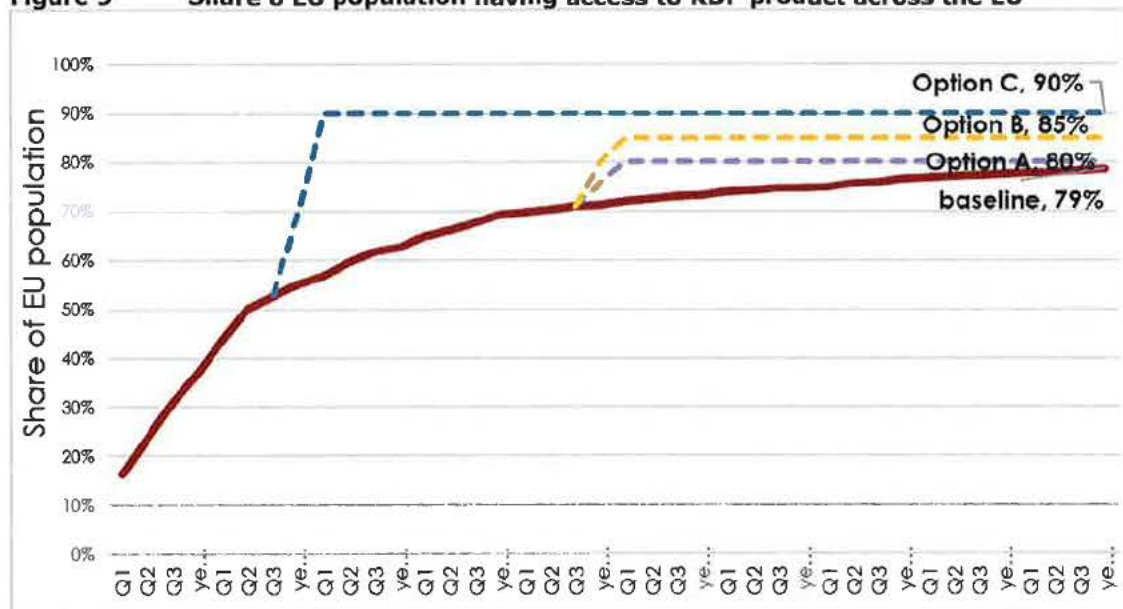
Based on the size of the incentives/losses we estimated the compliance as percentage of medicines. From this, we could calculate the costs or savings to the public (Table 8). For option A, we used the same model as for the special incentive for comparative trials, but expecting that only the higher sales medicines would comply, we used a higher average peak sales in the model. For option B and C, the model of the reduced regulatory protection was used (from option B), to calculate public savings stemming from non-complying medicines. Again, we adjusted the average peak-sales value, assuming that the low-sales medicines will be the ones not complying.

Table 8 Compliance estimate for each option, commercial value and cost/benefit for public

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

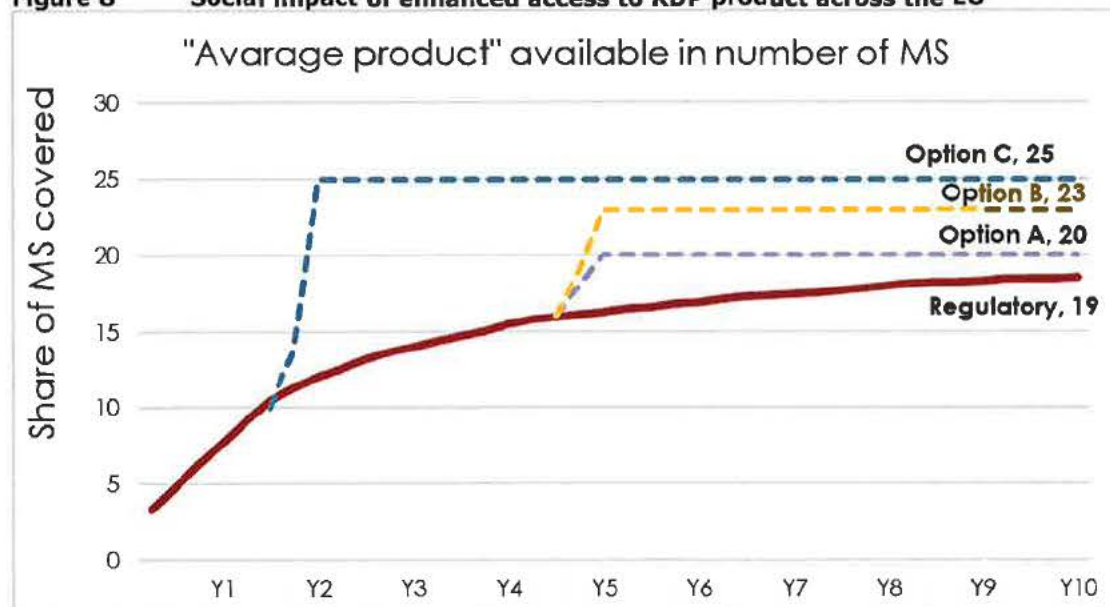
Again, launching products in all EU member states requires additional investments by companies compared to baseline, which will reduce the net gain experienced by companies.

Figure 9 Share of EU population having access to RDP product across the EU



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

Figure 8 Social impact of enhanced access to RDP product across the EU



6. *AMR transferable voucher*

Antimicrobial resistance is a global challenge and the cost of inaction is very high when compared to expected societal benefits and cost savings in the mid/long term¹⁵¹. Antimicrobial products are not expected to be sold in large volumes on the market or generate large revenue stream and therefore the commercial incentive through the RDP system will have limited value. Developers of antimicrobials are often innovative SMEs without significant resources to take these products through the regulatory approval pathway and require alternative instruments for ensuring sustainable R&D of antimicrobials. A transferable regulatory protection voucher (or transferable exclusivity voucher) allows the developer of an antimicrobial product to benefit from an additional year of data exclusivity period on another product in their portfolio or sell the voucher to another company that would use the voucher for their own benefit. This mechanism could provide the developer a reward (or an incentive) for developing an antimicrobial product and meet (partially) the related investment needs of an estimated €1bn per product.¹⁵² While the reward will directly be paid to developer by the buyer of the voucher, the cost of the voucher would eventually be met by healthcare payers of the product developed for other diseases (potentially also benefitting from lower level of AMR).

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

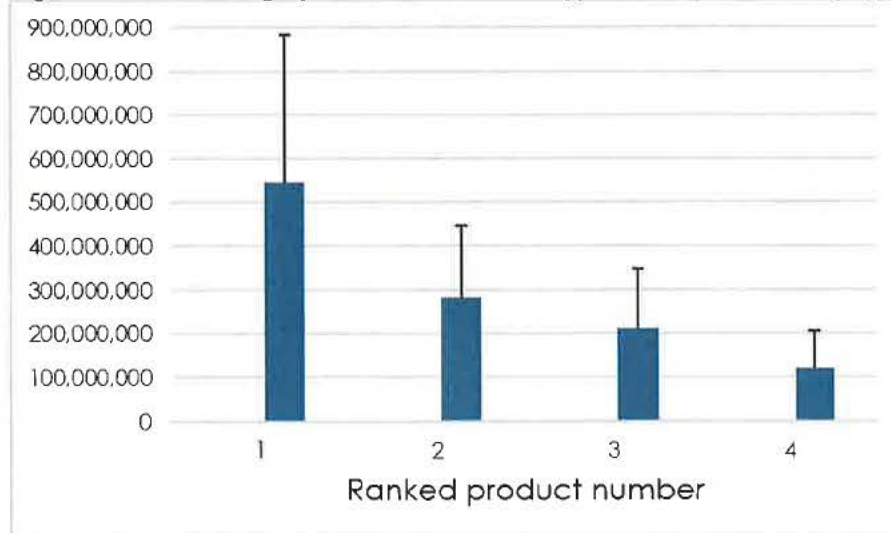
It should however be pointed out that when the voucher is sold on, only part of the value will be captured by the developer of the antimicrobial product (the seller) and the other part will go to the buyer of the voucher. The larger the share that goes to the seller, the more efficient the voucher is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

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

¹⁵¹ <https://www.oecd.org/health/health-systems/Averting-the-AMR-crisis-Policy-Brief-32-March-2019.PDF>

¹⁵² New drugs to tackle antimicrobial resistance (2011) The Office of Health Economics

Figure 9 Average peak annual sales of products with RDP expiry 2014-2024



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

Figure 10 Share of the seller and buyer in the value of the voucher for (top) n=1 voucher per year and (bottom) n=3 vouchers per year



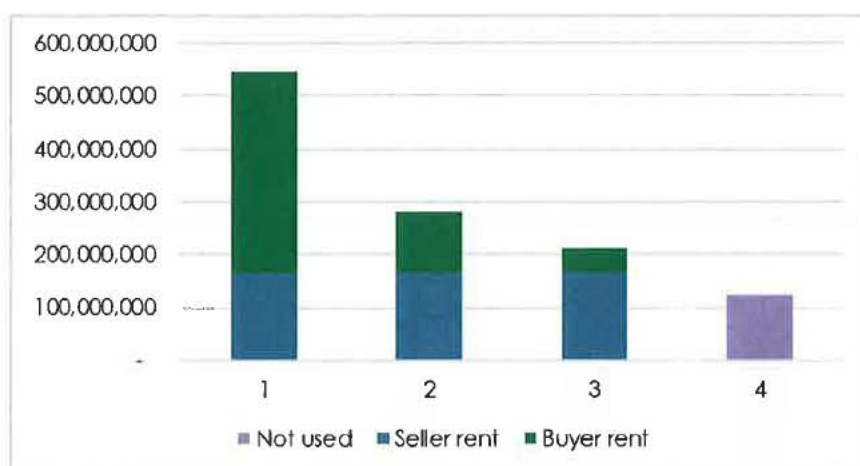
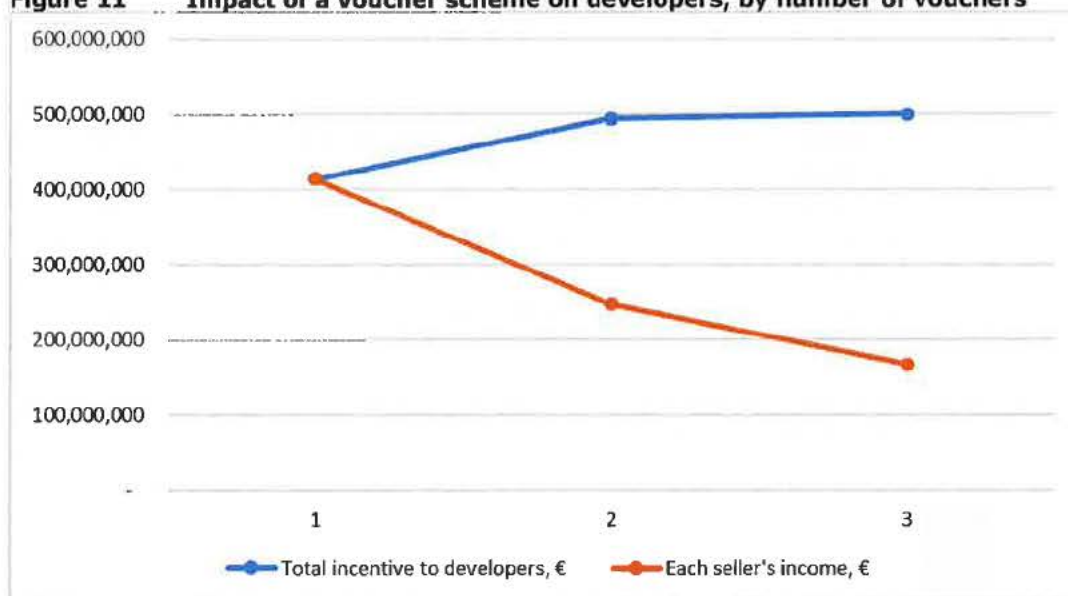
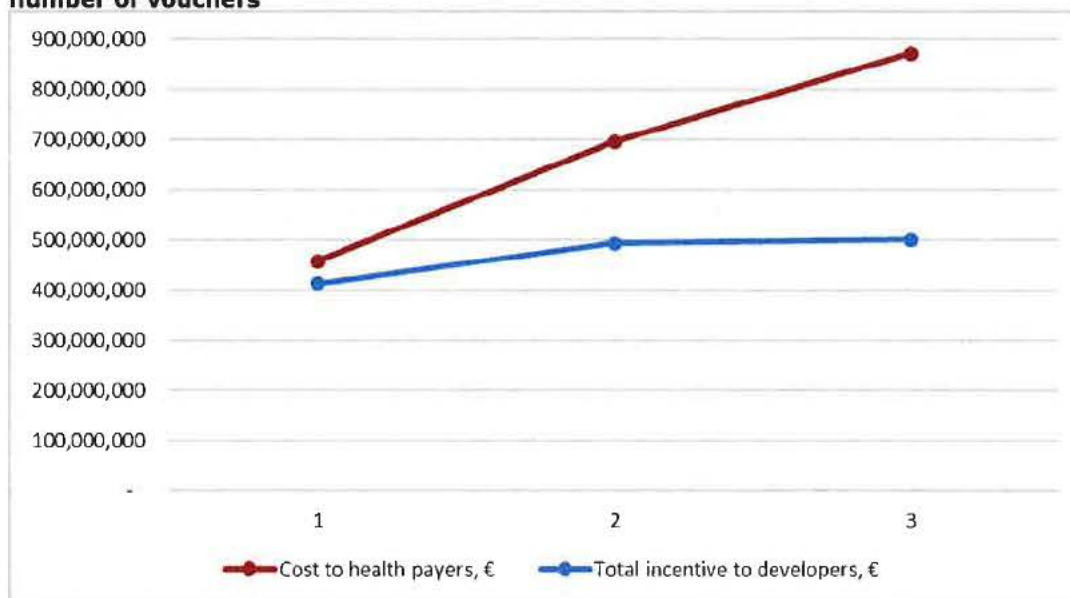


Figure 11 Impact of a voucher scheme on developers, by number of vouchers



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

Figure 12 Comparison of total incentive to developers and total cost to health payers, by number of vouchers



The distribution of the average peak sales of products that have RDP expiry as LOP and the number of vouchers will therefore determine the cost and benefit to the various stakeholders. In our cohort we focussed on high-revenue products and therefore we used a normalised product sales and volumes curve that is expected to represent this cohort of products more closely (i.e. higher rate of generic entry and originator price erosion, see Figure 2). We use the model introduced earlier and apply to the three scenarios that link to the number of simultaneous vouchers in issue. The corresponding costs and benefits are detailed below:

1. Three transferable vouchers are granted per year

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

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

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

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

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

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

2. One transferable voucher is granted per year

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

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

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

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

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

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

3. Transferable voucher is granted every two years

Here we assume that only the top selling product will benefit from an extra year of RDP extension every other year. There is however the potential for higher selling products on the market. The Table below It does not appear to provide any further efficiency gain in the system compared to the previous scenario and selecting this makes no policy sense as a large share of the originator's gain will already have been paid to developers, long before originators can reap the benefits of their

investment. Of course, if there is no qualifying antimicrobial for a transferable voucher each year (which may well be the case if no sufficient incentive/profit margin exist in the system) pipelines will dry up, and the system will have reduced direct costs and benefits for all stakeholders. Nevertheless, there remains a distinct risk that a resulting lack of preparedness for a future pandemic of antimicrobial resistance will be counted in trillions of euros lost globally.

Table 9 Average peak annual sales of top products with RDP expiry 2014-2024 segmented bi-annually

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

7. Costs and benefits of Option C (preferred option)

The following table summarises the benefits and costs for the preferred option. Taken together, the sum of the **benefits is €2.27bn a year** and €34bn over 15 years (incl. pivotal measures of €1.99bn pa and €29.8bn over 15 years). The sum of the total costs is €2.2bn per year and €28.9bn over 15 years (incl. €1.8bn pa and €27bn over 15 years).

		1 year low	1 year high	15 years low	15 years high	1 year average	15 years average
Benefits (pivotal measures)							
UMNs	number	2	4	30	60		
UMNs	€ millions	320	640	4,800	9,600	480	7,200
Comparative trials	number	8	10	120	150		
Comparative trials	€ millions	640	800	9,600	12,000	720	10,800
Market access	number	10	12	150	180		
Market access	€ millions	210	270	3,150	4,050	240	3,600
AMR	number	1	1	15	15		
AMR	€ millions	545	545	8,175	8,175	545	8,175
Sum of	€ millions					1,985	29,775

benefits (pivotal measures)							
Benefits (horizontal measures)							
Streamlining savings for businesses	€ millions	15	30	225	450	22	337
Streamlining savings for regulators	€ millions	33.5	67	502	1005	50	754
Streamlining income for generics	€ millions	55	110	825	1650	82	1,237
Sum of benefits (streamlining)	€ millions					155	2,329
Digitalisation savings for businesses	€ millions	7	15	112	225	11	169
Digitalisation savings for regulators	€ millions	67	134	1,005	2,010	100	1,507
Sum of benefits (digitalisation)	€ millions					112	1,676
Enhanced support for SMEs and non- commercial	€ millions	7	15	112	225	11	169
		5	10	75	150	7	112
		2	3	26	52	3	39
Sum of benefits (SME support)						21	321
TOTAL benefits						2,273	34,101

		1 year low	1 year high	15 years low	15 years high	1 year average	15 years average
Costs (pivotal measures)							

UMNs	Cost for public payers	163	326	2,445	4,890	244	3,667
UMNs	Costs for generics industry	77	154	1,155	2,310	115	1,732
Comparative trials	Cost for public payer and patients	326	408	4,890	6,120	367	5,505
Comparative trials	Costs for generics industry	154	192	2,310	2,880	173	2,595
Market access	number	10	12	150	180		
Market access	€ millions	352	422	5,280	6,336	387	5,808
AMR	cost for public payer	283	283	4,245	4,245	283	4,245
AMR	cost for 'unserved' patients	158	158	2,370	2,370	158	2,370
More stringent reporting on shortages	costs for originators	10	20	150	300	15	225
More stringent reporting on shortages	costs for regulators	10	20	150	300	15	225
More stringent environmental assessment	costs for originators	20	25	300	375	22	337
More stringent environmental assessment	costs for regulators	20	25	300	375	22	337
Sum of costs (pivotal measures)	€ millions					1,803	27,048
Costs (horizontal measures)							
Streamlining costs for regulators	one-off	16.8	33.6	16.8	33.6	25.2	25.2
Streamlining costs for	recurrent	33.5	67.5	502.5	1012.5	50.5	757.5

regulators							
Sum of costs (streamlining)	€ millions					75.7	782.7
Digitalisation costs for regulators	one-off	120	350	120	350	235	235
Digitalisation costs for regulators	recurrent	24	70	360	1050	47	705
Sum of costs (digitalisation)	€ millions					282	940
Enhanced support for SMEs and non-commercials	cost for industry (recurrent)	1.6	2.4	24	36	2	30
Enhanced support for SMEs and non-commercials	cost for regulators (recurrent)	4.8	7.2	72	108	6	90
Sum of costs (SME support)	€ millions					8	120
TOTAL costs	€ millions					2,169	28,891

Methodology and analytical models used for the evaluation

This section summarises the methods used for task 2 (data identification, collection and analysis) and task 3 (stakeholder consultations). The tables below outline the specific work packages and the related outcomes of how the findings were used and/or reported.

Table 9. Task 2: Data identification, collection and analysis.

Work package	Outcomes and reports
2.1 Literature Review	Integrated throughout analytical report, case studies, evaluation report and impact assessment.
2.2 Comparative Legal Analysis	7 Country reports
2.3 Secondary Data Analysis	Analytical Report
2.4 Case Studies	Case Study Report and Case Studies

Table 10. Task 3: Stakeholder consultations.

Work package	Outcomes and reports
2.1 Literature Review	Integrated throughout analytical report, case studies, evaluation report and impact assessment.
2.2 Comparative Legal Analysis	7 Country reports

2.3 Secondary Data Analysis	Analytical Report
2.4 Case Studies	Case Study Report and Case Studies
3.2 Feedback Analysis	5-page report annexed to the inception report
3.3 Public Consultation	Integrated throughout analytical report, case studies, evaluation report and impact assessment.
3.4 Targeted Survey	Annex to the evaluation report
3.5 Interviews	Individual interview summary notes and integrated throughout analytical report, case studies, evaluation report and impact assessment.
3.6 Workshops	Workshop summary notes (2)

1. Data Identification, collection and analysis

Literature Review

Peer-reviewed literature and policy document review was conducted to gather existing knowledge-base and served as a source of facts and figures. We conducted a comprehensive literature review by first defining relevant search terms (Keywords in English, Dutch, German, French and Spanish 2). Abstracts were screened for relevance and for those relevant full text was obtained. For scientific literature (Peer reviewed papers) online databases PubMed and Scopus were utilised. Grey literature (such as government or business reports, policy documents, theses or conference presentations) were identified from the following sources:

- Key EU institutions and agencies such as the European Parliament, the Council, DG SANTE, DG RTD, HaDEA, ECDC and EMA;
- Websites and online repositories of relevant public competent authorities (European and Member State regulators, pricing & reimbursement bodies) and health technology assessment institutions within the scope of this review;
- Google Scholar;
- Wider information sources including industry organisations (e.g. EFPIA, EuropaBio, Medicines for Europe) and patient associations and civil society organisations at EU and Member State level usually as submissions as part of the stakeholder consultation activities.

All full text documents (>550) were catalogued with their meta data (title, year, authors, item type, ISBN, ISSN etc), read and categorised for relevance and then managed using Mendeley where they could be easily identified, accessed and referenced during the writing of subsequent analytical and evaluation reports.

Comparative Legal Analysis

Comparative legal analysis aimed to provide information around whether proposed EU policy options for the revision of the general pharmaceutical legislation have been implemented or are currently being considered for implementation in other jurisdictions. The analysis presented the elements that had been implemented (if any) and the assessment or evaluation data that was available.

Five countries (Japan, Canada, South Korea, Australia, USA) were selected based on the secondary data analysis (Task 2.3) which identified them as relevant markets with developed economies. Two

additional countries were included after discussion with the EC; 1) China as the largest market in Asia and a major generic medicine producer and sophisticated regulatory system for the same, 2) Israel where innovative legislative solutions were expected.

Information was collected via a standardised country reporting template and accompanying guidance document that clearly laid out the scope of the review and was approved by the EC prior to commencement of data collection. The template contained the following sections:

- Context and background to the legal framework on human medicinal products in [X]
- Overview and mapping of the institutional set-up in [X]
- Authorisation procedure
- Incentives and obligations to address antimicrobial resistance
- Future proofing: Adapted, agile and predictable regulatory framework for novel products
- Rewards and obligations related to improved access to medicines
- Facilitate generic and biosimilar entry to ensure affordable established therapies
- Notification and monitoring to ensure security of supply / availability measures
- Quality and environmental sustainability
- Resolving competing aims and interests within the legislation
- Bibliography

The template was completed based on substantive in country legal research and a literature review in both English and national languages. They were completed by national legal experts who had a good understanding of the context and legal systems. National experts were briefed on the project, the methodologies and the templates, and afforded the opportunity to ask questions via a group webinar to ensure methodological consistency across all countries.

The templates were supplemented by targeted interviews (Table 12) with key stakeholders (competent authorities, pharmaceutical industry association, patient association, payers) which were also conducted by the national experts. Potential interviewees were identified, contacted and followed up at least once in order to get an interview (Table 11). In some cases, interviewee's opted to provide written feedback which was accepted and annexed to the report.

Table 11. Interview Schedule.

Country	Contacted and followed up	Interviewed	Written responses
Australia	7	0	1
Canada	17	2	0
China	6	6	0
Israel	4	0	0

Japan	5	5	0
South Korea	4	0	0
USA	13	0	0

Table 12. Indicative Questions for interviewees

<ul style="list-style-type: none"> • Compared with foreign regulatory frameworks, which features of your country's regulation of pharmaceuticals do you consider distinctive/unorthodox (if any)? When were they introduced? Do you consider these to be advantageous? why? • How does your country evidence the performance of your pharmaceutical regulatory framework? What are the reported indicators (if any)? How do you demonstrate an acceptable trade-off between speed of regulatory approval and clinical performance evaluation? • Which foreign regulatory frameworks have the greatest influence on your country's regulation of pharmaceuticals? • What good practices exist in [X] to: <ul style="list-style-type: none"> ○ Support innovation and address unmet medical needs? ○ Ensure the prevention of antimicrobial resistance while promoting the development of new products? ○ Regulate new products, new technologies in medicinal products as well as new manufacturing processes? ○ Promote wide market coverage by marketing authorisation holders and access to medicines for patients? ○ Facilitate the entry onto the market of generics and biosimilar medicinal products? ○ Ensure the security of the supply and secure the availability for patients? ○ Ensure a high level of quality throughout the supply chain in various production settings, and mitigate the environmental impact of the production of medicinal products? • What formal <i>international</i> regulatory collaborations do you have in place? <ul style="list-style-type: none"> • Is there work on-going regarding regulatory agility? • What are the challenges that remain to be addressed by the legal framework of your country? Have some legislative or policy attempts at addressing these issues remained unsuccessful? • What legislative or policy priority changes were required during the COVID-19 pandemic. What were the related lessons learnt? Are these changes going to be sustained in your country? • What is X's vision, strategy or roadmap for pharmaceutical regulatory framework? What are the related timelines? • <p>+ Country-specific questions to explore the innovative legal options in the country identified via desk research and literature review.</p>

Following completion each country report went through several rounds of review and clarification to increase consistency, address gaps and maximise comparability.

Secondary Data Analysis

Secondary data analysis comprised compiling over 50 macro indicators relevant to several policy areas and conducting statistical, econometric and trend analysis within the EU and compared to data from other jurisdictions.

In the first instance indicators were defined. SMART¹⁵³ indicators were proposed based on the objectives of the original legislation and the 2020 pharmaceutical strategy. These were verified and matched against data sources during a series of online working sessions and final selection made based on availability of data. There was prioritisation of time series data reaching back to pre 2005 as well as availability across the markets of EU, Switzerland, USA, Canada, Australia, Japan, and Korea.

In total we identified 55 indicators (Table 13 by policy area). The indicators were grouped in seven policy areas to address the policy elements in scope for the study with specific indicators selected to inform the main evaluation criteria of effectiveness, efficiency, coherence, relevance and EU added value of the legislation.

Table 13. Total number of indicators selected by policy area.

Policy Area	Number of Indicators
Industrial and Economic Competitiveness	13 (IEC 1-13) International (1,2,3,4,5,6,) Internal (7,8,9,10) Sector Profitability (11) Other (12,13)
Research and Innovation	9 (RI 1-9) Conversion rates (1,2,3,4,5,6) Public Research Funding (7) Private Investment (8) Innovative Products (9)
Single Market	6 (SM1-6) Shortage (1,2,3,4) Therapeutic Area Competition (5,6)
Accessibility	10 (ACC1-10) Access to approved medicines (1,2,3) Time to coverage (4,5,6,7,8,9,10)
Affordability	6 (AFF 1-6)
Efficiency	3 (EFF 1-3)
Manufacturing	3 (M1-3)
AMR	3 (AMR1-3)
Environmental	2 (E1-2) Residues (1) Manufacturing Emissions (2)

The indicators were populated using 24 existing proprietary or public databases or sources as listed in Table 14. While each specific indicator must be treated individually depending on completion, coverage, data type and presence of time series element, analysis was conducted to the following plan wherever data allowed and as appropriate. Statistical tests were not applied where the relevant observations were less than 30.

¹⁵³ Specific Measurable Achievable Relevant Timebound

- Presentation of longitudinal data covering the period 2000-2020 with stratification where appropriate (e.g. along therapeutic area, indication, product type, company size, legal basis of applications, approval pathway etc).
- Comparison of pre and post legislation periods using parametric (Welch's t-test) or non-parametric (Mann Whitney U test) tests for significance between the pre and post periods.
- Difference-in-differences estimation by comparing the evolution of the EU 'treated' countries relative to other similar but 'untreated' countries, before and after the 2004 revision of the general pharmaceutical legislation.
- Presentation and descriptive analysis of reference groups in other jurisdictions (Japan, US, Switzerland) with statistical comparison wherever possible.

Table 14. List of secondary data sources.

#	Data Source
1	Belkhir et al. Carbon footprint of the global pharmaceutical industry and relative impact of its major players. Journal of Cleaner Production (2019)
2	Drugs@FDA
3	EFPIA
4	EFPIA Report on Key Trade Data Points on the EU27 Pharmaceutical Supply Chain based on Eurostat
5	EU Industrial R&D Investment Scoreboard
6	EU Shortages Database
7	EudraGMDP/GMP/Sites
8	Eurostat /Eurostat Healthcare expenditure statistics
9	IFPMA
10	Informa Biomedtracker
11	Informa Datamonitor Healthcare
12	Informa in-house dataset collected from 20 major funding bodies including Horizon 2020
13	Informa Outlook 2019
14	Informa Pharmaprojects
15	Informa Sitetrove
16	Informa Trialtrove,
17	IQVIA MIDAS sales/sales volume data
18	OECD Health statistics/STAN Database
19	Publicly available trade/economics ministry data
20	Statista
21	Umwelt Bundesamt Database "Pharmaceuticals in the environment", including substances on the European Watch List.
22	US Bureau of Labour Statistics
23	Utrecht University MAA database
24	WHO Health Expenditure

Detailed methodology per indicator along with results of the analysis can be found in the Analytical Report.

Case Studies

Case studies were developed focused on specific issues to illustrate linkages and mechanisms behind trends observed in the data.

Alongside ongoing data identification, collection and analysis the 'focus areas' of each case study were agreed iteratively with the EC. The final selection and structure were based upon feasibility criteria (potential to showcase legislative contribution, researchable) and linkage to objectives of policy revisions and intervention logic. Seven case study topics were agreed: 1. Antimicrobial resistance (AMR), 2. Agile/adaptive regulatory systems, 3. SMEs/Regulatory support, 4. Improved access, 5. Affordable generics, 6. Emerging manufacturing and 7. Unmet Medical Need.

Within the scope of and specific to each case study, we next conducted a search of the literature. 1) defining relevant search terms, 2) defining relevant data sources, 3) defining relevant time period, 4) screening and selection of relevant papers, 5) snowballing. For scientific literature online databases PubMed and Scopus were utilised, while for grey literature online search engines (e.g. Google) and databases (e.g. Google Scholar, Policy Commons, Overton) were used along with websites of relevant international organisations (e.g. EMA, EFPIA, International society of pharmaceutical engineering, European Association of Hospital Pharmacists, etc) being screened. Additional sources identified on selected and screened sources were also included where relevant. The documents were analysed and information was put under topic headers to structure the data (different for each case study).

Where relevant and applicable, quantitative analysis of secondary data was undertaken specific to the case study to which it applied. Where this has occurred, methods are provided in detail in the individual case studies.

An overall case study format was proposed based around key research questions and sub questions and is presented below.

- Summary (0.5 pages)
- Retrospective view
 - 1: Nature and extent of the problem (1 page)
 - 2: Objectives of the 2004 regulation (0.5 page)
 - 3: Evaluation of the achievements of the regulation (2 pages)
- Forward looking view
 - 1: Evolution of the problem and residual challenges (1 page)
 - 2: Enhanced policy options (2 pages)
 - 3: Potential impacts of the revisions (2 pages)
 - 4: Synergies and interplay (1 page)
- Key conclusions
- Case study references and data sources

In the case of case study 3. SMEs/Regulatory Support there were substantial knowledge gaps and key information interviews were used to address these. We used semi- structured interviews (Table 15) with representatives of 5 leading industry associations to address knowledge gaps that are not

covered by the higher levels of evidence. Interviews were performed with relevant stakeholders. Notes were taken and sent back to the interview respondents for validation. The interview notes were analysed and collated in the same way as the documents and referenced in the case study.

Table 15. Interview Protocol for SMEs.

Specific for SMEs...	What goes well at the moment?	What can/ should be improved?	Suggestions for improvement?
Innovation ecosystem (drug discovery and development): 1 resources (capital, human, etc.) 2 risks 3 collaborations (relationship w/large companies, knowledge institutes) 4 IPR			
Pre-marketing phase: • Regulatory advice, dialogue and training (early-stage SME/ITF Brief Meetings on marketing authorization filing, strategies, orphan drug designation applications, PIPs, scientific advice, etc.) • Scientific advice and protocol assistance (vs. other sources of information; satisfaction; and reasons for asking for advice) • Financial support (financial incentives (fee reductions) in regulatory process; other incentives for SME innovation) • General on: European versus National (CP/MRP/DCP); GMP/GLP; Clinical Trial Directive			
Regulatory approval and requirements: • clinical • non-clinical • manufacturing			
Post-approval management (e.g. fee incentives, advice): • label • pharmacovigilance • HTA			

Further information including search terms and inclusion and exclusion criteria for each case study specifically plus the seven case studies can be found in the Case Study Report.

2. Stakeholder Consultation: Primary Data Collection

Feedback for the consultation on the Roadmap/Inception Impact Assessment

The Roadmap /Inception Impact Assessment was developed by the EC to inform stakeholders and gather feedback on the possible actions at EU level. The study team received an excel file containing 173 answers (feedbacks) to the published Roadmap/Inception impact assessment along with the 86 attachments in PDF format. The answers were translated from other languages to English, the data was checked for duplicates and campaigns were identified using both Excel and manual checking. When respondents did not use open text answers, the attached PDF documents were consulted in detail. The analysis of the answers was based on a set of topics developed after an initial assessment of all submissions. Using Excel and Word, manual cross-checks of all answers were completed, recording topics and sub-topics as well as the number of times they were mentioned.

A factual summary report in English was produced. This comprises a succinct 5-page report, profiling the participants, highlights of the main topics raised overall and by stakeholder groups, following the elements as set out in the technical specifications.

Open Public Consultation

A survey questionnaire developed in English and agreed with the EC was conducted electronically and it was published on the Commission's 'Have your say' web portal in all European languages for 12 weeks, from 28 September to 21 December 2021 – along with information materials.

The survey had two main topics and several sub-topics (bulleted in Table 16) and served to determine the balance of opinion (overall, and by stakeholder group) on the relative importance of a given issue. The OPC was a mixture of open and closed questions and utilised skip codes to guide participants through the relevant questions depending on their self-categorisation into stakeholder group. There were no character limits imposed on open answers.

Table 16. OPC survey structure.

1) Backward-looking questions
<ul style="list-style-type: none"> • Other issues to be addressed in this revision • Positive and unintended effects of the legislation
2) Forward-looking questions
<ul style="list-style-type: none"> • Unmet medical needs • Incentives for innovation • Antimicrobial resistance • Future proofing: adapted, agile and predictable regulatory framework for novel products • Rewards and obligation related to improved access to medicines • Enhance the competitive functioning of the market to ensure affordable medicines • Repurposing of medicines • Security and supply of medicines • Quality and manufacturing • Environmental challenges

It was anticipated that 500 responses would be received and in total 478 responses were received – shown below -by stakeholder group.

Table 17. Number of OPC Responses by stakeholder group.

Stakeholder	Responses Received
Industry	179
Public Authorities	37
Health Service Providers	85
Academic	39
Civil Society Organisations and Citizens	106
Other	32
Total	478

All 478 responses were downloaded from the EU Survey portal, translated into English, checked for duplicates and campaigns were identified, using a combination of Excel, statistical software STATA and manual checking. The study team conducted quantitative statistical analysis of closed answers and qualitative analysis of the answers provided in text form. All answers provided in text form (over 4,000 entries across 14 questions) were manually checked and emerging themes for each question were reported in a descriptive narrative for each stakeholder group.

A factual summary report in English, comprising of a succinct 8-page report, was produced. An in-depth analysis report was also produced with more profiling of participants, campaign identification and detailed analysis of stakeholder views on the two main topics of the OPC as well as summary of the position papers submitted in PDF format.

Targeted Survey (Survey Report)

Targeted surveys with key stakeholder groups through an online questionnaire were designed to obtain facts and figures – as well as opinions – on the relevance, efficiency, costs and benefits of the current legislation and the scale of anticipated positive or negative impacts of potential new policy elements.

A survey tool was developed and signed off by the EC. The survey had several modules (bulleted in Table 18 below) and incorporated skip codes such that different stakeholder groups were automatically navigated through the questions appropriate for them. All questions were optional and could be skipped or answered with don't know.

Table 18. Targeted Survey Structure.

- | |
|--|
| <ul style="list-style-type: none"> • Survey explanation (purpose, privacy, scope, time, instructions) • About you/your organisation (Organisation name, type, participant name) • Functioning of the legislation since 2005 (effectiveness, relevance, coherence, value add) <ul style="list-style-type: none"> ◦ To what extent has the legislation been effective/relevant/coherent/added value with respect to objectives ◦ Where has the legislation been most/least effective/relevant/coherent/added value ◦ Provision of supporting evidence or data ◦ Efficiency (costs and benefits and explanations of answers) • Elements of future policy options (incentives UMN, AMR, Futureproofing, Access, Competitive Market Functioning, Manufacturing Quality and Environment, Security of Supply, Streamlining) <ul style="list-style-type: none"> ◦ Please rate the impact of the following measures on UMN/AMR/Futureproofing/Access/Competitive Market Functioning/Manufacturing Quality and Environment/ Security of Supply/ Streamlining ◦ Further comments on your answers above • Conclusion (the greatest impacts with supporting data) • Close (invitation to be contacted with follow up questions) |
|--|

The questionnaire was delivered electronically using the tool 'Survey Monkey' and 220 participants were directly invited. Invites were sent as individual links were possible to enable tracking of participation and were supported by a letter from the EC endorsing the survey. The EC also shared the survey link within relevant networks of public authorities. Of the total number of invitations, over 90 invitations were sent to 'intermediary' organisations who were asked to disseminate the survey link through their networks (e.g civil society or association members) in order to snowball the sample further. The survey targeted five main stakeholder groups (industry, public authorities, health service providers, academic and civil society) and had agreed participant targets that were considered suitably representative. The survey remained open for just under 15 weeks between the dates 16th November 2021 and 14th January 2022, and invited participants were followed up multiple

times in this period to try and boost participation. The number of individuals and intermediaries invited is shown in Table 19.

Table 19. Targets and invited participants per stakeholder group.

Stakeholder	Targeted	Invited (intermediary)
Industry	65	63 (38)
Public Authorities	50	15 (6)
Health Service Providers	20	40 (33)
Academic	20	63 (7)
Civil Society Organisations	45	39 (11)
Total	200	220 (95)

Upon closing the survey, data was downloaded to an excel spreadsheet and imported to STATA. Data was cleaned extensively in STATA with suspected duplicate, test, empty and “nonsense” entries exported in full to excel. Within excel the responses were manually reviewed and decisions taken and recorded on their inclusion. In one case two entries from a single person were combined, where the survey had been completed in two separate and distinct parts. One person submitted an amendment to their responses by email which was enacted into the data set. Two people’s data sent by email were manually entered into the data collection tool by the evaluation team and then downloaded with the rest of the data. Having received and downloaded 440 entries to the survey, 209 responses remained for analysis after data cleaning.

The process of identification of campaigns was conducted using a combination of statistical software and manual checking in excel according to the following process:

- Identifying responses that matched on all of the 46 closed questions
- Identifying responses that matched identically on any one of the open questions
- Identifying responses that matched to a score of 94% of characters on any one of the open questions using the function ‘matchit’ in STATA using the “bigram” option for fuzzy logic.
- Exporting all potential campaign respondents to excel where they were manually grouped
- Any that could not be assigned to a campaign were decategorized and considered independent entries.

Campaigns of ten or more responses matched by any of the three methodologies were considered for further analysis and separate presentation of the key points from open questions. In accordance with the guidance received on the use of data for campaigns one copy of the campaign response was selected per stakeholder group from blocks of matching closed question answers while others were disregarded from any quantitative presentation.

Quantitative analysis focussed on the tabulation and description of the closed questions where in each case the questions were asked with a 5-point scaled response. There was always a ‘don’t know’ option and respondents also had the option to skip any question. The responses were divided into 5 different stakeholder group to which they had self-categorised: i) Industry ii) Civil Society iii) Public Authorities iv) Academic v) Health Services.

Answers were first tabulated as frequencies of each response per question and stakeholder and then individually attributed a score (1 -5) and these scores were tabulated along with the 'don't know' and 'skipped' options. Following this for each question an average score was calculated per stakeholder. These were then normalised into an "all stakeholder score" which weighted each stakeholder group's score equally and accounted for the different participation rates. Within each subcategory the different aspects were ranked to identify overall which were considered the most/least effective, relevant etc. The average scores were mapped back to the original categories through assignment to five evenly sized groups with 3 at the centre so <1.8 was very small/not at all, 1.8-2.59 was small/slightly, 2.6-3.39 was moderate/moderately, 3.4-4.19 was large/largely >=4.2=very large/extremely.

Agreement between stakeholders was assessed using ANOVA. Agreement between stakeholders was classified as high, medium, and low where $p < 0.05$ combined with an F score greater than 4 was considered low agreement with strong evidence that stakeholders did not have consensus between them – inter-stakeholder consensus. Medium agreement was assumed where the P value was < 0.06 and the F score was above 3. Those with medium and low inter-stakeholder consensus were further explored using Tukey's test for multiple comparisons to identify the divergent stakeholders.

Finally, the standard deviation was calculated per question and per stakeholder and utilised as an indicator of within (intra) stakeholder consensus. A higher standard deviation signalled less intra-stakeholder agreement with those above 1.1 being classified as low agreement and below 0.7 high agreement. Where intra-stakeholder consensus was low and sample size permitted these differences were explored related to geographical area of respondent (public health authorities) and subcategory of the stakeholder group (Industry, public health authority, academic).

Open questions were analysed qualitatively. Data was outputted to Excel where questions were allocated to Effectiveness, Relevance, Coherence, Efficiency (retrospective) or to policy blocks (anticipated impacts) and then coded into deductive themes. This data was analysed and summarised integrated with interview and open public consultation data.

Interviews

Semi-structured interviews supported our qualitative and in-depth explorations of the functioning of the current legislation. They also gathered feedback and input on the initial policy elements described in the Inception Impact Assessment, as seen from the perspective of the key stakeholder groups, across the EU member states.

Candidate interviewees were identified by a range of methods (drawing on the study team's knowledge of the sector and preliminary desk research, expression of interest via the targeted survey, Pharmaceutical Committee workshops, recommendation by other interviewees) and the list was verified and inputted to by the EC. Participants met simple selection criteria: senior figures with good knowledge of the legislation either as individual experts or as senior representatives of organisations with a mandate that encompasses the legislation. Interviews targeted participants across all the identified stakeholder group.

Interviews were conducted according to a topic guide enabling them to be loosely structured. Individual questions were tailored to each interviewee. The topic guide was designed in two parts with the first covering the evaluation criteria while the second part of the discussed the problem analysis, policy options and comparison of the policy options.

Interviews were conducted remotely via Zoom or Teams by a team of ten consultants over the period 7th December 2021 and 26th January 2022. A shortened version of the topic guide was shared ahead of the interview. Interviews were an hour and half long and were recorded (with permission) and an auto-transcription created and stored. On some occasions interviews were conducted in groups with multiple participants and organisations in attendance (Table 20 shows interviews as groups and individuals). Following completion of the interviews, summary notes were written up and key meta data (participant(s), organisation, stakeholder group) were transcribed onto them.

Table 20. Interviews targeted and conducted by stakeholder group.

Stakeholder	Targeted	Conducted	Individuals
Industry	40	29	57
Public Authorities	35	9	10
Health Service Providers	15	26	45
Academic	15	4	6
Civil Society Organisations	25	16	20
Total	130	84	138

Summary notes were imported into Nvivo, coded thematically according to the 2020 objectives of the revisions and abstracts were exported for synthesis into the reports.

Workshops

Two remote stakeholder workshops with participants from across the stakeholder groups provided opportunity for the community to deliberate on progress and conclusions to date and supplement previous data collection.

Each half day workshop was hosted via zoom and followed the structure of:

- Introduction from the EC
- Plenary presentation including opening slido (interactive poll) from Technopolis Project Lead
- Breakout groups: Brief presentation followed by participatory discussion.
- Plenary presentation from each breakout group
- Closing presentation on next steps and closing slido from Technopolis Project Lead

In both cases a 'save the date' was followed by an invite and a discussion paper on the workshop topics 2 weeks prior to the event. Breakout group topics were provided in advance after agreement with the EC. Participants were able to state a first and second preference for their breakout groups and first choices were facilitated the vast majority of the time. Each breakout group had a facilitator and a presenter (from either Technopolis or a project partner) and a technical support from Technopolis Group. Breakout groups were large and to facilitate participation muting and unmuting of mics was strictly led by the facilitator while participants were also free to use the chatbox continuously and this was tracked and responded to. Observers from the EC were in attendance in all breakout groups. Key details about the workshops are shown in Table 21.

Table 21. Details of the workshops.

	Workshop 1: Evaluation	Workshop 2: Impact Assessment
Date	19 th January 2022	25 th April 2022
Invited	246	339
Attended	208	199
Retention at final plenary	80%	90%
Breakout Groups	<ol style="list-style-type: none"> 1. Safeguarding Public Health 2. Europe's regulatory Attractiveness 3. Accommodating advances in science and technology 4. Ensuring access to medicines 5. Functioning of the EU market for medicines 	<ol style="list-style-type: none"> 1. Enabling innovation including for UMN 2. Ensuring Access to Affordable Medicines for Patients 3. Enhancing the security of supply of medicines and addressing shortages 4. Reducing the regulatory burden and providing a flexible regulatory framework

ANNEX 5: EVALUATION

The Evaluation is provided in a separate document, in attachment.

ANNEX 6: COHERENCE WITH THE REVISION OF THE ORPHAN AND PAEDIATRIC REGULATION

The general EU pharmaceutical legislation regulates the way medicines (including medicines for rare diseases and children) are *authorised* across the EU and sets the framework in which they are marketed. Specialised legislation for rare diseases and children, entered into force in 2000 and 2007 respectively and currently being revised, complements the general EU pharmaceutical legislation to specifically support the development in these previously neglected areas, mainly through additional incentives and obligations.

Both the revision of the general pharmaceutical legislation and the revision of the legislation for medicines for rare diseases and children adjust the system of incentives and depart from the 'one size fits all' approach to a 'modulated' one. Therefore, regulatory data protection for medicines and market exclusivity (in the case of orphan medicines) are modulated to reward companies developing medicines that deliver on needs of patients. Such needs are primarily reflected in the concepts of 'unmet medical need'. Furthermore, it is of utmost importance that patients across the EU also have access to such medicines (which is currently not the case).

Unmet medical need / *highest* unmet medical need

Both revisions will include a criteria-based definition on unmet medical need. The general pharmaceutical legislation will contain a definition for 'unmet medical needs' (UMN). The legislation on rare diseases will contain a definition of '*highest* unmet medical needs' (HUMN), as in principle all orphan medicines will automatically satisfy the definition of UMN under the general rules; only a small subgroup of orphan medicines will qualify as 'HUMN'. The Commission has worked with Member States and the EMA and received input from stakeholders via consultations to develop criteria that can be introduced in the legislation. These criteria relate to disease level (whether the disease is life-threatening and/or seriously debilitating) and they relate to product level (whether there is another medicine or therapy already authorised and, if so, whether the treatment under development can satisfactorily cure the disease).

In principle, medicines that satisfy the definition of UMN or HUMN will receive (a) access to early scientific advice and regulatory facilities and (b) access to longer regulatory protection periods (market exclusivity for medicines for rare diseases and data protection for other medicines).

Other points of coherence between the general and orphan medicines legislation are listed below. Together they create an integral system through:

- The revision of procedures for accelerated development and assessment of medicines for major public health needs taking into account novel technologies, in particular, the implementation of the PRIME scheme.
- Upstream cooperation among actors of the pharmaceutical lifecycle which foresees the reinforcement of mechanisms for cooperation and coordination between the regulatory authorities, Health Technology Assessment (HTA) authorities and payers building on the possibilities of the new HTA rules.
- Simplification of procedures and reduction of burden for generic/biosimilars. For example, currently it is not possible to apply for a marketing authorisation for a generic/biosimilar before the orphan market exclusivity period is over (i.e. 10 years after obtaining the marketing authorisation) whereas for other medicines this is possible when the data protection expires and before expiry of market protection. In the new system, application for

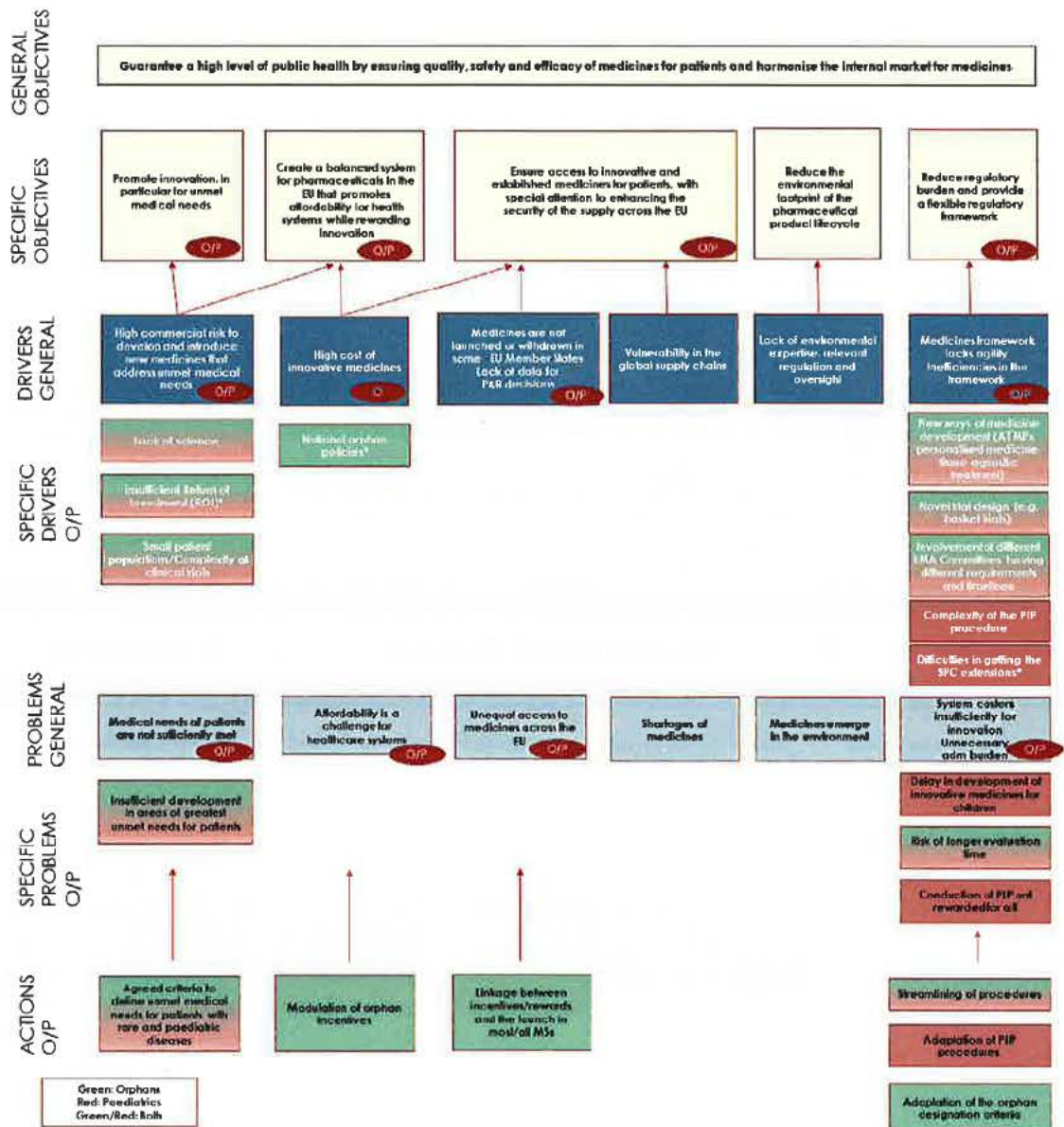
marketing authorisation for generic or biosimilar medicines will become possible *before* the expiry of market exclusivity.

- Future-proofing of the legislation, meaning its adaptation to rapid technological changes, including personalised medicine, will benefit patients as described in section 8. This will allow the full use of opportunities brought by gene therapies and personalised medicine which in many cases may concern medicines for rare diseases.

In the case of transferable exclusivity vouchers (TEVs), at first glance, there may seem to be incoherence between the two regimes. The conclusion in the Impact Assessment for the revision of the legislation on medicines for rare diseases is that TEVs can be considered as an ineffective incentive to generate innovation, whereas in the case of antimicrobials they may be a more plausible incentive if applied strictly.

In fact, this different conclusion stems from the 'special' character of the antimicrobial sector and the particularity of the market failure in this case. Both cases relate to incentivising products for a limited number of patients (rarity of the disease in the first and desire to use the new antimicrobial as little as possible in the second). However, contrary to rare diseases, the societal risk of AMR (which potentially concerns the whole population and not just a few patients) and its actual and potential economic consequences combined with the very limited pipeline of antimicrobials with a new mechanism of action suggests that the advantage of having TEVs specifically for novel antimicrobials as an 'insurance policy' against resistant antimicrobials may surpass the disadvantages of the high costs for the very limited number of TEVs that are likely to enter the market.

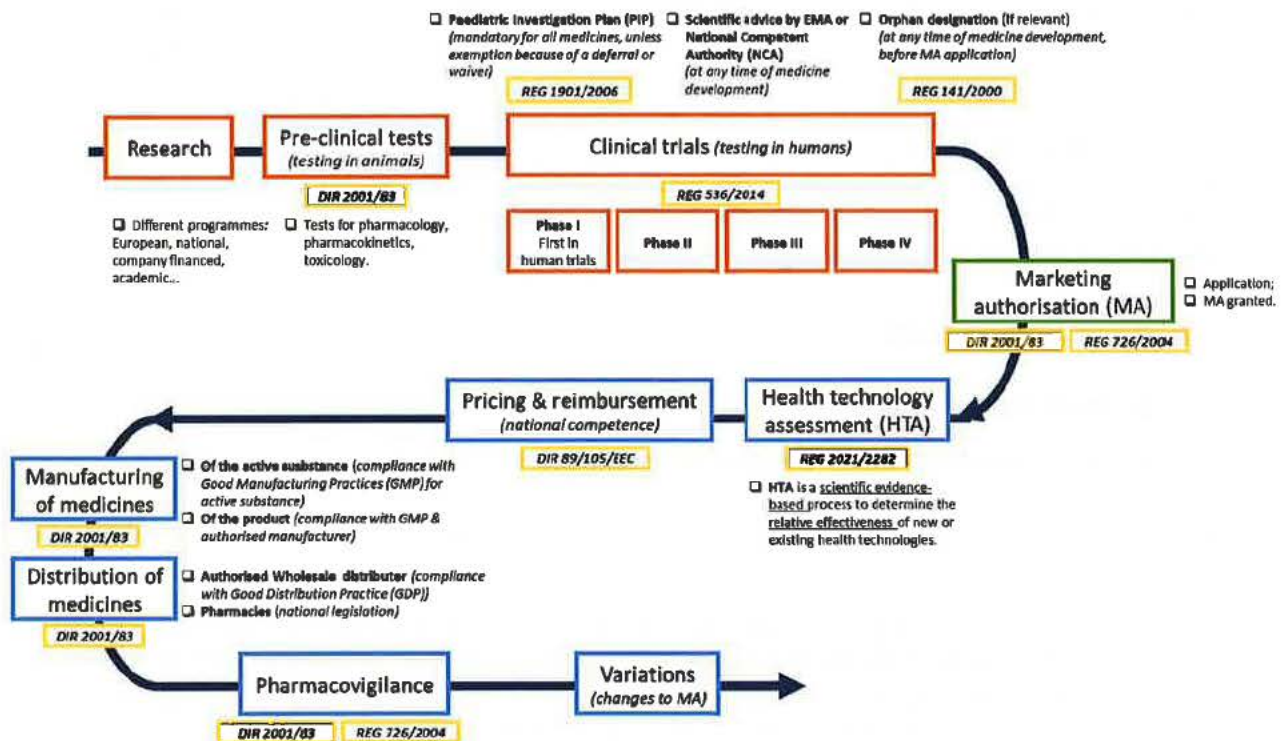
ANNEX 6B: INTERVENTION LOGIC OF THE REVISION OF THE ORPHAN AND PAEDIATRIC REGULATION



ANNEX 7: OVERVIEW OF MARKETING AUTHORISATION PROCEDURES

National procedure	Mutual recognition procedure (MRP)	Decentralised procedure (DCP)*	Centralised Procedure (CP)
... where one MS authorise medicines for its own territory.	...where additional MSs recognise the national MA of another MS and authorise the medicine for their own territory.	...where several MSs authorise a medicine for their own territory.	...where a MA is valid in all MSs. This procedure is <u>mandatory</u> for some products.
Market access			
National territory.	National territory of all MSs involved.		EU internal market.
Procedure overview			
Procedures and assessment time depend on national legislation.	Based on MA already granted by one MS; Recognition of that MA by other MSs.	Scientific assessment by one MS; Consultation of MSs involved.	Scientific assessment by EMA; Consultation of the MSs; Authorisation granted by COM.
	Total time if agreement among MSs → 210 days → 240 days		Total time if positive opinion by EMA
	If disagreement among MSs → referral procedure to CMD(h)/CHMP		→ 277 days

ANNEX 8: OVERVIEW OF THE LEGAL FRAMEWORK



ANNEX 9: OVERVIEW OF ECOSYSTEM AND THE LEGAL FRAMEWORK

1. The pharmaceutical ecosystem

The Pharmaceutical Strategy for Europe¹⁵⁴ describes the pharmaceutical ecosystem and changes in the landscape that transform industry and medicines development from the old model of chemical blockbuster medicines to biological medicines, advanced therapy medicines, combined medicines with software and personalised medicines. Health data is key to fully exploiting the huge potential of new technologies and digitisation. This vision is echoed in the health ecosystem of the updated European industrial strategy¹⁵⁵.

The EU pharmaceutical ecosystem covers activities from pre-clinical research to manufacturing and includes actors ranging from manufacturers (including medical devices and equipment and personal protective equipment), healthcare services; health tech and related services¹⁵⁶. Overall, it covers **24.8 million direct jobs, 493 000 firms** (including 99.7% SMEs) and contributes to **9.5% of EU value added**¹⁵⁷. The EU provides an attractive market for the pharmaceutical industry, especially with regards to the activities and support provided by the European Medicines Agency and the EU-wide marketing authorisation. These elements are key in attracting R&D to the EU and are regulated by the general pharmaceutical legislation. At global level, the EU health industries are also key players in competition with North America and Asia. As an example, in 2018, North America accounted for 48.9% of global sales of medicines compared to Europe (incl. Switzerland) accounting for 23.2%¹⁵⁸. The EU also accounts for 24% of the world's API production compared to 65.5% being produced in Asia Pacific. The EU pioneered in sophisticated biologic innovative medicines (and biosimilar medicines), however, Asia and the US are rapidly catching up¹⁵⁹.

2. The legal framework

a. Basic legislative acts

The **general EU pharmaceutical legislation** harmonises the way medicines are authorised across the EU. This legislation is grounded on the principle that a medicine for human use may only be placed on the market once authorised based on a positive benefit-risk of its quality, safety and efficacy.

Medicines may either be authorised centrally by the Commission based on a positive scientific assessment by the European Medicines Agency (EMA), the centralised procedure (CP), or nationally by an individual or a group of Member States. A medicinal product authorised via the CP is not necessarily accessible in all Member States, as its actual placing on the market may depend on the launch strategy of companies and national pricing and reimbursement decisions.

The general pharmaceutical legislation also regulates the post-authorisation monitoring of the medicine (pharmacovigilance), as well as manufacturing, distribution and advertising.

¹⁵⁴ COM(2020) 761 final.

¹⁵⁵ COM(2021) 350 final [European industrial strategy | European Commission \(europa.eu\)](#).

¹⁵⁶ SWD(2021)351 final – page 138.

¹⁵⁷ SWD(2021)351 final – page 137.

¹⁵⁸ [Would the last pharmaceutical investor in Europe please turn the lights out \(efpia.eu\)](#).

¹⁵⁹ SWD(2021)351 final – page 139.

The specialised legislations for rare diseases and children¹⁶⁰ (“The Orphan and Paediatric Regulations”) complements the general EU pharmaceutical legislation (that also apply to medicines for rare diseases and children) to specifically support the development in these previously neglected areas, mainly through specific, additional incentives and obligations. Both the Orphan and Paediatric Regulations are designed to address specific unmet medical needs of small populations: (i) the Orphan Regulation aims at enabling research, development and authorisation of new medicines for rare diseases through specific incentives and (ii) the Paediatric Regulation works mainly with obligations. It compels companies already developing products for adults to screen them for possible use in children. It provides rewards once this obligation has been fulfilled, to compensate for the additional costs.

The revision of these specialised legislations, also ongoing, follows coherent objectives with the revision of the general pharmaceutical legislation: promoting innovation to better address unmet medical needs, ensuring access of patients to innovative medicines and reducing regulatory burden¹⁶¹. Taken together, they aim to ensure the right balance between giving incentives for innovation to strengthen the research base of the EU pharmaceutical industry and the need for patients to have access to affordable medicines.

These legislations are complemented by more specific ones, applicable at different stages of the lifecycle of medicines.

b. Other legislative acts and policies applicable to medicinal products

i. At the research and development stage

The **Regulation on clinical trials**¹⁶² harmonises the processes for the assessment and supervision of clinical trials throughout the EU. The evaluation, authorisation and supervision of clinical trials are the responsibilities of Member States and the Regulation ensures harmonisation. The regulation also allows as of 2022 a more efficient process for the approval of multinational trials. Having a single application and a single package will streamline the registration, assessment and supervision processes for EU clinical trials. This will also facilitate the conduct of trials in small populations scattered in several countries.

The **proposed Regulation on the European Health Data Space (EHDS)**¹⁶³ will provide a common framework across EU Member States for access to quality health data for use in research and development of new treatments.

The **European innovation Council (EIC)**¹⁶⁴ established under the Horizon 2020 programme aims at identifying and supporting breakthrough technologies and game changing innovations with the potential to scale up internationally and become market leaders. It supports all stages of innovation from R&D on the scientific underpinnings of breakthrough technologies, to validation and

¹⁶⁰ Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products, OJ L 18, 22.1.2000, p. 1, [EUR-Lex - 32000R0141 - EN - EUR-Lex \(europa.eu\)](#) and Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use, OJ L 378, 27.12.2006, p. 1, [EUR-Lex - 32006R1901 - EN - EUR-Lex \(europa.eu\)](#).

¹⁶¹ However, the revision of the general pharmaceutical legislation has also other aims (such as ensuring that medicines are affordable, reducing environmental footprint), not covered by the revision of the specialised legislations.

¹⁶² Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1 <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0536&qid=1653648430017>.

¹⁶³ Proposal for a Regulation of the European Parliament and of the Council on the European Health Data Space, COM(2022) 197 final, [Proposal for a regulation - The European Health Data Space \(europa.eu\)](#).

¹⁶⁴ For more details, see <https://eic.ec.europa.eu>.

demonstration of breakthrough technologies and innovations to meet real world needs, to the development and scaling up of start-ups and small and medium-sized enterprises (SMEs).

The **Innovative Health Initiative Joint Undertaking**¹⁶⁵ (IHI JU) is a public-private partnership between the European Union, represented by the European Commission, and several health industries from the biopharmaceutical, biotechnology and medical technology sectors. IHI brings together diverse stakeholders (universities, companies large and small, and other health stakeholders) in collaborative projects that address disease areas where there is a high burden on patients and/or society. The initiative focuses on cross-sectoral projects supporting the development of safe, effective, people-centred and cost-effective products and services that target key unmet public health needs.

ii. At the authorisation stage

The authorisation procedures are laid down in the general pharmaceutical legislation but aspects linked to authorisation are completed by other regulations.

Beyond the **general patent rules** applicable to medicines, the **Regulations on supplementary protection certificates (SPCs)**¹⁶⁶ provide for supplementary intellectual property rights extending patent protection for specific medicines. SPCs aim to offset the loss of patent protection for medicines that occurs due to the compulsory lengthy testing and clinical trials these products require prior to obtaining marketing authorisation.

The ongoing review of the SPC regulation¹⁶⁷ will put in place a unitary SPC and/or a single ('unified') procedure for granting national SPCs. This will make SPCs more accessible and efficient, and will impact the health sector.

iii. At the market launch stage

Following marketing authorisation companies take decisions on the market launch in Member States based on commercial considerations¹⁶⁸. These decisions are influenced by the national decisions on pricing and reimbursement of the medicines concerned, since pricing and reimbursement is the competence of Member States¹⁶⁹.

¹⁶⁵ Council Regulation (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe and repealing Regulations (EC) No 219/2007, (EU) No 557/2014, (EU) No 558/2014, (EU) No 559/2014, (EU) No 560/2014, (EU) No 561/2014 and (EU) No 642/2014, OJ L 427, 30.11.2021, p. 17, [EUR-Lex - 32021R2085 - EN - EUR-Lex \(europa.eu\)](#)

¹⁶⁶ Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products, OJ L 152, 16.6.2009, p. 1, [EUR-Lex - 32009R0469 - EN - EUR-Lex \(europa.eu\)](#) and Regulation (EU) 2019/933 of the European Parliament and of the Council of 20 May 2019 amending Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products, OJ L 153, 11.6.2019, p. 1, [EUR-Lex - 32019R0933 - EN - EUR-Lex \(europa.eu\)](#).

¹⁶⁷ [Medicinal & plant protection products – single procedure for the granting of SPCs \(europa.eu\)](#).

¹⁶⁸ The authorisation of a medicinal product does not mean that it will be immediately accessible to all European patients. Factors such as the size of the population or the organisation of health systems and national procedures influence these decisions. Companies tend to begin negotiations with the Member States that may grant a higher price, often the countries with the highest GDP per capita. The willingness to pay a high(er) price in a Member State with a high GDP may limit the ability of a smaller Member State to negotiate a price in line with its GDP; hence, differences in the accessibility and affordability across the EU.

¹⁶⁹ The decision for pricing and reimbursement is based on national policies, which pertain to Member States and thus are outside the remit of the EU legislation and of this revision.

The **Directive on transparency of measures regulating the prices of medicines** and their inclusion in the scope of national health insurance systems¹⁷⁰ aims at obtaining an overall view of national pricing arrangements, and providing public access to them for all those involved.

To help national authorities in their reimbursement decisions national Health Technology Assessment (HTA) bodies may assess the medicines. The HTA is a scientific evidence-based process to determine the relative effectiveness of new or existing health technologies.

The **Regulation on HTA**¹⁷¹ establishes a Coordination Group of HTA national or regional authorities, a stakeholder network and lays down rules on the involvement in joint clinical assessments and joint scientific consultations of patients, clinical experts and other relevant experts. The regulation also reduces duplication of efforts for national HTA bodies and industry, facilitates business predictability and ensures the long-term sustainability of EU HTA cooperation. The new rules will come in to force in 2025 and should complement the efforts of the EU general pharmaceutical legislation to incentivise innovation with a strengthened and expanded HTA capacity.

iv. After the market launch stage

Once a medicine is authorised and placed on the market, it is subject to pharmacovigilance. Pharmacovigilance relates to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The general EU pharmaceutical legislation details the pharmacovigilance obligations.

In addition, the **Regulation on the performance of pharmacovigilance activities**¹⁷² outlines the practical details to be respected by marketing authorisation holders, national competent authorities and the EMA and the **Regulation on post-authorisation efficacy studies**¹⁷³ specifies the situations in which such studies may be required.

After an initial authorisation has been granted, market authorisation holders can also develop changes to the medicines. The **Regulation on variations**¹⁷⁴ sets the procedures for post-authorisation changes to a marketing authorisation for medicines. These changes can e.g. be changes in address of the company, active substance, strength, pharmaceutical form or route of administration. The Commission also intends to review this regulation so as to simplify the system and reduce administrative burden for medicine authorities and companies.

c. Legislation in adjacent areas

¹⁷⁰ Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems, OJ L 40, 11.2.1989, p. 8, [EUR-Lex - 31989L0105 - EN - EUR-Lex \(europa.eu\)](#).

¹⁷¹ Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU, OJ L 458, 22.12.2021, p. 1, [EUR-Lex - 32021R2282 - EN - EUR-Lex \(europa.eu\)](#).

¹⁷² Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council, OJ L 159, 20.6.2012, p. 5, [EUR-Lex - 32012R0520 - EN - EUR-Lex \(europa.eu\)](#).

¹⁷³ Commission Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required, OJ L 107, 10.4.2014, p. 1–4, [EUR-Lex - 32012R0520 - EN - EUR-Lex \(europa.eu\)](#).

¹⁷⁴ Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, OJ L 334, 12.12.2008, p. 7, [EUR-Lex - 32008R1234 - EN - EUR-Lex \(europa.eu\)](#).

The **legal framework for blood, tissues and cells**¹⁷⁵ (BTC) is used for medical treatments and therapies, including innovative therapies. The ongoing review will promote the safety of patients and donors, facilitate innovation and contribute to adequate supply of the relevant therapies. Blood, tissues and cells may be starting materials for medicines. Particularly important for the pharmaceutical sector is the strengthening the safety and quality requirements of BTC to align with the standards of the pharmaceutical framework for the highest risk preparations. It will also address the (re)emergence of communicable diseases, including lessons learnt from the COVID-19 pandemic, and is thus contributing to the European Health Union.

The **regulation on medical devices**¹⁷⁶ and the **regulation on in vitro diagnostic medical devices**¹⁷⁷ deal with medical devices, which are products or equipment intended for a medical purpose. In the EU, they must undergo a conformity assessment to demonstrate they meet legal requirements to ensure they are safe and perform as intended. They are assessed at Member State level, but EMA is involved in the assessment sometimes. In some cases, the bodies responsible for the conformity assessment must seek a scientific opinion from EMA before issuing a CE certificate. This is the case essentially when medicines are concerned (e.g. medical devices with an ancillary medicinal substance, companion diagnostics). In some other cases (when the device is ancillary to the medicines), the combined product requires a marketing authorisation.

¹⁷⁵ Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC, OJ L 33, 8.2.2003, p. 30, [EUR-Lex - 32002L0098 - EN - EUR-Lex \(europa.eu\)](#) and Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 7.4.2004, p. 48, [EUR-Lex - 32004L0023 - EN - EUR-Lex \(europa.eu\)](#).

¹⁷⁶ Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, OJ L 117, 5.5.2017, p. 1, [EUR-Lex - 02017R0745-20200424 - EN - EUR-Lex \(europa.eu\)](#).

¹⁷⁷ Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU, OJ L 117, 5.5.2017, p. 176, [EUR-Lex - 02017R0746-20170505 - EN - EUR-Lex \(europa.eu\)](#).

ANNEX 10: ANALYTICAL REPORT

The Analytical report is provided in a separate document, in attachment.

ANNEX II: IMPACT ANALYSIS OF ALL MEASURES

The Impact analysis of all measures is provided in a separate document, in attachment.

ANNEX 12: STUDY REPORT ON IMPACT ASSESSMENT

The Study report on impact assessment is provided in a separate document, in attachment.

ANNEX 13: STUDY REPORT ON EVALUATION

The Study report on evaluation is provided in a separate document, in attachment.

