Annex 5: Evaluation Staff Working Document

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Glossary

Term or acronym	*Meaning or definition*
Accessibility	A medicine becomes accessible to patients once it has been authorised, is being marketed, and can be reimbursed in a Member State.
Affordability	Relates to payments to be made by patients (out of pocket on healthcare or through co-payments) which can be described as affordability at micro level and to the sustainability of public funding of the healthcare sector raised through social security contributions or taxes (affordability at macro level).
AMR	Antimicrobial resistance.
API	Active Pharmaceutical Ingredient.
ATMPs	Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells defined in Artcicle 2 of Regulation (EC) No 1394/2007.
Biological medicine	A medicine whose active substance is made by or derived from a living organism. Biological medicines contain active substances from a biological source, such as living cells or organisms (human, animals and microorganisms such as bacteria or yeast).
Biosimilar	A biosimilar is a biological medicine that is highly similar to another biological medicine which has already been approved. Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines.
BTC	Blood, tissues and cells.
CAT	The Committee for Advanced Therapies is the European Medicines Agency's committee responsible for assessing quality, safety and efficacy of advanced therapy medicinal products (ATMPs) and following scientific developments in the field.
CBA	Cost-benefit assessment.
CHMP	The Committee for Medicinal Products for Human Use is EMA's committee responsible for human medicines.
CMA	Conditional marketing authorisation is the approval to market a medicine that addresses patients' unmet medical needs on the basis of data that is less comprehensive than that normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide comprehensive clinical data in the future.
CMDh	The Coordination Group for Mutual recognition and Decentralised Procedures – Human is EMA's committee responsible for the examination and coordination of questions relating to the marketing authorisation of human medicines in two or more Member States in accordance with the mutual recognition or decentralised procedure.
COM	European Commission.

COMP	The Committee for Orphan Medicinal Products is the Agency's committee responsible for recommending orphan designation of medicines for rare diseases.
CP	The centralised authorisation procedure (CP) is the European Union-wide procedure for the authorisation of medicines, where there is a single application, a single evaluation and a single authorisation granted by the European Commission valid throughout the European Union.
Data protection	Period of protection during which pre-clinical and clinical data and data from clinical trials handed in to the authorities by one company cannot be referenced by another company in their regulatory filings.
DCP	The decentralised procedure (DCP) is the procedure for authorising medicines in more than one European Union Member State in parallel. It can be used for medicines that do not need to be authorised via the centralised procedure and have not already been authorised in any Member State.The DCP was introduced by Directive 2004/27/EC, after the 2004 revision.
EEA	The European Economic Area (EEA) include all EU Member States and also Iceland, Liechtenstein and Norway.
EFTA	The European Free Trade Association (EFTA) include Iceland, Liechtenstein, Norway and Switzerland.
EMA	The European Medicines Agency ('the Agency') is an EU agency founded in 1995 which is responsible for the scientific evaluation, supervision and safety monitoring of medicines, both human and veterinary, across Europe.
ERA	Environmental Risk Assessment.
ERN	European reference networks (ERNs) are virtual networks involving healthcare providers across Europe. Directive 2011/24/EU on patients' rights in cross-border healthcare together with Delegated Decision 2014/286/EU and Implementing Decision 2014/287/EU provide for the setting up of ERNs, 24 of which were established in 2017. The purpose of these networks is to facilitate discussion of complex or rare diseases and conditions that require highly specialised treatment, and concentrated knowledge and resources.
EU	European Union
EudraVigilance	A centralised European database of suspected adverse reactions to medicines that are authorised or being studied in clinical trials in the European Economic Area (EEA).
FDA	United States Food and Drug Administration.
GDP	Good Distribution Practices
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GMO	Genetically Modified Organism

Generic medicine	A generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s). The generic can only be marketed after expiry of the data and market protection.
IA	An impact assessment (IA) identifies and describes the problem to be tackled, establishes objectives, formulates policy options, assesses the impacts of these options and describes how the expected results will be monitored. The Commission's impact assessment system follows an integrated approach that assesses the environmental, social and economic impacts of a range of policy options, thereby ensuring that sustainability is an integral component of Union policymaking.
ICER	An incremental cost-effectiveness ratio (ICER) is a summary measure representing the economic value of an intervention, compared with an alternative (the comparator). An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of 'extra cost per extra unit of health effect' for the more expensive therapy versus the alternative.
IP	Intellectual property
IQVIA	IQVIA is a contract research and analyticalservices organisation that collects data including global pharmaceutical sales data. Such sales databases were used for this evaluation.
MA	A marketing authorisation (MA) is the mandatory approval process before a medicine enter the market of one, several or all European Union Member States.
MAH	Marketing authorisation holder
Marketing authorisation application	An application made to a European regulatory authority for approval to market a medicine within the European Union.
Marketing authorisation grant	A decision granting the marketing authorisation issued by the relevant authority.
Market exclusivity	The period after the marketing authorisation of a medicine for a rare disease when similar medicines for the same indication cannot be placed on the market. Under the current legislation, the market exclusivity has a duration of 10 years.
Market protection	Period of protection during which generics cannot be placed on the market.
Medical condition	Any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome).
Megatrend	Megatrends are long-term driving forces that are observable now and will most likely have significant influence on the future. Megatrends are closely interlinked between each other and simultaneously affect many different stakeholders. Thus, a systemic and global understanding of the issue under study is

	necessary to fully picture and illustrate the dynamics at stake. See also: https://knowledge4policy.ec.europa.eu/foresight/tool/megatrends-hub_en" \l "explore
MRP	The mutual recognition procedure (MRP) is a procedure through which an authorisation of a medicine in one European Union Member State is recognised by another Member State.
MS	Member States (MS) are countries member of the EU.
National authorisation procedure	The national authorisation procedure is a marketing authorisation procedure where individual Member States authorise medicines for use in their own territory. This procedure depends on national legislation.
NAS	New active substances.
NCA	National Competent Authority.
NCE	New Chemical Entity.
"Off-label" use	Use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration.
Oncology	A branch of medicine that specialises in the prevention, diagnosis and treatment of cancer.
Orphan condition	A medical condition, as defined above, that meets the criteria defined in Article 3 of Regulation (EC) No 141/2000; a life-threatening or chronically debilitating condition affecting no more than five in 10 thousand persons in the EU.
Orphan designation	A status assigned to a medicine intended for use against a rare/ orphan condition. The medicine must fulfil certain criteria for designation so that it can benefit from incentives such as market exclusivity.
Orphan indication	The proposed therapeutic indication for the purpose of orphan designation. This specifies if the medicinal product subject to the designation application is intended for diagnosis, prevention or treatment of the orphan condition.
Payer	An entity responsible for financing or reimbursing healthcare.
PDCO	The Paediatric Committee (PDCO) is EMA scientific committee responsible for activities associated with medicines for children. It supports the development of such medicines in the European Union by providing scientific expertise and defining paediatric need.
Personalised medicine	A medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy

	for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.
Pharmacovigilance	The monitoring of the safety of an authorised medicine and the detection of any change to its benefit-risk balance.
PIP	A paediatric investigation plan is a development plan designed to ensure that the data required to support the authorisation of a paediatric medicine are obtained through studies of its effect on children.
PRIME	The priority medicine (PRIME) scheme has been launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need. Through this voluntary schemethe Agency offers early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks, to optimise development plans and enable accelerated assessment of medicines applications.
QALYs	Quality-adjusted life years (QALYs) refers to a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to one year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life and freedom from pain and mental disturbance.
Rare disease	Diseases with a particularly low prevalence; the European Union considers diseases to be rare when they affect no more than 5 per 10,000 people in the European Union.
RUP	Repeat Use Procedure is the use of the Mutual Recognition Procedure (MRP) after the completion of a first MRP or Decentralised Procedure (DCP) for the recognition of a marketing authorisation by other Member States.
SA	A scientific advice (SA) is the provision of advice by the Agency on the appropriate tests and studies required in developing a medicine, or on the quality of a medicine.
SDGs	The United Nations Sustainable Development Goals (UN SDGs) are 17 goals with 169 targets that all UN Member States have agreed to work towards achieving by the year 2030. They set out a vision for a world free from poverty, hunger and disease.
SmPC	A summary of product characteristics (SmPC) describes the properties and the officially approved conditions of use of a medicine.
SMEs	Micro, small and medium-sized enterprises.
SPC	The supplementary protection certificate (SPC) is an intellectual property right that serves as an extension to a patent right. The

	patent right extension applies to specific pharmaceutical and plant protection products that have been authorised by regulatory authorities.
SWD	Staff working documents (SWDs) are required to present the results of all impact assessments and evaluations/fitness checks.
Therapeutic indication	The proposed indication for the marketing authorisation. A medical condition that a medicine is used for. This can include the treatment, prevention and diagnosis of a disease. The therapeutic indication granted at the time of marketing authorisation will be the result of the assessment of quality, safety and efficacy data submitted with the marketing application.
UMN	Unmet Medical Need.

Certain footnotes use abbreviated references; full references can be found in the bibliography at the end of this Staff Working Document.

1. INTRODUCTION

1.1 Purpose and scope of the evaluation

The purpose of this evaluation is to assess how well the EU general pharmaceutical legislation, i.e. Directive 2001/83/EC[1] and Regulation (EC) No 726/2004[2], has performed since the last comprehensive revision in 2004. Its objective is to check whether the legislation is still 'fit for purpose' to protect public health, and to meet the needs of the EU patients in terms of access to innovative medicines, their availability and supply across the EU, as well as in terms of competitiveness of the EU pharmaceutical industry. The evaluation looks into the performance of the legislation during the COVID-19 pandemic and its suitability to achieve the objectives of the Pharmaceutical Strategy for Europe[3].

The Pharmaceutical Strategy for Europe aims at creating a future-proof regulatory framework that supports industry and promotes research in therapies that actually reach patients in order to fulfil their therapeutic needs, while addressing market failures. It provides among its flagships initiatives a revision of the general pharmaceutical legislation to help achieve the following objectives of the strategy, while guaranteeing the authorisation of safe, efficacious, high-quality medicines:

- Ensure greater access and availability of pharmaceuticals to patients;
- Ensure affordability of medicines for patients and health systems financial and fiscal sustainability;
- Enable innovation including for unmet medical needs, in a way that harnesses the benefits of digital and emerging science and technology and reduces the environmental footprint;
- Support EU influence and competitiveness on the global level, reduce direct dependence on manufacturing in non-EU countries, seek a level playing field for EU operators.

Given the political priority and importance of this initiative, this evaluation is part of a 'back-to-back process,' i.e. a single process of evaluation and impact assessment based on the same consultation strategy. The findings of the evaluation informed the impact assessment for the revision of the general pharmaceutical legislation.

The evaluation covers most parts of Directive 2001/83/EC and Regulation (EC) No 726/2004 (further details in Annex 9). Provisions on pharmacovigilance[4] are included as far as they are relevant to the objectives of the evaluation. Out of scope of this evaluation are provisions in Directive 2001/83/EC concerning:

- The registration of homeopathic medicinal products[5];

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[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67.
[2] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.4.2004, p.1.
[3] COM(2020) 761 final, Pharmaceutical Strategy for Europe.
[4] Title IX of Directive 2001/83/EC and Title II, Chapter 3 of Regulation (EC) No 726/2004.
[5] Title III, Chapter 2.

- The registration of traditional herbal medicinal products[6];
- Advertising and information to patients[7];
- Safety features and falsified medicines[8]; and
- Sale at a distance to the public[9].

The evaluation includes aspects of medicines covered by the *specialised* EU legislation i.e. on advanced therapy medicinal products[10], medicine for rare diseases[11] and medicines for children[12], insofar these are under the *general* pharmaceutical legislation (further details in Annex 9). The legislation on medicines for rare diseases and on medicines for children were subject to a separate evaluation[13]. The results of this evaluation have been taken into account.

The evaluation covers all 27 EU Member States, the three EEA-EFTA countries[14] and the United Kingdom; the latter applied the legislation for the entire evaluation period, i.e. 2005-2020.

The legislation is assessed using the evaluation criteria of effectiveness, efficiency, relevance, coherence and EU added value. A mixed quantitative and qualitative **methodology** was used (see Annex 4). It included peer-reviewed literature and policy document review to gather existing knowledge base and as a source of facts and figures; secondary data analysis of over 50 macro indicators relevant to industrial & economic competitiveness, research & innovation, to access, affordability and single market effects, including statistical, econometric and trend analysis in the EU, compared to data from other jurisdictions. In addition, case studies were developed focusing on specific issues[15] and illustrating linkages and mechanisms behind trends observed in the data. Finally, extensive stakeholder consultations were conducted and resulting primary data analysed from the feedback on the Roadmap/Inception Impact Assessment[16] and the public consultation, targeted surveys, interviews and a workshop.

Nonetheless, some **evidence limitations** affect the robustness of findings: (1) Stakeholders were often unable to break down observed effects to drivers of those effects and link those

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[6] Title III, Chapter 2a.
[7] Titles VIII and VIIIa.
[8] The provisions introduced by the Falsified Medicines Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.
[9] Title VIIa.
[10] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 324, 10.12.2007, p.121.
[11] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, OJ L 18, 22.1.2000, p. 1, (Orphan Regulation).
[12] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use, OJ L 378, 27.12,2006, p. 1, (Paediatric Regulation).
[13] SWD(2020) 163 final.
[14] Iceland, Liechtenstein and Norway.
[15] Topics covered: Unmet medical needs; Antimicrobial resistance (AMR); Agile / adaptive regulatory systems; SMEs / Regulatory support; Improved access to medicines; Regulatory barriers for emerging manufacturing technologies; Generic competition of complex medicines: biosimilars and complex non-biological medicines.
[16] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en.

to specific legislative measures in scope. (2) Due to the extended time period of the evaluation, many stakeholders consulted were not able to provide historic perspective on the situation before 2005, or the early years of the implementation of the 2004 revision. (3) Some stakeholder groups (especially civil society and public authorities) found it challenging to mobilise internal resources to provide information, data and evidence across all evaluation dimensions, and provided mainly opinions. As a result, qualitative and quantitative data collected during the evaluation show large variations of quality across stakeholder groups. Much of the quality data collected are linked to more recent years and therefore direct attribution of these effects to the 2004 revision remains limited.

Further, quantitative data definition and data collection approaches changed over time making it challenging to conduct a continuous trend analysis over the 2000-2020 time period. As data collection and indicators are not uniform across all countries, extensive data cleaning and data verification were applied.

2 WHAT WAS THE EXPECTED OUTCOME OF THE INTERVENTION?

2.1 Description of the intervention and its objectives

Since 1965, the EU pharmaceutical legislation has had the dual objective to safeguard public health and harmonising the internal market for medicines.

It is grounded on the principle that a medicine may only be placed on the market following the granting of a marketing authorisation based on a positive benefit-risk assessment of its quality, safety and efficacy. This requirement safeguards public health.

The general pharmaceutical legislation also regulates the safety monitoring of a medicine (pharmacovigilance), as well as manufacturing, distribution and advertising. The application of the legislation is based on cooperation and division of responsibilities between the EU level and Member States. Medicines may either be authorised centrally by the Commission on the basis of a positive scientific assessment by the European Medicines Agency (EMA), or nationally by an individual or a group of Member States. Moreover, Member States are responsible for the authorisation of manufacturers and wholesale distributors.

The general pharmaceutical legislation is supplemented by *specialised* legislation for medicines for rare diseases, medicines for children, advanced therapy medicines; it applies to these specialised medicines, while the specialised frameworks provide measures to address their specific characteristics. The Orphan Regulation was adopted in 1999 to enable research, development and authorisation of new medicines for rare diseases through specific *incentives*, given the small number of patients affected by rare diseases. The Paediatric Regulation was adopted in 2006 fostering the development and availability of medicines for children, without subjecting children to unnecessary trials or delaying the authorisation of medicines for use in adults. In doing so, the Paediatric Regulation obliges companies already developing medicines for adults to screen them for possible use in children and provides rewards once such obligation – the paediatric investigation plan – has been fulfilled. The Regulation on advanced therapy medicinal products (ATMPs) adapts the technical requirements for the authorisation of medicines that are based on genes, tissues or cells. Specific scientific committees at the EMA have been established to support assessment in all three specialised areas[17]. The Orphan and Paediatric Regulations are currently under revision, following an evaluation published in 2020.

[17] Committee for Orphan Medicinal Products (COMP), Paediatric Committee (PDCO), Committee for Advanced Therapies (CAT).

In addition, the general pharmaceutical legislation is complemented by the clinical trials Regulation[18] which harmonises the processes for assessment and supervision of clinical trials throughout the EU. Clinical trials generate data to substantiate the efficacy and safety of a medicine. Annex 9 provides an overview of the lifecycle of a medicine with the major touchpoints between the general pharmaceutical legislation.

Finally, the general pharmaceutical legislation links to other legal frameworks as medicines may be integrated or used in combination with medical devices[19] or in vitro diagnostics[20]. A medicine may be based on a substance of human origin[21] (e.g. blood, tissues or cells).

Despite the harmonisation provided by the EU pharmaceutical legislation, there is an inherent fragmentation of the EU market for medicines in terms of access, as most medicines go through national pricing and reimbursement processes prior to market launch. Pharmaceutical expenditure is largely subsidised by national health systems in order to ensure the adequate provision of medicines to all citizens. In this context, Member States adopt measures to regulate the prices of medicines and the conditions of their public funding based on their exclusive competence in this field (Article 168 TFEU). Such measures influence the prescription and utilisation of medicines in each country. They also affect the capacity of pharmaceutical companies to sell their products in domestic markets.

Before the 2004 revision, there were three **ways of obtaining a marketing authorisation**[22]:

- Centralised authorisation procedure - the marketing authorisation holder (MAH) can market the medicine and make it available to patients and healthcare professionals throughout the EU on the basis of a single marketing authorisation (MA);

- National authorisation procedure – the MAH can market the medicine and make it available to patients and healthcare professionals in the EU Member State where it was authorised;

- Mutual recognition procedure (MRP) – several Member States recognise the national MA of another MS and authorise the medicine in their own territory;

The 2004 revision added the decentralised procedure (DCP) (several Member States simultaneously authorise a new medicine on their respective territory).

Prior to the 2004 revision, there was an erosion of the EU's position as a leading hub for the pharmaceutical industry and R&D investment[23]. The EU pharmaceutical industry was losing competitiveness and growing less compared to the USA and Japan.

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[18] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1.

[19] Regulation (EU) No 745/2017 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, OJ L 117, 5.5.2017, p. 1.

[20] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU, OJ L 117, 5.5.2017, p. 176.

[21] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 7.4.2004, p. 48 and Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC, OJ L 33, 8.2.2003, p. 30.

[22] The main features are outlined in Annex 7.

In addition, science had progressed steadily and new therapies were on the horizon. There was progress of applied sciences (particularly in biotechnology) and also likely future developments (for example, gene therapy). In parallel, an ever-increasing globalisation in research and development as well as in regulatory practices on scientific and technical criteria for assessment of medicines had taken place. This was not adequately reflected in the EU regulatory framework. This also affected the attractiveness of the EU as a place to research, develop and supply medicines in a timely manner.

The risk of exacerbation of a fragmented EU pharmaceutical regulatory system with further enlargement of the market with new Member States prompted the Commission to devise a number of measures to reverse these trends.

An evaluation study[24] of the marketing authorisation procedures and the regulatory framework showed that the scope of the centralised procedure should be expanded, the EMA's scientific role should be reinforced and more Union coordination was required to resolve disagreements on nationally authorised medicines and to have more efficient market surveillance. There was a need to improve the mutual recognition system, increase harmonisation and facilitate the market entry of generic medicines and biosimilars.

As a consequence, the 2004 revision built on the strengths of the established system with **four main objectives**: i) ensure quality, safety and efficacy of medicines; ii) enable access to medicines; iii) ensure the competitive functioning of the EU internal market; and iv) ensure attractiveness in the global context.

Specific objectives aimed to ensure accommodation of innovation; reduction of administrative burden and improvement of adaptability of the regulatory environment; reduction of disparities across Member States and of duplication of effort; and facilitation of free movement of medicines.

To take advantage of the scientific and technological developments and to accommodate **innovation** the intervention changed and expanded EMA's scientific committees to ensure relevant expertise. It mandated EMA to provide scientific advice to marketing authorisation applicants. A new pathway for biosimilar medicines was introduced. It also provided for more effective coordination among Member States' regulatory authorities.

The intervention took measures to **facilitate faster authorisation and access to medicines** for medicines of major interest for public health and therapeutic innovation and for unmet medical needs and through introduction of accelerated assessment of the application for marketing authorisation (reduction from 210 to 150 days) and conditional marketing authorisation[25], which allows earlier authorisation on the basis of less comprehensive clinical data than normally required, where the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required.

Another strand of actions aimed to improve access by making the framework more friendly to generic medicines through the introduction of the decentralised procedure, the optimisation of the mutual recognition procedure and the reduction of the frequency of the renewal of marketing authorisation. The intervention introduced the so-called Bolar provision that allowed companies to start testing generic or biosimilars in advance of patent expiry of the reference medicine. The Bolar provision was expected to speed up market launch of generics as soon as the regulatory or intellectual property (IP) protection lapsed

[23] COM(2003) 383 final and Danzon, 1997.
[24] Study on the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use (January, 2020), available at mphu-map-eyrep_en_0.pdf (europa.eu).
[25] CMA defined in the Glossary.

(Day 1 launch). Other measures aimed to reduce the costs for generic medicines. These measures were expected to reduce market barriers, ensuring the **competitive functioning of the single market**.

Measures to accommodate innovation aimed to ensure **attractiveness of the EU system in the global context** together with measures to reduce disparities across Member States. They included an expansion of the centralised procedure to more innovative medicines and a single application to EMA for an EU wide marketing authorisation by the Commission.

An overview of the relationship between objectives, actions, results and impacts of the intervention is set out in Appendix A. As the impact assessment accompanying the legal proposals of the 2004 revision did not include an intervention logic, this document uses an intervention logic that was created retrospectively for the purposes of this evaluation.

Regarding the broader policy context, the United Nation's Sustainable Development Goals (SDGs)[26] take a holistic approach to achieve better and more sustainable future for all. Although the 2004 revision precedes the SDGs, its objectives are aligned:

- **SDG 3** "*good health and well-being*" and especially **target 3.8**, which aims among others to ensure *"access to safe, effective, quality and affordable essential medicines and vaccines for all";*
- **SDG 9** "*industry innovation and infrastructure*" and especially **targets 9.1** and **9.5,** which focus on the development of "*quality, reliable, sustainable and resilient infrastructure […] to support economic development and human well-being, with a focus on affordable and equitable access for all […]*" and on the need to "*enhance scientific research, upgrade the technological capabilities of industrial sectors in all countries […] to encourage innovation and substantially to increase the number of research and development workers*"

2.2 Points of comparison

The main point of comparison is the situation before the 2004 revision. A specific programme to monitor the legislation impacts was not established, though the authorisation procedures were assessed every 10 years[27]. Key performance indicators were not identified, but the revision was expected to provide more authorisations of innovative medicines and faster access to these medicines in the EU, facilitate the market entry of generic medicines and biosimilars as well as strengthen innovation and competition within the pharmaceutical industry to ultimately promote growth and enhance employment opportunities in the sector.

Comparisons are made with third countries in relation to: competitiveness/ attractiveness of EU regulatory system, innovation, access, affordability and antimicrobial resistance both for trends over the evaluation period and for the current situation. The main countries included in this comparison are Japan, Switzerland and US, though certain comparisons also include Australia, Canada, China and Korea.

3 HOW HAS THE SITUATION EVOLVED OVER THE EVALUATION PERIOD?

3.1 Implementation of the legislation

Even though several Member States were delayed to implement the changes to Directive 2001/83/EC in their national legislation, this had not substantial impact on the actual use of

[26] The 17 Sustainable Development GOALS, United Nations https://sdgs.un.org/goals.
[27] COM(2021) 497 final and Evaluation of the European Medicines Agency – Final report (January 2010).

the new measures. Some differences have been noted though across Member States in the implementation of parts of the legislation. One examlpe is the implementation of the **'Bolar'[28] provision**, a patent derogation to facilitate filing of generic applications. While transposed by all Member States the text adopted in each country allows different interpretations[29]. Implementation ranges from a derogation that is limited to 'experimental' purposes only with no commercialisation activity (like manufacturing) allowed in preparation for market launch (Spain), to the possibility for generic manufacturers to prepare production and regulatory procedures (Netherlands).

Another example is the **Hospital Exemption (HE)** which was introduced by the ATMP regulation and allows for the use of an ATMP without a marketing authorisation, when prepared in a hospital setting on a non-routine basis for an individual patient under the exclusive professional responsibility of a medical practitioner[30]. The HE has been implemented differently across Member States. A recent study covering seven European countries, showed great variations in how quality, safety and efficacy standards are implemented and controlled (i.e. there is substantial variability in the interpretations of HE terminology and the requirements imposed by national competent authorities (NCAs) for its use)[31]. This evidence draws concerns around its potential impact on public health and risks to patient safety.

Furthermore, differences in GMO risk classifications and data requirements (content and format)[32] across the EU. Indeed, assessments of medicines containing or consisting of **genetically-modified organisms (GMOs)** are complex and vary across the Member States (e.g. assessment of their environmental safety). On occasion, it leads to delays in clinical trials and authorisation of GMO-containing medicinal products, making the EU a less attractive region for clinical development and, ultimately, delaying patient access.

In addition, the implementation of provisions related to medicine **shortages**, such as the notification requirements and obligations to ensure appropriate and continued supply, varies significantly across Member States[33]. For instance, whilst some countries require notification of any medicine shortage, regardless of the expected duration, others only require notification if the shortage is expected to last longer than three weeks[34]. As regards obligations on continued suppy, these can vary from stock keeping obligations, to mandatory reporting on stock levels and export restrictions[35].

Within the evaluation period, the **EU Courts** (the Court of Justice and the General Court) provided **guidance on the interpretation** of a number of provisions. This concerns *inter*

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[28] The 'Bolar' provision allows certain experiments to be conducted on a patented pharmaceutical during the lifetime of the patent, to enable generic manufacturers to demonstrate bioequivalence prior to the expiry of a patent.

[29] CMS Cameron McKenna, & Andersen Consulting. (2000). Evaluation of the operation of Community procedures for the authorisation of medicinal products.

[30] Article 28(2) of Regulation (EC) No 1394/2007.

[31] Hills, A., Awigena-Cook, J., Genenz, K., Ostertag, M., Butler, S., Eggimann, A. V., & Hubert, A. (2020). An assessment of the hospital exemption landscape across European Member States: regulatory frameworks, use and impact. Cytotherapy, 22(12), 772-779.e1. https://doi.org/10.1016/j.jcyt.2020.08.011.

[32] Beattie, 2021; Lambot et al., 2021

[33] de Jongh et al., 2021

[34] European Commission, Directorate-General for Health and Food Safety, Jongh, T., Becker, D., Boulestreau, M., et al., Future-proofing pharmaceutical legislation : study on medicine shortages : final report (revised), Publications Office of the European Union, 2021, https://data.europa.eu/doi/10.2875/211485

[35] See Footnote 35

alia definitions (e.g. medicinal product by function[36], pharmacological action[37], reference medical product[38]), the scope of the legislation including exceptions (e.g. pharmacy preparations[39], blood products[40] and industrial process[41]), the interaction of off-label use and authorised use[42], the global marketing authorisation concept[43], parallel trade[44], advertising provisions[45], and the marketing authorisation requirements (e.g. on summary on product characteristics[46], burden of proof[47], precautionary principle for the suspension or restriction of the marketing authorisation[48], involvement of experts[49], mutual recognition procedure[50], centralised procedure[51], conditions for taking regulatory actions[52]). While the case law developed provided authoritative interpretation of those provisions of pharmaceutical legislation, it also points to the need for additional clarity, e.g. the provisions on the relation between the scope of Directive 2001/83/EC and the exemptions[53].

3.2 A regulatory framework to support innovation and access to medicines

The Commission has worked to balance competition and affordable access to medicines[54] and supported efforts to improve cooperation and coordination between Member States in

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[36] See e.g. judgment of 15 January 2009, *Hecht-Pharma GmbH v Staatliches Gewerbeaufsichtsamt Lüneburg*, C-140/07, EU:C:2009:5, para. 37 and 39.

[37] See e.g. judgment of 6 September 2012, *Chemische Fabrik Kreussler & Co. GmbH v Sunstar Deutschland GmbH*, C-308/11, EU:C:2012:548, para. 29 and 36.

[38] See e.g. judgment of 18 June 2009, *Generics (UK) Ltd, Regina v Licensing Authority (acting via the Medicines and Healthcare products Regulatory Agency*, C-527/07, EU:C:2009:379, para. 24.

[39] See e.g. judgment of 16 July 2015, *Abcur AB v Apoteket Farmaci AB and Apoteket AB.* joined Cases C-544/13 and C-545/13, EU:C:2015:481, para. 60, 61, 64, 67 and 70.

[40] See e.g. judgment of the Court (First Chamber), 13 March 2014, *Octapharma France v Agence nationale de sécurité du médicament et des produits de santé (ANSM), Ministère des affaires sociales et de la santé*, C-512/12, EU:C:2014:149, para. 40.

[41] See e.g. judgment of the Court (First Chamber), 13 March 2014, *Octapharma France v Agence nationale de sécurité du médicament et des produits de santé (ANSM), Ministère des affaires sociales et de la santé*, C-512/12, EU:C:2014:149, para. 46 or judgment of 16 July 2015, *Abcur AB v Apoteket Farmaci AB and Apoteket AB.* joined Cases C-544/13 and C-545/13, EU:C:2015:481, para. 71.

[42] See e.g. judgment of the Court (Grand Chamber) of 23 January 2018, *.F. Hoffmann-La Roche AG, La Roche SpA, Novartis AG and Novartis Farma SpA v Autorità Garante della Concorrenza e del Mercato,* C-179/16, EU:C:2018:25, para. 59.

[43] See e.g. the judgment of 28 June 2017, *Novartis Europharm Ltd v European Commission*, Joined Cases C-629/15 P and C-630/15 P, EU:C:2017:498, para. 65, 69, 71 and 72.

[44] See e.g. the judgment of 6 December 2012, *AstraZeneca AB and AstraZeneca plc v European Commission*, :EU:C:2012:770, para. 130.

[45] See e.g. judgment of 5 May 2011, *Novo Nordisk AS v Ravimiamet*, C-249/09, EU:C:2011:272, para. 51.

[46] See e.g. judgment of 14 February 2019, *Staat der Nederlande v Warner-Lambert Company LLC, C-423/17,* EU:C:2019:125, para. 47.

[47] See e.g. judgment of 3 September 2020, *BASF AS v European Commission* T-472/19, para. 49.

[48] See e.g. judgment of 19 September 2019, *GE Healthcare A/S v European Commission*, T-783/17, EU:T:2019:624, para. 48.

[49] See e.g. judgement of 28 October *2020*, *Pharma Mar, SA v European Commission*, T-594/18, EU:T:2020:512, para. 77 to 85.

[50] See e.g. judgment of 16 October 2008, *Synthon*, C-452/06, EU:C:2008:565, para. 29.

[51] See e.g. judgment of 14 February 2019, *Staat der Nederlanden v Warner-Lambert Company LLC* C-423/17, para. 42.

[52] See e.g. judgement of 14 March 2018, *Proceedings brought by Astellas Pharma GmbH*, C-557/16, EU:C:2018:181, para. 39.

[53] See e.g. judgment of the Court (First Chamber), 13 March 2014, *Octapharma France v Agence nationale de sécurité du médicament et des produits de santé (ANSM), Ministère des affaires sociales et de la santé*, C-512/12, EU:C:2014:149, para. 46 or judgment of 16 July 2015, *Abcur AB v Apoteket Farmaci AB and Apoteket AB.* joined Cases C-544/13 and C-545/13, EU:C:2015:481, para. 71.

[54] Vancell, 2012

areas such as procurement[55]. The HTA regulation contributes to improving the availability for EU patients of innovative health technologies through joint clinical assessments, joint scientific consultations and voluntary cooperation[56].

The 2004 revision was underpinned by measures to facilitate faster authorisation and access to medicines of major public health interest, therapeutic innovation and targeting unmet medical needs, through the introduction of the accelerated assessment procedure and the conditional marketing authorisation procedure (see Section 2.1).The role of the EMA was reinforced, including through its central coordinating role in the European medicines regulatory network and the set up of the SME's office[57]. The office provides advice and assistance to SMEs wishing to bring innovation to the market[58]. Financial incentives (full or partial fee exemptions for pre- and post-authorisation procedures) were also created for SMEs[59].

Furthermore, the mandatory scope of the centralised procedure for authorisation has been gradually extended to new active substances in a number of conditions, including cancer, diabetes, neurodegenerative, viral and autoimmune diseases; medicines derived from biotechnology processes, advanced-therapy medicinal products and orphan medicines. New active substances outside the mandatory scope can use the centralised procedure; as well as those that represent major scientific and technical innovation. As a result, the great majority of new, innovative medicines go through the centralised procedure. Only 3 new active substances were approved via national procedures from 2016 to 2020. Total central EU wide authorisations have more than doubled from a baseline of 30-40 products per year until 2004 to over 80 products by 2020, with new active substances[60] making up about half of all central authorisations[61] (Figure 1).

[55] de Jongh et al., 2021

[56] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU, PE/80/2021/INIT, OJ L 458, 22.12.2021, p. 1.

[57] Set up by Commission Regulation (EC) No 2049/2005 of 15 December 2005 laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises, OJ L 329, 16.12.2005, p. 4, OJ L 321M , 21.11.2006, p. 371.

[58] Support to SMEs increased from 366 requests for scientific advice to the EMA in 2013 to 436 in 2017. In that period, SMEs consistently accounted for around 30% of all requests at EMA level. Source: COM(2021) 497 final – Report from the Commission to the European Parliament and the Council on the experience acquired with the procedures for authorising and supervising medicinal products for human use, in accordance with the requirements set out in the EU legislation on medicinal products for human use.

[59] Financial advantages of SME status https://www.ema.europa.eu/en/human-regulatory/overview/support smes/financial-advantages-sme-status.

[60] New active substances are an indication of genuine innovation, versus authorisation of existing molecules for new indications, or combinations of molecules.

[61] SEC(2006)832 In the first five years of REG (EC) No 141/2000, 22 orphan medicines were authorised for the treatment of 20 different life-threatening or chronically debilitating rare diseases. SWD(2020) 163 final By 2017, 142 unique orphan medicines had received an EU marketing authorisation for 107 orphan indications. In a best case scenario, they were estimated to address the needs of 6.3 million EU patients (out of 35 million people suffering from rare diseases in the EU).

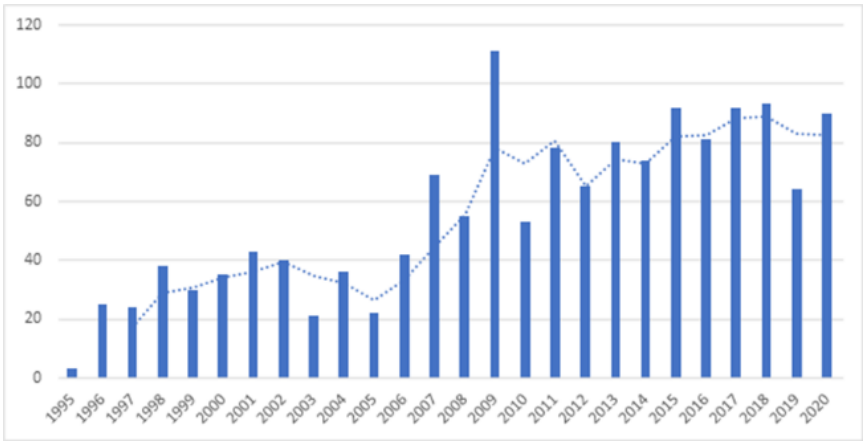

Figure 1: Total number of centrally authorised medicinal products in the EU (yearly, 1995-2020)
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

When comparing central authorisations of new active substances in the EU with equivalent numbers in the US (Figure 2), between 2006-2016 annual authorisations in the two jurisdictions have a smaller gap. However, a new gap opened up in recent years as US FDA authorises more new molecular entities, compared to the EU. Indeed, the majority of new active substances were authorised first by the US FDA over the entire period 2001-2020 (53% to 75%), however 55% of the new active substances were authorised in the EU within 1 year from US FDA approval over 2016-2020.

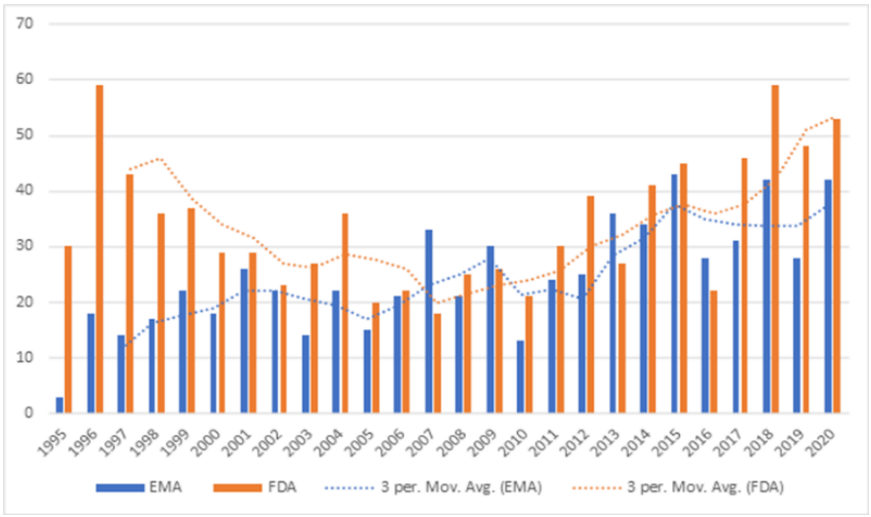

Figure 2: Total number of new active substances/new molecularentities authorised by EMA and FDA
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

By absolute numbers the vast majority of product approvals remains at the national level through MRP/DCP procedures (usually over 1000 products per year). Since the introduction of DCP in 2005, the number of products seeking authorisation through the DCP has shown a marked increase with a parallel reduction in the MRP (Figure 3). The majority of MRP/DCP procedures concern generic medicines: 799 procedures in 2020 related to generics or similar applications.

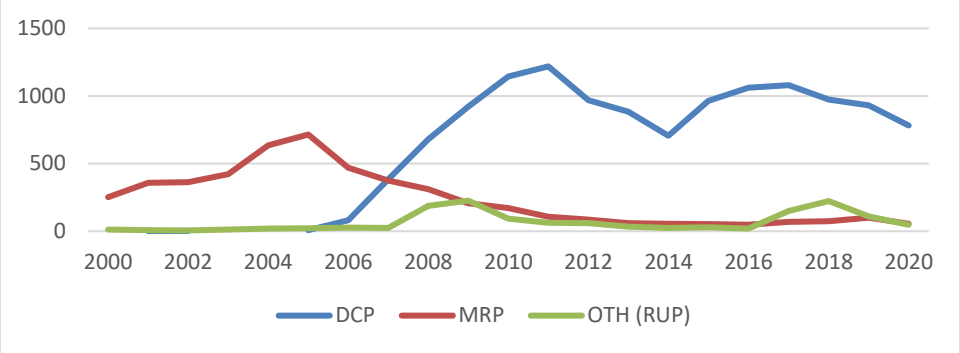

Figure 3: Trend in the number of products seeking authorisation through MRP, DCP and other Repeat Use Procedures (*RUP*) Source: Mutual Recognition Index (MRI) data.

3.3 Intellectual property and regulatory protection of pharmaceuticals in the EU

To **incentivise innovation, research and development** of medicines and to allow investment to be recouped, innovative medicines and certain developments such as new indications are protected through *various* forms of intellectual property (IP) rights (patents or supplementary protection certificate) and regulatory protection periods (data protection, market protection as well as market exclusivity for medicines for rare diseases). The same product can benefit from several protection mechanisms in parallel.

Patents give their owner the right to prevent others from making, using or selling the invention without permission. They may be granted for the active substance of a medicine, a production process or use of the medicine. Patent is the basic incentive to pursue activities taking an innovative concept to industrial application by excluding others from exploiting the invention for 20 years from filing date. Secondary patents are usually filed for improved variants of the basic product, new therapeutic indications, or new combinations.

The actual marketing of medicines can often take place late in the patent protection period, due to the lengthy testing and clinical trials these products require prior to authorisation and the duration of authorisation procedure. Therefore, the EU introduced supplementary protection certificates in 1992 to offset part of the loss of patent protection time, by extending the patent expiry by 5 years. The combined IP protection period from marketing authorisation is limited to a maximum of 15 years.

Data and market protection are granted to a specific medicine at the moment of authorisation and protect the medicine against competition from generic or biosimilar medicines. Data and market protection are regulated in the general pharmaceutical legislation, while additional incentives and rewards for orphan and paediatric medicines follow from the specialised legislation.

Regulatory protection periods are linked to the proprietary data on the safety and efficacy of the product generated for the purpose of marketing authorisation. This protection period was standardised at 8 years of data protection, 10 years of market protection and one additional year of market protection for a new indication with significant clinical benefit (8+2+1) in the revised pharmaceutical legislation. Previously there had been variation of the period between Member States. The new system applied from 30 October 2005 onwards. Figure 4 presents a schematic overview of the interplay among patent, SPC and regulatory protection.

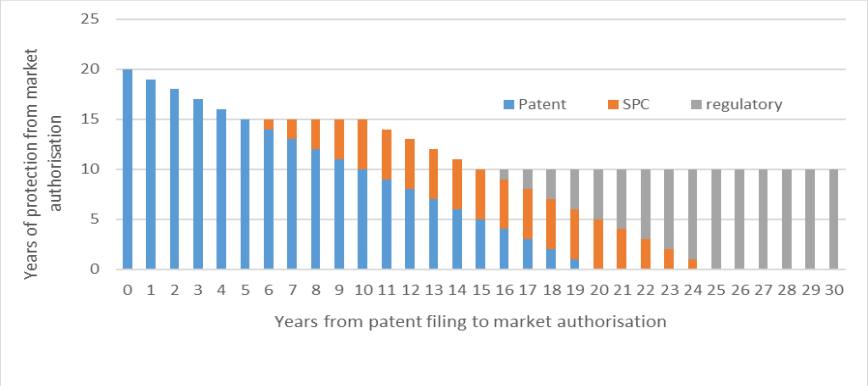

Figure 4: Intellectual property and regulatory protection periods in the EU
Source: DG SANTE, European Commission

Further to the data and market protection periods, an additional year of market protection in case a new therapeutic indication that brings significant clinical benefit; 10-year of market exclusivity for orphan medicinal products, protecting from competition from medicines with the same therapeutic indication; and an extension of 6 months of SPCs to reward paediatric investigations of medicines, and if the investigation concerns an orphan medicine, the orphan market exclusivity may be extended to 12 years.

Due to the multiple possible protections it is useful to focus on the expiry date of the last measure in place that protects the innovator medicine from generic competition. This may be SPC, patent expiry or the regulatory protection expiry, and in some occasions the orphan market exclusivity. A sample of 200 products in France, Germany, Italy and Spain with protection expiry between 2016-2024 shows that IP rights are the last to expire for 60% of the products in the basket, while regulatory protection is the 'last line of defence' for one third of the products (Figure 5). Orphan market exclusivity accounts for 6% of the products. In terms of total sales revenue, SPC protected medicines account for more than 70% of all revenues, this number is 20-23% for those with regulatory protection.

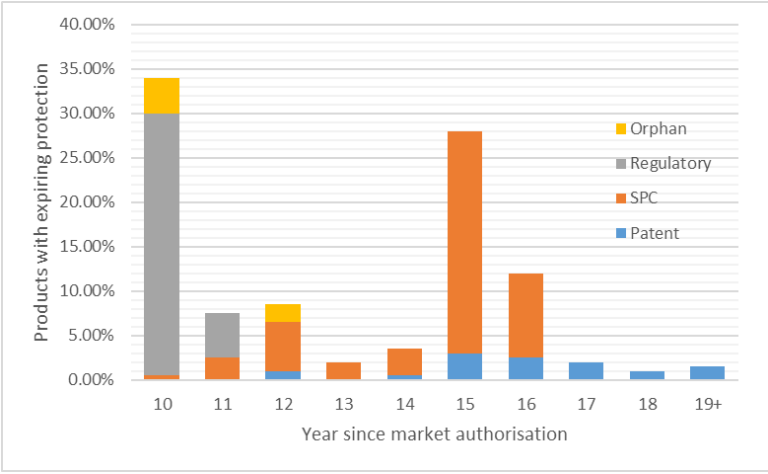

Figure 5: Ratio of medicines by the length of last layer of protection and type of protection
Source: DG SANTE, European Commission, based on IQVIA data

Similar results obtained in a recent study[62] found that 32-40% of products are protected by market protection and showed that pharmaceutical incentives and rewards in the EU are among the most attractive when compared to Canada, China, India, Japan and the United States with regard to the basic regulatory protection periods (Table 1).

[62] Copenhagen Economics, 2018

Country	Protection	Duration
Australia	New Chemical Entity + Market Protection	5 years
Canada	New Chemical Entity+ Market Protection	6+2 years
EU	New Chemical Entity+ Market Protection	8+2+1 years
Switzerland	New Chemical Entity	10 years
USA	New Chemical Entity (small molecule)	5 years
USA	Biosimilar Application Approval Exclusivity (biologic)	4+8 years
Israel	Market Protection	6 or 6.5 years
China	New Chemical Entity	6 years
Korea	Post-Marketing Surveillance	Up to 6 years
Japan	New Chemical Entity	8 years

Table 1: Basic regulatory protection periods for pharmaceuticals globally

3.4 Global position of the EU pharmaceutical industry

In the last 20 years, the global market for medicines has rapidly grown. Between 2001 and 2020 global revenues tripled, reaching US$1.27 trillion (€1.2 trillion) in 2020 (Figure 6). The US is the largest market for pharmaceutical products, accounting for about 47% of the global market in 2021, followed by the EU, the second largest market, accounting for 17%. Revenue generated by pharmaceutical companies in the EU has increased over time and was approximately €200 billion in 2020[63].

Increasing revenues and high profitability attract investment into development of medicines. In 2020, the total global spending on pharmaceutical R&D was US$198 billion (€188 billion)[64]. The total number of products in active development globally in 2021 exceeds 6,000, up 68% over the 2016 level[65]. Rich pipelines also translate into more medicine approvals and market launches – 84 new active substances were launched globally in 2021, doubling the number from five years before. 61% of these new launches were first-in-class[66].

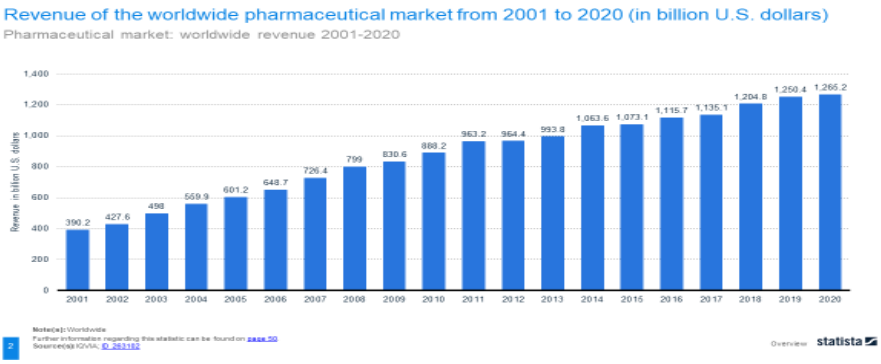

Figure 6 – Revenue of the worldwide pharmaceutical market from 2001 to 2020 (in billion US dollars)
Source: Statistica, 2021

[63] IQVIA data
[64] Statistica, 2021
[65] IQVIA, 2022
[66] Idem. I.e., medicines that use a new and unique mechanism of action for treating a medical condition.

The intensively growing global market has provided the opportunity for the EU's pharmaceutical industry to evolve and capture a significant share of the increase. The EU's total R&D expenditure doubled from around €20bn in 2000 to more than €40bn in 2019[67]. In the US, R&D investment remained almost stationary from 2003 until 2011 (close to €40 billion) and experienced significant growth in the period between 2014 and 2019 (reaching €74 billion). The EU maintained a leading position for new active substances from 1982 to 2003[68], after which time US caught up and is in the lead. Indeed, more recently, 83% of the new medicines approved by the US FDA between 2017 and 2018 originated in the US.

Among other competitors, China is a notable one. R&D investment in the health sector is 23% of the EU's. However, it has been increasing sharply over the last couple of years and is set to level up with the Western peers in the foreseeable future. China's growth in R&D investment is most visible in small biotechs, or emerging biopharma firms[69].

While US firms display an advantage in developing innovative medicines, the EU has become a global champion in manufacturing high-value medicinal products. Looking at the import/export levels and trends of medicines (vaccines, finished products and active pharmaceutical ingredients (APIs)) between 2000-2020, EU exports have multiplied by five and with €215bn worth of exports (Figure 7) Mediciness make up 10% of all exported EU goods in value. Imports have increased too but at a lower rate, resulting in a massive €122bn trade surplus in this product category.

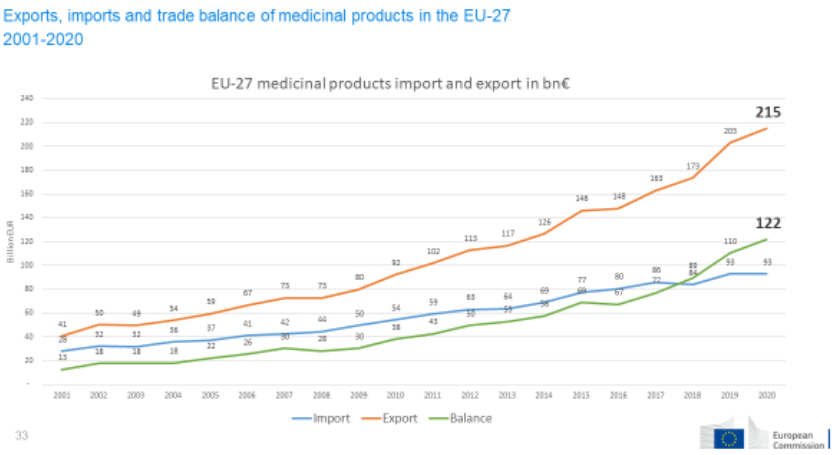

Figure 7: Exports, imports and trade balance of medicinal products n the EU-27. Source: DG SANTE, European Commission, based on Eurostat trade data

Despite the fact that the EU imports large quantities of cheap generic medicines, vaccines and APIs from outside the EU (e.g., from India and China), exports are greater than the imports except for APIs which are almost equal in value[70].

Looking at the profitability of the sector, according to public data, aggregated annual profits of pharmaceutical companies in the USA and Europe grew at annual growth rates of 6.6% and 3.1%, respectively during the 2003-2020 period[71]. Nevertheless, the lower growth rates in Europe are influenced by a marked reduction in profits during 2016-2020. This period of decline in Europe was not observed in Switzerland or Japan, but Canadian companies reported negative profits during the same period.

[67] Analytical report , indicator RI 8, Annex 10
[68] Grabowski and Wang 2006
[69] Ellis, Shannon. "Biotech booms in China." Nature 553.7688 (2018): S19-S19.
[70] Erixon & Guinea, 2020
[71] Analytical report, indicator IEC-11:Profits generated by pharma companies, annex 10.

4 EVALUATION FINDINGS

4.1 To what extent was the intervention successful and why?

The 2004 revision of the general pharmaceutical framework achieved all four high level objectives to a certain extent. The intervention provided an appropriate regulatory framework for ensuring access to high quality, safe and efficacious medicines to all Member States. It has also enabled competition within the EU internal market and maintained regulatory attractiveness in the global context. Yet, the extent to which each objective was achieved varied, notably ensuring equitable access to medicines for patients in all EU Member States has had the least success. Thus, there are several areas where improvements can be made to build on the achievements of the 2004 revision.

4.1.1 Effectiveness and coherence

This section looks into how effective the general pharmaceutical legislation has been in achieving the main objectives of the 2004 revision, its internal coherence and level of aligment with other legal frameworks.

The evaluation and the feedback of the consultation activities have not revealed specific issues of internal coherence. On the contrary, several (public authorities, industry and healthcare professionals) mentioned explicitly the good internal coherence.

There are also several in-built mechanisms to ensure an adequate coherence between the general pharmaceutical legislation and the specialised pharmaceutical frameworks[72]. While the objectives of the general pharmaceutical legislation are aligned with other specialised pharmaceutical frameworks, there is a varying degree of alignment between the objectives of general pharmaceutical and other EU health and non-health legislation, as well as other EU policies. Indeed, in the past 18 years new challenges have emerged. The Commission President's mission letter[73] to the Commissioner for Health and Food Safety of 2019 spells out supply of medicines, affordability, innovation and a world leading European pharmaceutical industry as key policy objectives. Below, the legislation's performance is measured against these objectives as well.

4.1.1.1 Ensure quality, safety and efficacy of medicinal products

A recent study assessing the extent to which the current marketing-authorisation system for medicines met its objectives in the period 2010-2017, found that the current system meets the objectives laid down in the legislation. In particular, it gurantees a high level of health protection in the EU. However, rapid scientific developments continue to challenge the system, and the number and complexity of procedures increased substantially[74].

There is consensus across all stakeholders that the **legislation has provided a good framework for safeguarding public health**, and no doubt it has been very successful in addressing this overarching objective. The majority opinion in the targeted survey indicates

[72] (e.g., Article 2, 7, 27, 47 of Regulation (EC) No 1901/2006; Article 10a (1) of Regulation (EC) No 141/2000; Article 8(3) and 3(7) of Directive 2001/83/EC); without prejudice clauses (e.g. Article 2 or Regulation (EC) 1394/2007) and derogations (e.g. Article 9 of Regulation (EC) No 1901/2006; Article 10 to 13 of Regulation (EC) No 1394/2007).

[73] https://ec.europa.eu/commission/commissioners/sites/default/files/commissioner_mission_letters/mission-letter-stella-kyriakides_en.pdf.

[74] COM(2021) 497 final.

that the legislation has been most effective in areas that fall under the objective of ensuring quality, safety and efficacy of medicinal products (see Appendix B[75]).

A few individual academics and NCAs[76] in the public consultation and in interviews highlighted challenges that follow from an early efficacy assessment for other decision-makers (e.g. oncology medicines). A study[77] reported that of the 48 cancer medicines recommended for approval based on a positive benefit/risk assessment by the EMA between 2009 and 2013, 37 out of 68 indications entered the market without evidence of benefit on survival or quality of life. A minimum of 3.3 years after market entry, there was still no conclusive evidence on extended or improved life according to health technology assessment methodologies, and when survival gains were observed over existing treatment options or placebo, they were often marginal. A 2021 study shows that launch prices and post-launch price changes of patented anticancer medicines do not correlate with their clinical benefit[78]. It becomes difficult for payers to justify spending large amounts of their budgets on medicines granted accelerated approval, due to the context of the disease and the unmet need, but which cannot show proven benefit on patient-centred outcomes (e.g. quality of life and survival) in the context of health technology assessment (HTA). There is concern that innovative medicines may not always provide patient benefits commensurate with their costs. It needs to be noted that the EMA's evaluation of medicines is based on their benefits and risks, whilst HTA determines relative effectiveness and the added value of a health technology in comparison with other health technologies, for the purpose of informing national budgetary decisions in health. If the totality of the evidence shows convincingly that a medicine's benefits outweigh its risks, despite possible weaknesses in clinical trials design, medicine regulators can take decisions to bring new medicines to patients in a timely fashion. EMA communicates about its scientific assessment, including any uncertainties identified and the measures taken to minimise any risks in its assessment reports.

The centralised procedure (CP) is one of the **major enablers for providing a good framework to safeguard public health** according to interviewees across all stakeholder groups. It has allowed effective and robust authorisation of medicines at EU level. Alongside the CP, the decentralised procedure/mutual recognition procedure (DCP/MRP), the pre-authorisation scientific advice and other services provided by EMA, accelerated assessment and streamlining of processes were acknowledged as key achievements. These procedures have improved quality standards and have ensured safe and efficacious medicines for the EU population.

There has been a clear increase in the use of the centralised procedure over time, with the annual number of authorisations more than doubling on average (Figure 1). However, this may is also be a result of the expansion of the scope of the centralised procedure.

Civil society and health services actors highlighted in interviews that EMA's engagement, involvement and consultation with different stakeholders (including patients) and the scientific advice improved significantly. This has benefited patient safety. Several stakeholders in interviews[79] considered that the 2004 changes led to better quality and safety of product manufacturing. This has been exemplified by the coordinated regulatory action at

[75] Appendix B: Targeted survey overview – areas where the legislation has been effective

[76] Views of two academics (out of forty-two that replied to the open public consultation) and four public authorities (out of forty-eight interviewed).

[77] Davis et al., 2017

[78] Vokinger et al., 2021

[79] All healthcare professionals (total interviewed = 8), 46,6% of industry representatives (total interviewed = 60), 75% of public authorities (total interviewed = 48) and 21% of academics (total interviewed = 13).

EU level to reduce the risk of nitrosamine impurities in medicines, described in the short case study below.

Regulatory action on nitrosamine impurities

In 2018, regulators were alerted to high level of nitrosamine impurities, a probable human carcinogen, in blood pressure medicines called 'sartans' produced by one API manufacturer. The EC mandated the EMA to launch a review of all sartans to assess the impact on the impurities on the benefit-risk of these medicines. This was later extended to other categories of medicines. Based on the the review, EMA set a temporary limit for nitrosamine impurities in concerned medicines within a transition period of two years. Medicines that were found to contain unacceptable levels were subsequently suspended (European Medicines Agency, 2019).

In parallel, an EU-wide review in 2019 was launched to understand the presence of nitrosamines in all human medicines and to investigate the risks of presence of nitrosamines through manufacturing. The 2020 review[80] identified several root causes based on which several recommendations were made to reduce the risks of nitrosamine impurities in medicines. The 2021 implementation plan[81] outlined how the EU would work to implement the recommendations for all medicines authorised in the EU. Proposed steps range from providing guidance to reduce nitrosamines impurities to penalties for MAHs and other stakeholders if the quality of medicines is not ensured. However, some API manufacturers encountered challenges in complying with the new requirements, which could lead to medicines shortages. To mitigate the risk of shortages of critical medicines the EMA established a centralised benefit-risk assessment where higher limits might be accepted so that these medicines can continue to be available to patients.

Medicines quality and consistency can be indirectly measured by the outcome of inspections on good manufacturing practice (GMP). There has been a strong year-on-year growth in the numbers of GMP inspections in the five years following the implementation of the 2004 revisions (EudraGDMP database)[82]. This reflects the legislative decision to expand and harmonise the oversight of MAHs, manufacturing and supply chains as a means to ensure quality. These activities have been strengthened further over the following 15 years[83]. This extensive programme has resulted in a small number of non-compliance statements (i.e. identified quality problems) of 0.1-1% of inspections (1-24 non-compliance statements each year in the past 10 years)[84]. The number of GMP inspections and certificates issued by EEA authorities was running at around 2 500 a year during the pre-COVID times[85]. Due to the pandemic, the number of inspections – on-site in particular – reduced substantially. To mitigate the impact of disruptions on GMP inspections, the Commission, EMA and the NCAs put forward guidance to MAHs on regulatory expectations and flexibility during the COVID-19 pandemic[86].

The pharmacovigilance revision in 2010 and the creation of the Pharmacovigilance Risk Assessment Committee (PRAC) in 2012 provided the legal basis for improved central **monitoring of suspected side effects of medicinal products**, submitted in the

[80] European Medicines Agency, 2020a
[81] European Medicines Agency, 2020b
[82] The data derive from the EudraGDMP database, however, the EMA Annual Reports include a chapter on inspections and compliance that provides a more accessible analysis of activities over the current and two previous years. As a case in point, see page 59 of the 2007 Annual Report.
[83] European Medicines Agency, 2021b
[84] Data extracted from EudraGDMP database.
[85] See the results of an annual survey of inspections and audits.
[86] EC-HMA-EMA Questions and Answers on regulatory expectations for medicinal products for human use during the covid-19 pandemic (September 2021) https://ec.europa.eu/health/system/files/2021-09/guidance_regulatory_covid19_en_0.pdf.

EudraVigilance database[87] as individual case study reports (ICSR). This reporting allows identifying side effects early on and to act (e.g. by improving product information). The number of ICSRs being submitted and screened annually following the 2004 revision, has shown a growth rate[88]. Around 10% of the individual safety reports had in-depth review by the EMA for a possible adverse drug reaction (ADR), around 20% of these were assessed by PRAC, with half of those resulting in an update of the product information. These potential safety issues can have many causes, therefore the current statistics might not provide sufficient basis for measuring quality improvements directly attributable to the legislation.[89] Still, the above figures provide good indication that the surveillance system was successfully enhanced. Recent studies show the process is identifying more potential risks and enabling quicker and more decisive follow-up action[90].

There was difference of opinion between and within the different stakeholder types as regards pharmacovigilance. Some public authorities, civil society, healthcare professionals and industry were of the view that pharmacovigilance has substantially ensured the safety and quality of medicines; while several healthcare professionals, and industry stakeholders stated that the new pharmacovigilance requirements have considerably increased the resource burden with little added value, albeit without providing examples or data to substantiate their views.

The European medicines agencies regulatory network strategy to 2025[91] confirms there is a need for appropriate **regulatory pathways for alternative preventive and therapeutic approaches** such as bacteriophages and microbiome products which was echoed by interviewed academic stakeholders[92].

Stakeholders' concerns regarding **GMO requirements to medicines** are mirrored in the Commission's study on new genomic technologies[93]. As already mentioned in section 3.1, assessments of medicines containing or consisting of genetically-modified organisms (GMOs) are complex and vary across the EU (e.g. assessment of their environmental safety); this also came out in the public consultation from and in interviews with civil society organisations, industry and public authorities. On occasion, this can lead to delays in clinical trials and authorisation of GMO-containing medicines according to industry stakeholders. Only few industry stakeholders (33 respondents) expressed an opinion on coherence in this area, but more than 20% rated that the frameworks are not at all coherent[94].

During the COVID-19 pandemic, clinical trials with investigational medicines containing or consisting of GMOs intended to treat or prevent COVID-19 received a temporary

[87] EudraVigilance | European Medicines Agency (europa.eu).
[88] European Medicines Agency, 2020c. In 2020, 1.8 million ICSRs related to suspected adverse reactions occurring in the post-authorisation phase were collected and managed in EudraVigilance (1,821,211 – a 9% decrease compared to the previous year). reference: https://www.ema.europa.eu/en/documents/report/2020-annual-report-eudravigilance-european-parliament-council-commission_en.pdf.
[89] Better monitoring may mean revealing pre-existing issues to an extent and there can be many reasons why you have ADR which can include genuine scientific unknowns at the time of the original authorisation or time-limited manufacturing issues and even off-label uses.
[90] Potts et al., 2020.
[91] https://www.ema.europa.eu/en/documents/report/european-union-medicines-agencies-network-strategy-2025-protecting-public-health-time-rapid-change_en.pdf.
[92] Three academics out of the fourteen interviewed.
[93] European Commission, 2021.
[94] Technopolis Study, 2022b.

derogation[95] from EU legislation on GMOs to ensure that the conduct of clinical trials was not delayed due to the complexity of differing national procedures. This derogation is limited to the emergency generated by COVID-19.

As regards protection of public health, stakeholders in the targeted survey were not convinced that this objective was reached as concerns reducing the **environmental footprint of medicines**[96]. Across the different stakeholder consultations, civil society organisations, public authorities and academics in particular highlighted the need for strengthening environmental risk assessment (ERA) requirements and more generally the environmental sustainability aspects in the legislation. Some stakeholders suggested exploring a more explicit role for ERAs in benefit-risk analysis during the assessment process, or even in pharmacovigilance[97].

The ERA was introduced by the 2004 revision for all new marketing authorisation applications[98] and covers environmental risks on the use, storage and disposal of medicines. The largest source of medicines entering the environment is use, however residues of pharmaceutical products may enter the environment during their manufacture or disposal. The ERA has improved transparency around the environmental risks of specific products / APIs, facilitating environmental management. Nonetheless, risks arising from the synthesis, or manufacture of medicines, as well as risks related to antimicrobial resistance fall outside the current scope of the ERA.

Several EU legislative frameworks concern environmental protection and relate to pharmaceuticals in the environment. The evaluation of the **REACH Regulation**[99] showed that regulatory gap exist regarding the risks to the environment and human health (e.g. antimicrobial resistance) related to the manufacturing of active pharmaceutical ingredients (API) and formulation of medicines, due to the fact that medicinal products are exempted from several Titles of REACH and that the pharmaceutical legislation does not cover these risks.

The Water legislative framework, including the **Environmental Quality Standard Directive**[100], the **Groundwater Directive**[101] and the **Waste Water Treatment Directive**[102] aim to ensure the good chemical and ecological status of water bodies and not the

[95] Regulation (EU) 2020/1043 of the European Parliament and of the Council of 15 July 2020 on the conduct of clinical trials with and supply of medicinal products for human use containing or consisting of genetically modified organisms intended to treat or prevent coronavirus disease (COVID-19), OJ L 231, 17.7.2020, p. 12.
[96] See Appendix B: Areas where the current legislation has been effective (survey analysis).
[97] Technopolis, 2022a.
[98] The European Medicines Agency Guidelines on the Environmental Risk Assessment of Medicinal Products for Human Use came into effect in December 2006 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.pdf
[99] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC, OJ L 396, 30.12.2006, p.1.
[100] Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council, OJ L 348, 24.12.2008, p. 84.
[101] Directive 2006/118/EC of the European Parliament and of the Council of 12 December 2006 on the protection of groundwater against pollution and deterioration, OJ L 372, 27.12.2006, p. 19.
[102] Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment, OJ L 135, 30.5.1991, p. 40.

authorisation of chemical substances. Finally, the **Industrial Emission Directive**[103] (IED) does not require a substance specific environmental risk assessment and emissions from the pharmaceutical industry are only generally covered in the CWW (Common Waste Water and Waste Gas Treatment/Management Systems in the Chemical Sector) BAT Conclusions[104] and the WGC (Waste Gas Treatment/Management Systems in the Chemical Sector) BAT Conclusions (under development). Those do not contain emission levels for individual active substances used in medicinal products.

The Commission adopted recently proposals for the revision of the Environmental Quality Standards Directive, the Groundwater Directive[105] and the Urban Waste Water Treatment Directive[106]. These proposals include limits set for some individual pharmaceutical products raising environmental concerns, a limit set for total pharmaceuticals detected and quantified in groundwater and also an additional treatment step for waste water treatment plant that would reduce the release of pharmaceuticals in the treated water. The IED, also under revision, includes the obligation for each installation manufacturing pharmaceuticals in its scope, to implement an Environmental Management System, including a chemical inventory of the hazardous substances present in the installation and an assessment of these substances on human health and the environment. Nevertheless, there is no holistic and systematic approach to address individually the environmental concerns of each pharmaceutical product over its entire life-cycle.

The **European Union Strategic Approach to Pharmaceuticals in the Environment**[107] contains several actions concerning the general pharmaceutical legislation and its actors such as ways to improve the ERA of medicines, completion of assessment by the time of the authorisation with adequate risk management measures, possibility of reducing waste by optimising the package size of pharmaceuticals, and by safely extending expiry dates; facilitate the exchange of best practices among healthcare professionals on the environmentally safe disposal of medicines and clinical waste, and the collection of pharmaceutical residues as appropriate. Several of these aspects are covered in draft guidelines that detail the aspects to be covered by an environmental risk assessment[108] explain how a PBT[109] assessment must be carried out, set a list of precautionary and safety measures in case environmental risks cannot be excluded[110] and a proposed labelling aimed

[103] Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control), OJ L 334, 17.12.2010, p. 17.
[104] Commission Implementing Decision (EU) 2016/902 of 30 May 2016 establishing best available techniques (BAT) conclusions, under Directive 2010/75/EU of the European Parliament and of the Council, for common waste water and waste gas treatment/management systems in the chemical sector, OJ L 152, 9.6.2016, p. 23–42

[105] https://environment.ec.europa.eu/publications/proposal-amending-water-directives_en COM(2022) 540 final
[106] https://environment.ec.europa.eu/publications/proposal-revised-urban-wastewater-treatment-directive_en COM(2022) 541
[107] COM(2019) 128 final.
[108] Determination of physico-chemical properties, fate and ecotoxicity, trigger values for soil, groundwater and secondary poisoning, surface water, sediment, sewage treatment plant, groundwater, soil, secondary poisoning, antibotics, endocrine active substances.
[109] Persistent, bioaccumulative and toxic.
[110] Such as appropriate product storage and disposal, appropriate measure regarding the use of medicinal products, appropriate disposal of unused pharmaceuticals.

at minimising discharge of unused medicine into the environment. Despite these interlinkages the general pharmaceutical legislation is not fully coherent with EU frameworks and policies concerning environmental protection.

Challenges in definition and classification can potentially expose patients to unsafe and/or ineffective products. For example, Directive 2001/83/EC covers all 'medicinal products' that are "either prepared industrially or that are manufactured by a method involving an industrial process." This scope does not fully consider changes in the manufacturing of medicines, e.g. low-volume products, bedside-manufactured or single batch personalised medicines, that do not involve an industrial manufacturing process. This situation reduces legal certainty for developers. Concerns were expressed that these medicines may be excluded from the scope of the legislation with less regulatory oversight, thus jeopardising quality and safety of these medicines[111].

The 2019 evaluation[112] and 2022 impact assessment[113] of the EU legislations on **Blood, tissues and cells** (BTC) identified further issues in this respect. Most BTC based substances fall clearly into either the medicinal or BTC legal framework, however, in some cases, it is challenging to decide on classification and determine which legislation applies[114]. While such classification decisions are taken at Member States level, leading to national differences[115], the criteria that define the BTC/medicine borderline are set in Article 2(1) of both Directives (2004/23/EC on the one side and Directive 2001/83/EC on the other side). The BTC framework applies only on the donation, collection and testing of tissues and cells if another legal framework applies on manufactured TC products. Thus, it is important to understand when the EU general pharmaceutical framework applies.

Indeed, there are challenges around the differing interpretation and implementation of the legislation at the Member State level and other relevant legislation (e.g. GMO, ATMP, BTC). Definitions such as 'substantial manipulation', 'use for a different essential function' introduced under Regulation (EC) No 1394/2007, and the use the 'hospital exemption' varies across the Member States in terms of how quality, safety and efficacy standards are controlled. For example, a recent study on how hospital exemption implemented in seven European countries, showed great variations in how quality, safety and efficacy standards are implemented and controlled across the Member States for ATMPs which draws concern around potential impact on public health[116]. This inconsistency across Member States on the implementation of the hospital exemption was also identified in interviews [117]. Another example on the interaction beween specialised pharmaceutical frameworks and implementation at national level concerns **the Paediatric Regulation**. Under this regulation, the differing national rules on the conduct of trials with children may still delay the completion of a paediatric investigation plan (PIP)[118].

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[111] Technopolis, 2022b.
[112] SWD(2019) 375 final - Evaluation of the EU blood and tissues and cells legislation (europa.eu).
[113] SWD(2022) [No number yet] – Impact Assessment of the EU legislation on blood, tissues and cells.
[114] SWD(2019) 375 final.
[115] See annex XVI SWD(2019) 375: Inconsistencies between EU-legal frameworks; a notable exemption to MS driven classification is a classification recommendation provided by EMA's CAT committee for ATMPs.
[116] Hills et al., 2020.
[117] A pathway that empowers EU Member States to permit the provision of an ATMP without a marketing authorisation under certain circumstances. It applies only to custom-made ATMPs used in a hospital setting for an individual patient. Such products may only be produced at the request of a physician and should only be used within the Member State where they are produced.
[118] SWD(2020) 163 final.

Stakeholders have also identified the classification of products as **medical devices and in-vitro diagnostics**[119] as a challenge. For the so-called **combined products**, combining medicines and medical devices, the responsibility of the marketing authorisation holder for respectively the medicine and the medical device part, the responsibility for the overall benefit-risk assessment of a combination product and the procedures involved may not be set out clearly in the frameworks. National competent authorities (NCAs) highlighted in the workshop the need for more clarity on roles and responsibilities and for a more integrated approach in relation to scientific advice on medicines and medical devices[120].

Regarding safety, to note the link of the general pharmaceutical legislation with the **Food Additives Regulation**[121], though only for colours**.** Colours can be used in medicines if they are authorised in the said regulation, subject to the compliance with the purity criteria. Some specific measures have been taken in the field of medicines to allow the necessary time to the pharmaceutical companies to develop alternatives to some food colours also used in medicines, to avoid shortages and ensure safety, quality and efficacy of the alternatives. The recently adopted Regulation (EU) 2022/63 is an example, as it bans the use of titanium dioxide as a food additive, but provisionally allows it in medicinal products (a review clause of three years is forseen for the Commission to re-assess the situation)[122].

4.1.1.2 Ensure access to medicines

Access to medicines[123] is an area where the legislation is seen to have underperformed the most according to all stakeholder groups, based on the survey responses[124]. Access was examined from three distinct angles: evaluation and marketing authorisation of medicines; approval and reimbursement decisions by HTA bodies and payers; and medicine shortages. Of these aspects, the general pharmaceutical legislation is mainly responsible for the marketing authorisation procedure and, to a lesser extent shortages. Pricing and reimbursement of medicines is completely out of its remit.

Authorisation procedures, especially the centralised procedure, have allowed more new medicines to become available for the EU population (see Figure 1) – this was emphasised by industry and public authorities in interviews. The EU system foresees the possibility for accelerated assessment[125] for medicines of major interest for public health and therapeutic innovation. The number of accelerated assessments in absolute terms and as a proportion of all assessments for new active substances increased in the period 2013-2018, having a decreasing trend after 2016 (Figure 8).

[119] For the evaluation period, the Medical Device Directive has applied, but the incoherences seem to continue under the new MDR and IVDR frameworks.
[120] Pharmaceutical Strategy for Europe Workshops March to June 2021 – Summaries (December 2021) Pharmaceutical Strategy for Europe Workshops March to June 2021 (europa.eu).
[121] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives, OJ L 354, 31.12.2008, p. 16.
[122] Commission Regulation (EU) 2022/63 of 14 January 2022 amending Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the food additive titanium dioxide (E 171), C/2022/77, OJ L 11, 18.1.2022, p. 1.
[123] A medicine becomes accessible once it has been authorised, is being marketed, and, if relevant, can be reimbursed in a Member State.
[124] See Appendix B: Areas where the current legislation has been effective (survey analysis).
[125] Article 14(9) of Regulation (EC) No 726/2004.

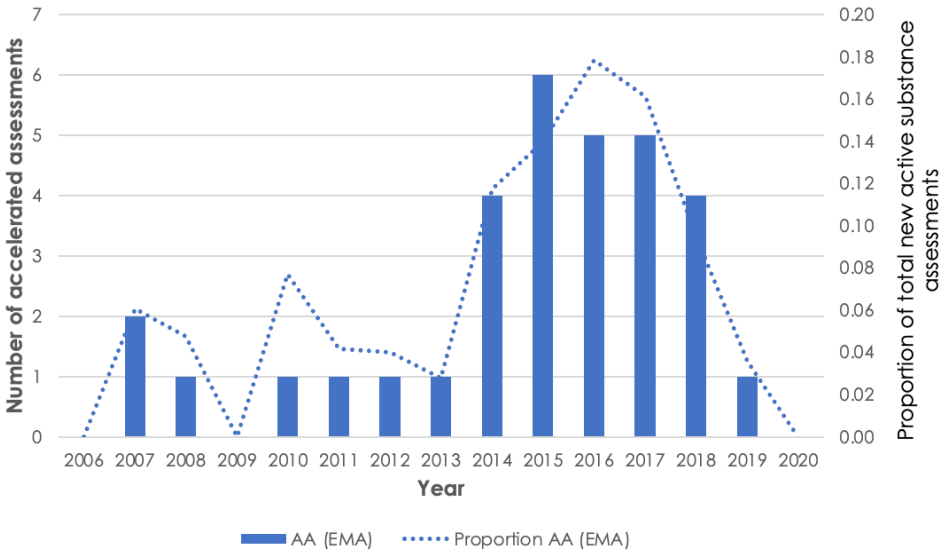


Figure 8: Number and proportion of accelerated assessments by EMA
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA

The 2004 revision aimed to increase access to innovative products. Based on the analysis of EMA's assessment times in days (yearly, 1995-2020), there has been an improvement inaverage assessment times between 2005 (380 days) and 2010 (270 days), which increased gradually over the next 10 years (340 days in 2020) (Figure 9). This suggests that the revisions improved timelines, for a period before other factors (e.g. resourcing, more complex dossiers) resulted in a reversal trend. Comparing with FDA's assessment times, EMA's average is shorter until 2015. After that, the situation reversed with the FDA taking 244 days on average compared with the EMA's 343.5 days. Whilst the difference is large, the indicators may not be fully comparable as the elements included in the assessment can vary[126]. The analysis also shows that, over time, average FDA assessment times have been more variable than the EMA's times.

Some industry stakeholders (eight of the sixty intereviwed) observed that accelerated approval pathways are not used as much as they are in the USA. According to the CIRS policy brief, 67% of new active pharmaceutical ingredients were approved through expedited approval procedures in the US, versus 14% in the EU[127].

[126] For example, the FDA time-data count from first application to approval even where initial applications may be refused and resubmitted several times, whereas the EMA counts time from the point of submission of the application to approval but only for the application that is ultimately approved.
[127] CIRS, 2021.

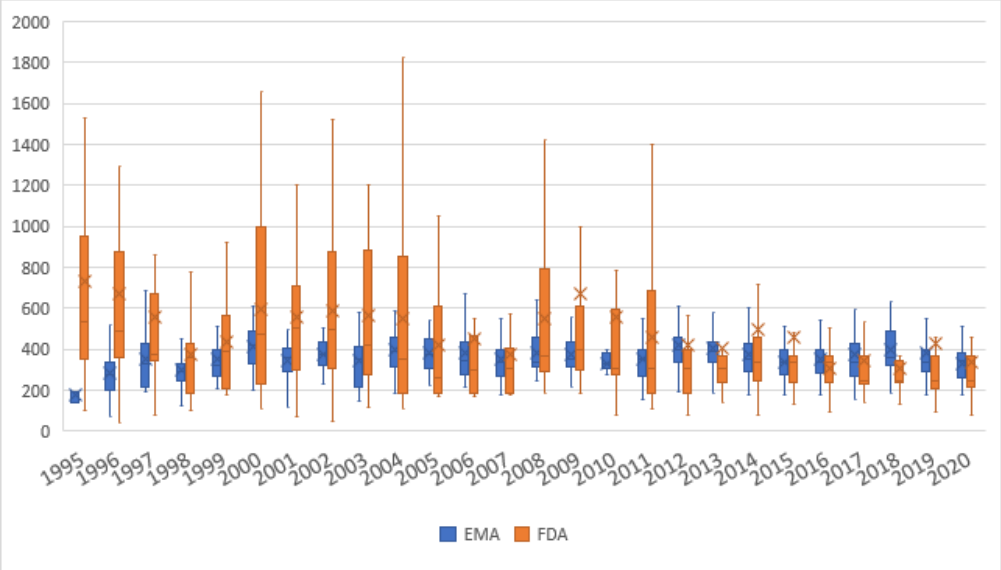


Figure 9: Total assessment times of new active substances/new molecular entities authorised by EMA and FDA in days (yearly, 1995-2020)
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA

On the basis of a a medicine's positive benefit-risk profile, the marketing authorisation – also in case of accelerated assessment or conditional marketing authorisation – ensures that medicines are safe, efficacious and of high quality.

The 2004 revision aimed to improve accessto centrally authorised medicines across the EU, even though the granting of a Union marketing authorisation does not oblige the marketing authorisation holder (MAH) to place that medicine on the market of all or most Member States. Contrary to the improvement in terms of authorised products the number of EEA countries in which a new chemical entity is launched has been steadily decreasing. Various studies have also shown that, even for products that have been approved through the centralised procedure, access remains uneven across the EU. The evaluation of the Orphan Regulation showed that, in the first three years after marketing authorisation, EU authorised orphan medicinal products (OMPs) reached, on average, fewer than six EU-12 Member States and that no medicine reached all Member States. A 2019 study in five European countries similarly found that in some countries less than a third of authorised OMPs were available to patients. Also, for other centrally authorised medicines, such as oncology medicines, substantial differences have been reported in availability and time to entry.

Crucially, however**, patient access to medicines is contingent on decisions post-authorisation**. Firstly, it requires a willingness by the MAH to place a product on a particular market, typically informed by expectations about a positive return on investment. Secondly, payers (health systems or insurers) need to agree to include the medicine into the package of reimbursed care.

This may depend on an assessment of the expected (relative) cost-effectiveness of the medicine by the public authorities and the outcome of price negotiations with the MAH. Such assessment procedures and outcomes may take months or even years[128] and strongly influence the time to launch.

The assessment of medicines' relative effectiveness and cost-effectiveness is outside the scope of the general pharmaceutical legislation. **HTA bodies and payers in Member**

[128] COM/2012/084 final.

States make decisions based on their national assessments of cost-effectiveness of a given medicine.

Whilst the legislation has led to improvements in the authorisation of medicines, the system has also become more complex over the years according to industry interviewees and delays in national pricing and reimbursement decisions were mentioned. According to healthcare payers in the public consultation and the interviews, the clinical data available in the marketing authorisation is often insufficient for HTA bodies for their assessment, in particular for medicines authorised with accelerated assessment or conditional marketing authorisation for faster access for patients in case of unmet medical need. While the general pharmaceutical legislation requires data for the assessment of the benefits and risks of a medicine, access to medicines may be delayed if the HTA bodies do not have relevant data for their assessment.

Medicines granted **conditional marketing authorisation** (CMA), thus on less compehensive clinical data, must fulfil post-marketing specific obligations for additional data. EMA's 10 year review of conditional marketing authorisations[129] concluded that 70% of the specific obligations were completed within the specified timelines. On average, a CMA is converted into a standard marketing authorisation within 4 years. A third of the requested data from clinical studies were more preliminary than phase III or uncontrolled single arm studies, or both. Two thirds were for open label studies. Out of the 77 studies requested, only nine — all oncology studies, not necessarily randomised — reported overall survival as the primary outcome, and not one reported quality of life. In a tenth of the cases, the deadline was extended by more than a year, due mainly to slow recruitment or difficulties in activating clinical sites.

Patient access can also be positively influenced by the entry of generics and biosimilars. Regarding **generic entry**, the **Orphan Regulation** lacks coherence with Directive 2001/83/EC. For medicines for rare diseases, generic companies can only submit an application for MA at the end of the 10-year market exclusivity period while for all other medicines, at the end of the market protection period generics can be placed directly on the market. This issue will be further considered in the on-going revision of the Orphan Regulation. Respondents to the targeted survey confirmed this view, especially civil society organisations (38%) estimated the legislation was "slightly" coherent). They identified incoherencies resulting in duplication of similar processes in the general legislation on unmet medical need. 35% of respondents to the targeted survey assessed the legislation as "moderately" consisent with specialised ones. In the public consultation concerns were shared on excessive data exclusivity due to the interplay between the general pharmaceutical legislation and the Orphan regulation. Some respondents suggested the orphan regulation would be better integrated in the general pharmaceutical legislation to also better address some issues arising from data exclusivity of old active substances. No specific concern of coherence were shared during the consultation activities on paediatric legislation.

The fact that **inequitable access is observed** even for centrally authorised medicines points towards 'downstream' factors beyond the authorisation process that affect whether and when products are placed on specific markets. Such factors relate significantly to the characteristics of national markets. Smaller countries and poorer countries tend to see fewer product entries. To illustrate, data provided by EFPIA member associations and IQVIA showed (Figure 10) that, whilst in Germany 133 out of 152 (88%) of all new medicines authorised between 2016 and 2019 were available to patients, small Member States such as

[129] Conditional marketing authorisation - Report on ten years of experience at the EMA (europa.eu).

the Baltic countries or countries with comparatively low prices, like Romania, had fewer than 50 of these available[130]. The difference is smaller when comparing the therapeutic availability (i.e. availability of the therapy - molecule) and not the product availability. The time to patient access is also significantly longer for most of these latter countries, at approximately two years or more in Romania compared to four months in Germany. Similar observations were made across different subsets of medicines, including oncology medicines and orphan medicines[131].

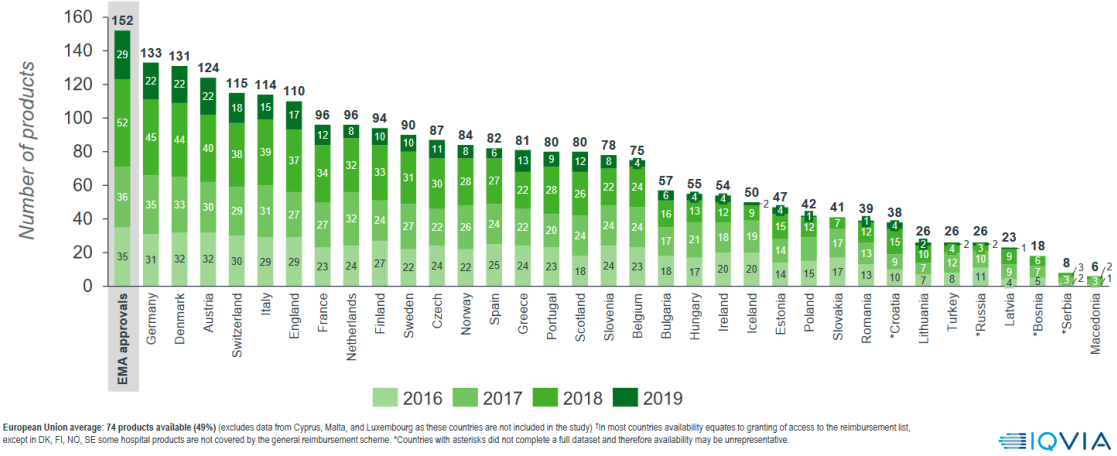


Figure 10: Availability of EU authorised medicines (2016-2019) and their availability in Member States by the end of 2020
Source: IQVIA

Collectively, these studies suggest that expanded access to the centralised procedure has not been an effective measure to improve access, because other factors, mentioned above, are much more relevant in influencing access. Hence, only 40-50% EU markets have access to innovative medicines.

Medicines shortages present a major problem for patient care. A recent study[132] considered how the EU legal framework has contributed to preventing and mitigating shortages, whilst assessing how this framework is consistent with and has been complemented by Member States' actions The current framework focuses on marketing authorisation holders notifying supply disruptions[133] and requires them and distributors to ensure appropriate and continued supply of the medicines they are responsible for[134]. Due to a lack of comparable data, it was not possible to asses the implementation and effectiveness of the provisions. Member States have transposed the supply requirement for MAH and distributors in different ways and at different levels of 'intensity', which have not been effective to ensure supply.

The outcome of the public consultation confirms the importance all stakeholders (in particular civil society and healthcare professionals) place on medicines shortages as a key issue impacting on access and ultimately public health. Healthcare professionals stress that the current legislation has not been effective as evidenced by rising shortage notifications. In the targeted survey, civil society, public authorities and health service stakeholders

[130] Newton et al., 2021.
[131] Oncology medicines and orphan medicines both fall within the mandatory scope of the centralised procedure and thus are authorised for marketing in all EU countries simultaneously.
[132] de Jongh et al., 2021
[133] Art. 23a of Directive 2001/83/EC.
[134] Art. 81 of Directive 2001/83/EC.

considered the security of supply of medicines and shortages to be an aspect that the legislation has been least effective in addressing.

Figure 11 presents an overview of the number of medicines shortages reported in the EU annually (total and average per Member State). It shows a strong increase in notifications over the last 10 years, suggesting an increasing disruption for patients and health systems. However, other factors contribute to the increase, e.g. more countries track and report shortages, and/or do so more effectively. Regardless, the increasing trend is clear. The implication is that, while the legislation helped generate more insight into the scale and prevalence of medicine shortages (through introduction of continuity of supply/ marketing notification requirements), it has not been sufficiently able to address their causes and to implement effective actions to prevent, mitigate or alleviate their impact.

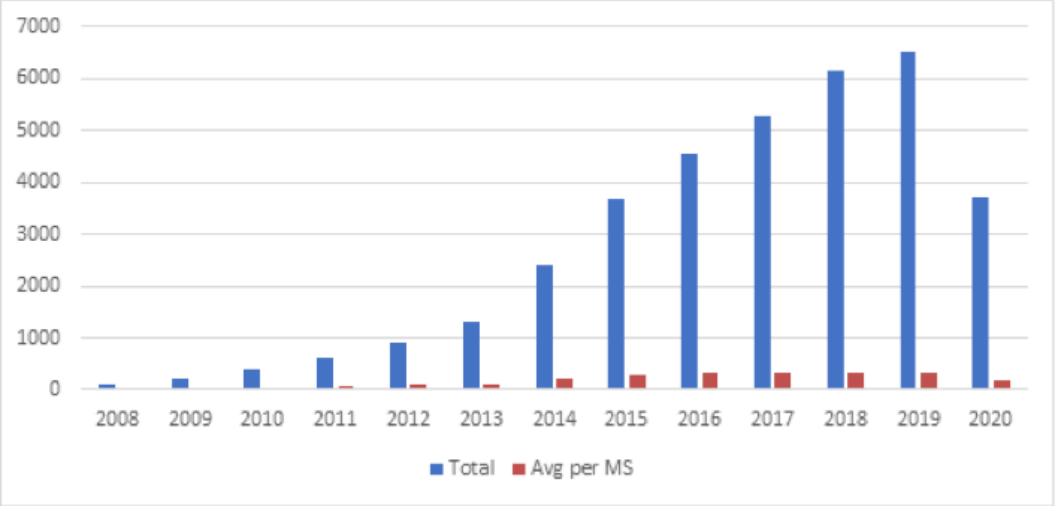
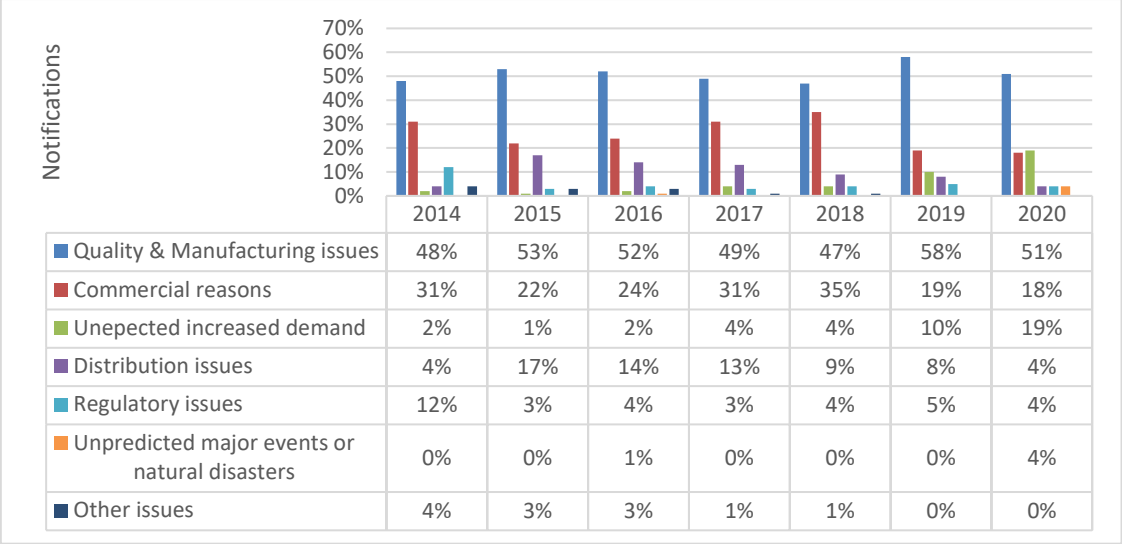


Figure 11: Total number of shortages reported across the EU
Source: Analysis of data from national shortage registries. Technopolis. The average number of countries reporting data on notifications from 2008-2010 is 2; from 2011-2013 is 7; and from 2014-2020 is 15.

The root causes of medicines shortages are divergent[135] (Figure 12). Quality and manufacturing issues, reflecting unforeseen problems with the quality of ingredients or processes that lead to distruptions in supply, recallsare the most common reasons. While the legislation has been successful in increasing the observance of good manufacturing and distribution practices (GMP/GDP) and the more comprehensive scrutiny of manufactured quality, this may have indirectly increased the number of shortages. While commercial issues have in the past been second as the root cause of shortages they have decreased, from around 30% of all causes in 2014 to 18% of the causes in 2020. Similarly, the proportion of notifications citing distribution issues as the root cause of shortages have declined over time. Instead, since 2019, unexpected increased demand became a major cause.

[135]de Jongh et al., 2021



	2014	2015	2016	2017	2018	2019	2020
Quality & Manufacturing issues	48%	53%	52%	49%	47%	58%	51%
Commercial reasons	31%	22%	24%	31%	35%	19%	18%
Unepected increased demand	2%	1%	2%	4%	4%	10%	19%
Distribution issues	4%	17%	14%	13%	9%	8%	4%
Regulatory issues	12%	3%	4%	3%	4%	5%	4%
Unpredicted major events or natural disasters	0%	0%	1%	0%	0%	0%	4%
Other issues	4%	3%	3%	1%	1%	0%	0%

Figure 12: Time trends in reported root causes of shortages (2014-2020)
Source: Analysis of data from national shortage registries. Technopolis

Stakeholders, particularly industry and NCAs, report that generic medicines are particularly at risk of shortages, given the higher relative fragility of their supply chains. Procurement practices have driven down the prices of generics to the extent that these products cannot be manufactured in the EU - profitably and suppliers need to be consolidated, sometimes to one global supplier.

Studies performed by pharmaceutical industry associations suggest that Asian producers of active pharmaceutical ingredients (APIs) hold a strong position in the large volume generic API market. Some of these APIs are no longer produced in the EU[136]. Industry reports that the EU has dependencies upstream in supply chains, for medicine precursors and intermediates[137]. In addition, some technologies, used upstream in the manufacturing chain of medicines, may no longer be available in Europe[138]. However, not every dependency on imports from third countries will automatically lead to a vulnerability that threatens the security of EU supplies. Due to the complexity of pharmaceutical supply chains further analysis of dependencies is necessary to identify specific vulnerabilities. In addition, diversification of supply chains can present important benefits to the EU's open economy and opportunities to strengthen security of supply.

4.1.1.3 Affordability

In the interest of public health, marketing authorisation decisions on medicinal products are taken on the basis of objective criteria of quality, safety and efficacy, to the exclusion of economic considerations. Decisions on setting of prices for medicines and their inclusion in the scope of national reimbursement schemes are a responsibility of the Member States[139].

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[136] Progenerica Study of 2020 Microsoft PowerPoint - Microsoft PowerPoint - 200929_Final Report_short_v04_en (progenerika.de) and SICOS study on vulnerabilities of supply chains Press-release-SICOS-Leem-Gemme-Etude-PwC_20211027-EN.pdf (cefic.org).
[137] IQVIA for EFCG study IQVIA for EFCG - Executive summary - EFCG (cefic.org); and ECIPE analysis for EFPIA, International EU27 pharmaceutical production, trade, dependencies and vulnerabilities: a factual analysis (efpia.eu).
[138] EU Fine Chemical Commercial KPI – executive summary, IQVIA, December 2020 https://efcg.cefic.org/wp-content/uploads/2021/06/20201211_IQVIA-for-EFCG_Executive-summary.pdf.
[139] Article 4 (3) Directive 2001/83/EC.

The general pharmaceutical legislation does not directly address affordability of medicines. Affordability was not among the objectives of the 2004 revision of the general pharmaceutical legislation. However, in the past years, the costs of medicines for health systems continue to rise impacting patient access.

Pharmaceutical spending is the third biggest cost element in healthcare spending, roughly responsible for 1/6 of healthcare spending. Spending in the retail pharmaceutical sector (on prescription medicine and non-prescription medicine but not on medicines consumed in healthcare settings) has remained stable over the last 20 years in EU27, at 17-21%, according to OECD Health statistics, pharmaceutical spending[140]. This is in line with the findings of a recent report that highlights that spending on pharmaceuticals has been growing more slowly than overall health spending in most countries, and below GDP growth[141]. Understanding the growing expenditures in hospital settings is more complex (due to lack and inconsistency of availability data, different tax and supply chain costs, leading to nominal list prices only), however, there are indications that this is driven by high cost speciality medicines[142].

In the consultations, regional public authorities noted that an assessment for better definition of 'innovative medicines' is needed, with **transparency of research and development (R&D) costs**. However, in interviews and in the workshop, industry stakeholders noted that transparency of R&D costs is not feasible as the methodology to calculate them would vary enormously and would contain sensitive information.

Enabling access to affordable medicines is among the areas where the legislation has been less effective and more needs to be done according to all stakeholder groups in the targeted survey and the public consultation[143]. The rising costs of medicines and affordability were key concerns for academics, healthcare professionals, public authorities and civil society stakeholders in the interviews[144]; they were open to any measures that could address these issues including incentives and new pricing models. The impact of the new HTA Regulation adopted in 2022 has yet to be seen.

Another angle supporting affordability relates to generic and biosimilar competition. Amongst other things generic/biosimlar entry is influenced by protection periods. The data and market protection provided by the general pharmaceutical legislation – together with patents, SPCs, and protection given to orphan and paediatric medicines – effectively prevent market entry for generic and biosimilar medicines. Several stakeholders perceived the protection periods as complex, suboptimal and referred to fragmentation. While fragmentation of the regulatory protection was phased out by 2016 as a result of the 2004 revision, the SPC system remains fragmented. Furthermore, where the intellectual property rights expire after the regulatory protection periods, access to generic or biosimilar medicines is delayed and affordability negatively impacted.

An analysis of a sample of products in France, Germany, Italy and Spain with protection expiry between 2016-2024 shows that two thirds of the products are protected by

[140] Analytical report, Figure AFF-3, Annex 10.
[141] IQVIA Institute, 2021
[142] Annual average growth in retail and hospital pharmaceutical expenditure, in real terms, 2008-2018. (OECD, 2020).
[143] See Appendix B: Tageted survey overview: Areas where the current legislation has been effective.
[144] Based on stakeholder interviews, 29% of academics (total interviewed = 14), 62.5% of healthcare professionals (total interviewed = 8), 44% public authorities (total interviewed = 48) and 75% of civil society representatives (total interviewed = 16).

intellectual property rights (patent and SPC) from generic competition, while one third of the products are protected by data and market protection[145].

The share of generics in total medicinal products sales revenue is modestly increasing in the EU (from 13% to 16%) between 2002-2020. The analysis shows the EU is on a similar trend as other comparator markets (Japan and USA). Competition from these products is expected to lower price levels and increase affordability of medicines[146]. An analysis of top selling medicine sales data indicates that branded product prices drop on average by one third of the price level prior to generic entry[147]. This is the highest level among comparator countries, and similar to that in Australia and Korea. The discount of the generic medicines (compared to the price level of branded equivalent prior to generic entry) is even larger in the EU and steadily increased since 2007 from 50% to 65%. However, the data also suggests that further efforts can be made - by Member States - to fully exploit the savings generated by generic competition, as there is variability in generic uptake at national level.

Stakeholders interviewed[148] agreed that the legislation has been beneficial for increasing competition in the EU by facilitating generics and biosimilar entry in the market. This has been also enabled by the Bolar exemption which has allowed generics and biosimilars to be brought on the market more quickly. However, according to interviewees, the benefits from the Bolar exemption can vary across MSs because of differences in how the exemption is interpreted and implemented[149].

4.1.1.4 Accommodating innovation

Developing new medicines is a very capital intensive, high-risk, high-gain business. Profits from new products and a supportive regulatory system with relevant incentives (e.g. intellectual property and regulatory protections) incentivise innovation. **Intellectual property rights**, i.e. patents and **supplementary protection certificates (SPCs)**, are key drivers of innovation, allowing return on R&D investment to be realised.

To take advantage of scientific and technological developments and to better accommodate innovation, the 2004 revision altered EMA's scientific committees to ensure relevant expertise, mandated EMA to provide scientific advice to marketing authorisation applicants and introduced a new pathway for biosimilar medicines.

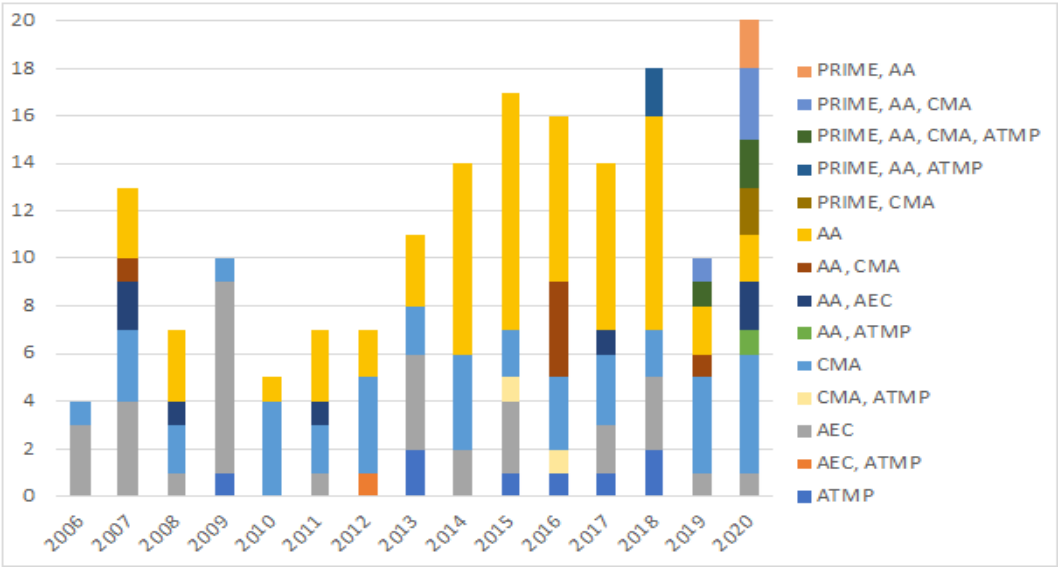
The interviews with stakeholders[150] confirmed that the general pharmaceutical legislation has provided a regulatory system which has facilitated innovation. The centralised procedure, the creation of the EMA, the scientific advice procedures and overall harmonisation of quality and manufacturing rules were cited as some of the main enablers accommodating innovation.

However, new types of medicines, approaches and processes may raise questions about whether they meet the medicinal product scope or definitions or whether they fully fit within the legislation, which can create unintended barriers to innovation, development, production or marketing authorisations. Challenges are particularly evident on advanced therapy

[145] This finding is line with that of the Copenhagen Economics study.
[146] Analytical Report, indicator AFF-6, Annex 10.
[147] Idem.
[148] 43% of academics (total interviewed = 14), 62.5% of healthcare professionals (total interviewed = 8), 29% public authorities (total interviewed = 48), 56% of civil society representatives (total interviewed = 16) and 53% of industry representatives (total interviewed = 60).
[149] CMS, 2007
[150] 36% of academics (total interviewed = 14), 50% of healthcare professionals (total interviewed = 8), 48% public authorities (total interviewed = 48), 94% of civil society representatives (total interviewed = 16) and 52 % of industry representatives (total interviewed = 60).

medicines, combined products (medicines used in combination with medical devices) and other novel technologies and approaches.

The **legislation has proven flexible enough to accommodate developments and innovations** in the pharmaceutical sector in the last two decades. There has been a growth in the number of innovative medicines authorised in the EU (Figure 13), including innovative medicines (e.g. ATMPs) and those addressing UMN (e.g. through PRIME[151] and conditional marketing authorisation (CMA) routes). However, it was the view of several stakeholders in the consultations[152] that the system has **not been fully able to accommodate other emerging technological developments,** as readily. These include, combined products/borderlines with medical devices or substances of human origin, digitalisation and new manufacturing methods. The creation of different committees for assessing ATMPs, orphan and paediatric medicines should facilitate pooling of expertise and thus contribute to ensuring safety and efficacy of such products. However, challenges related to the interaction and coordination between possibly 5 of EMA's scientific committees (CHMP, CAT, PDCO, COMP and PRAC) were identified[153] and different national implementations of the hospital exemption for ATMPs has given rise to public health concerns[154].



ATMP = Advanced Therapy Medicinal Product; CMA = Conditional Marketing Authorisation; PRIME = Priority Medicine; AA = Accelerated Assessment; AEC = Authorisation under exceptional circumstances.

Figure 13: The number of innovative medicines authorised by EC, 2006-2020

Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA

The lack of coordination and alignment of the CHMP and COMP processes with different timelines and data requirements was also shown by the **evaluation of the Orphan Regulation**. This may lead to delays in the assessment of the marketing authorisation[155]. Academic stakeholders highlighted that the legislation needs to promote more development of new paediatric indications where it currently focuses on repurposing of authorised adults' medicines for use in children.

[151] Defined in the Glossary.

[152] Based on stakeholder interviews, all healthcare professionals (n = 8), 69% of civil society representatives (total interviewed = 16), 29% of public authorities (total interviewed = 48), 24 % of industry representatives (total interviewed = 66) and one academic (total interviewed = 14).

[153] Orphan evaluation (SWD/2020/0163/final).

[154] Coppens et al, 2020

[155] Idem.

Scientific and technology developments in the pharmaceutical sector have disrupted the traditional model in which (most) activities are carried out by a single pharmaceutical company. These activities concern R&D, clinical development, manufacturing and marketing. The value chain of the pharmaceutical industry is now much more divided in tasks and specialisation, with academic institutions conducting basic research and usually small businesses taking scientific discoveries into product development. In the clinical development stage, costs sharply increase across the different phases of clinical trials, and usually this is the moment when small companies either licence out their product, partner with, or are acquired by large pharmaceutical companies. Large and well capitalised global companies have the means to conduct and finance late-stage clinical trials, experience in regulatory procedures and capacity to place a product on the market. A high concentration of large pharmaceutical companies is observed among the market authorisation holders of innovative products[156], but this can hide the original innovator. The 2004 revision aimed to encourage firms to increase their development efforts with harmonisation of the period of regulatory protection across the whole of the EU (8+2+1 system). This was expected to lead to increased R&D investment, more clinical trials in the EU and an expansion in the medicines pipeline. These three expectations have been met to some extent at least[157]. However, these effects cannot be solely attributed solely to the legislation or its revision.

While the legislation has been overall flexible to accommodate innovation, a broad range of stakeholders were of the opinion that the legislation has not been successful in increasing the **EU's regulatory attractiveness** in specific areas. These were related to a lack of adequate incentives for innovation by SMEs, academic/industry collaborations, innovation to address areas of unmet medical needs, biosimilar innovation, and antimicrobial innovation. These challenges are underpinned by several reasons which include complexity of disease pathologies, knowledge gaps in molecular and physiological elements of diseases, market failure, and high risk R&D. Prioritisation seems needed to balance investment in the development of highly innovative medicines to address unmet medical needs and investment in incremental innovation (i.e. medicines similar to pre-existing medicines). There is currently no distinction in regulatory incentives between different types of innovation. While out of scope of the general pharmaceutical legislation, there was also a broad consensus that health technology assessments (HTA) and pricing and reimbursement decisions are main drivers of innovation as these represent the return on investment into R&D.

Industry stakeholders[158] noted that the regulatory protection brought by the 2004 revision had improved the attractiveness of the EU's regulatory system globally. An international comparative legal analysis[159] confirmed the continuing relative advantage of the innovation incentives within the EU system as compared with those in operation in selected other regions, as did the international review reported by Copenhagen Economics (2018)[160]. Several stakeholders from patients' groups and academia[161] remarked on what they considered to be the overly generous provisions available within the EU, arguing it has favoured innovation over access. These stakeholder groups recommended the Commission to review the balance between innovation and access in the related Impact Assessment,

[156] European Medicines Agency, 2021a.
[157] Analytical report, indicators RI-8 and IEC-6, Annex 10.
[158] 167 out of 173 industry respondents open public consultation considered the current data and market protection period the most important incentives for innovation.
[159] Technopolis study 2022.
[160] Copenhagen Economics, 2018
[161] Views of nine civil society representatives (out of the sixteen interviewed) and of three academics (out of the fourteen interviewed.

suggesting there is scope to reduce innovation incentives, without damaging Europe's attractiveness globally, while also strengthening the rewards / obligations around access and affordability.

All stakeholder groups concurred that digitisation and emerging science and technology developments have not been adequately integrated in the current regulatory system. The majority of stakeholders see the need for improvement in the coherence of the general pharmaceutical legislation with the **EU digital agenda.** In particular, industry deems little coherence and public authorities medium[162]. There is a high level of fragmentation, lack of interoperability across the various databases and IT systems, lack of re-use of data for public interest - which is a general issue in the health sector. The general pharmaceutical legislation has no specific provisions supporting or facilitating the digitisation of the pharmaceutical sector and on certain aspects the lack of consideration for digital tools may have hindered its objectives with regard to innovation and reduction of administrative burden. As such, the general pharmaceutical legislation is not well aligned with the EU priority of "A Europe fit for the digital age,"[163] which negatively affects access to public information and transparency.

Most stakeholders[164] agreed that the legislation and related guidelines do not provide enough clarity for companies and national regulators when it comes to innovative combined products (i.e. medical devices that also contain medicines), use of real-world evidence for clinical trials and medicinal products consisting of or containing GMOs.

Similarly, radiopharmaceuticals have been cited during the consultation activities[165] as a key area where the legislation has not achieved a positive result in terms of facilitating innovation, with the lack of clarity in the regulatory framework for hospital preparations and lack of incentives for R&D in this area as main causes.

The 2004 revision introduced several new procedures to encourage pharmaceutical companies to pursue innovative products relevant to unmet medical needs with a strong public health benefit, including the conditional marketing authorisation (CMA).

However, the legislation has not fully managed to promote innovation in certain **areas of unmet medical need such as AMR**. AMR was not among the objectives of the previous revision of the pharmaceutical legislation and has become an issue of greater public health concern[166]. Bacteria and other microorganisms have become increasingly resistant to antimicrobial medicines, thus increasing mortality[167].The last entirely original class of antibiotic was discovered in the late 1980s[168]. Declining private investment, lack of innovation in the development of new antimicrobials, scientific challenges in finding new compounds, lack of profitability of antimicrobials are among the causes leading to fewer

[162] Academia considers the coherence high, though a reservation should be made for very few responses from academia in this regard.
[163] https://ec.europa.eu/info/strategy/priorities-2019-2024/europe-fit-digital-age_en.
[164] See Appendix B: Targeted survey overview: areas where the current legislation has been effective (survey analysis). Low score means that stakeholders ranked these topics, on average, below three (very small = 1, small = 2, moderate = 3).
[165] Based on the survey replies, views shared by 22 healthcare professionals out of the 77 respondents to the public consultation representing health services.
[166] https://www.who.int/news/item/17-01-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections
[167] Thompson, Tosin. "The staggering death toll of drug-resistant bacteria." Nature (2022).
[168] Plackett, Benjamin. "Why big pharma has abandoned antibiotics." Nature 586.7830 (2020): S50-S50.

new antibiotics reaching the market[169].Contrary to the veterinary medicines legislation, the general pharmaceutical legislation does not include specific provisions targeting AMR, based on considerations in the **EU Strategy on Antimicrobial Resistance**[170]. It currently lacks provisions to restrict and optimise use of antimicrobials and to promote development and the authorisation of new classes of antimicrobials.

Another objective of the legislation was to **attract R&D to the EU**. However, many contextual factors affect such anchoring within the EU. These include R&D capacity, market size, availability of public and private funding, tax system and incentives. While the growth in the pharmaceutical sector in the EU (as well as globally) has led to an increase in total R&D expenditure, doubling since 2000 to more than €40bn in 2019[171], it cannot be attributed to the implementation of the legislation. R&D investment in the EU has remained much lower than that in the US (€74 billion in 2019).

Funding instruments at EU level have worked synergistically with the general pharmaceutical legislation and have contributed to promote medical innovation and attract R&D to Europe. **Horizon Europe** (2021-2027)[172] is a key funding programme for EU research and innovation with dedicated instruments supporting basic research, EU-wide research collaboration and providing grants and investments to small innovative companies. The **Innovative Health Initiative** (IHI)[173] is a European public-private partnership between the EU, the pharmaceutical sectors and the life science industry (biopharmaceutial, biotechnology and medical technology sectors, incl. companies in the digital area). It co-funded by Horizon Europe and the health industry. IHI is based on an integrated, cross-sector approach between academia and industry to advance and accelerate medicine development. The partnership and its predecessor, the Innovative Medicines Initiative, can involve the participation of regulatory bodies, facilitating mutual learning.

The increase in R&D expenditure and introduction of revised procedures (e.g. PRIME, CMA) has led to an increase in the number of innovative medicines approved with a consistent rise year-on-year from 2012 onwards (Figure 13).

Still, despite a large amount of R&D in Europe concentrated in universities and public research organisations, translation of academic research and innovation to marketable medicines is suboptimal. Many academics work on developing cell and gene therapies for cancers and certain genetic diseases. However, academics do not necessarily have the required regulatory knowledge and capacity, are not very experienced with product development and have limited production capacity[174]. Moreover, sometimes guidelines and other regulatory standards are not available to support novel developments. Lastly, high-risk investments required for clinical trials are not always accessible. Collaborations between academics and industry can therefore provide an opportunity to advance research and bring medicines to market.

The number of applications marketing authorisation overall has increased across therapeutic areas (Figure 14). Since 2005, most therapeutic areas show a sustained increase in number

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169 https://www.efpia.eu/about-medicines/development-of-medicines/antimicrobial-resistance-amr/# and https://www.reactgroup.org/news-and-views/news-and-opinions/year-2021/the-world-needs-new-antibiotics-so-why-arent-they-developed/

170 EU One Health Action Plan against AMR (June 2017), https://ec.europa.eu/health/system/files/2020-01/amr_2017_action-plan_0.pdf.

171 Analytical report, indiator RI-8, Annex 10.

172 Horizon Europe | European Commission (europa.eu).

173 Innovative Health Initiative | IHI Innovative Health Initiative (europa.eu).

174 KWF, 2021

of authorised medicines following the expansion in the scope of the CP. A proportionately larger expansion (467%) in the number of authorisations of cancer medicines (antineoplastics) and immunomodulating agents, compared with the growth in all other therapeutic areas, likely reflecting the expansion in investments in oncology and ATMPs.

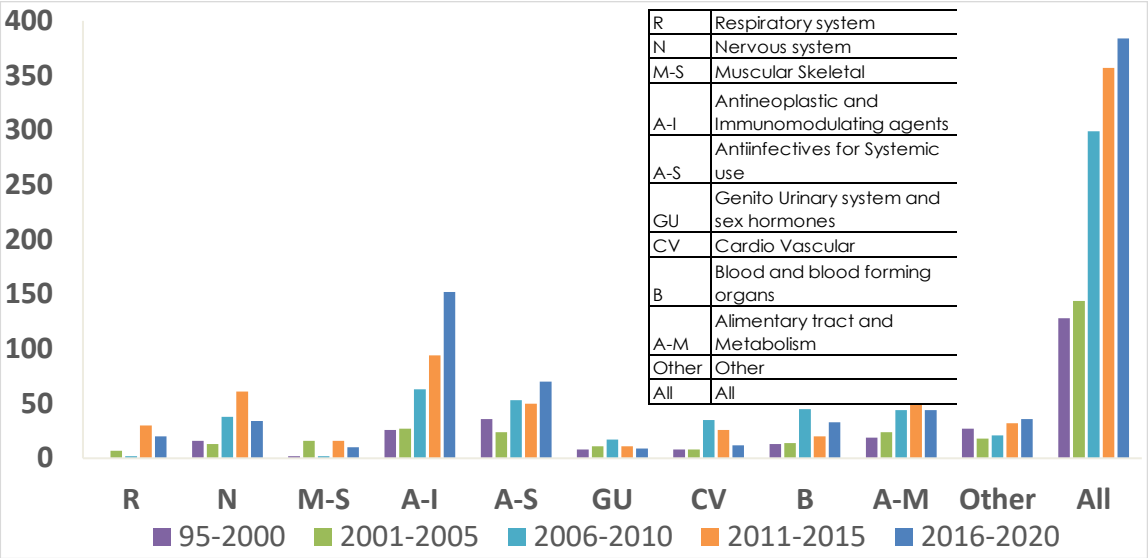

Figure 14: Number of EC authorised medicinal products by anatomic / therapeutic classification

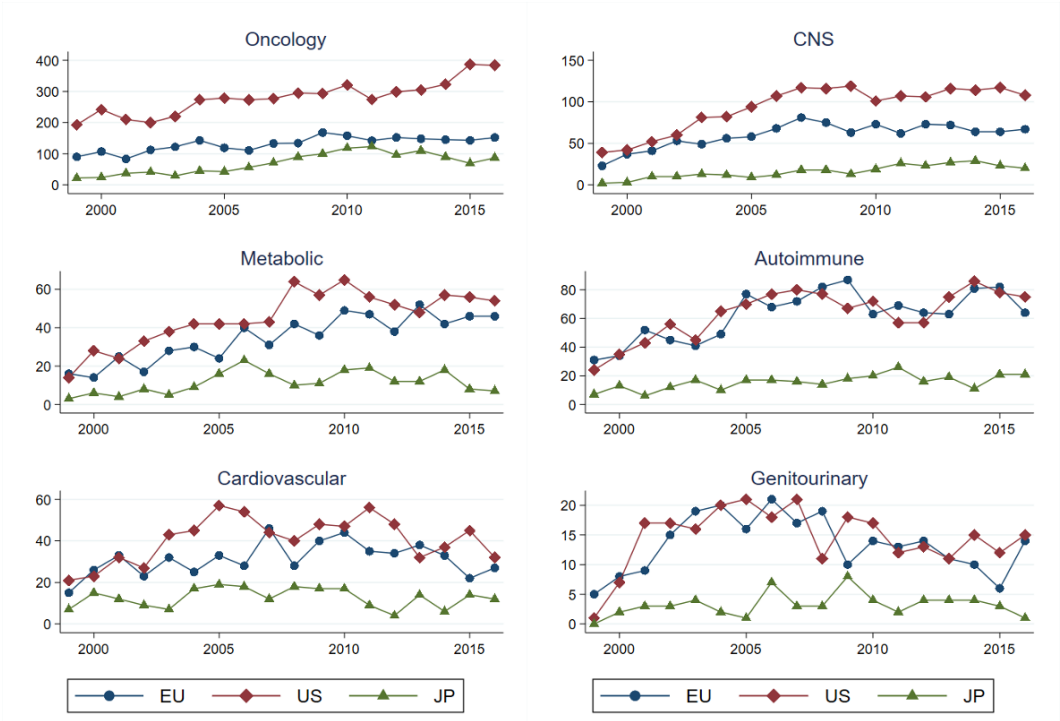

Figure 15: Trends in the number of new candidate medicinal products (pipeline) per year, by therapeutic area
Source: Informa Pharmaproducts and FDA databases

The number of new candidate medicinal products has increased steadily over time in all therapeutic areas, perhaps with the exception of genito-urinary medicines (Figure 15). The trends are broadly consistent across the EU, US and Japan, suggesting that the EU market functions in line with other international regions despite the different governance structures. However, there are no evident discontinuities in the EU trend data around the timing of the implementation of the 2004 revision. This suggests the legislation has not boosted

incentives substantially in the EU, nor has it hampered industry ambitions and competitiveness.

The general pharmaceutical legislation has few provisions on **digitisation**[175]. Though not a legal requirement, most applications under the CP are submitted electronically and some NCAs accept/require electronic information/applications[176]. Still, industry stakeholders find that digitisation is not adequately accommodated; while public authorities, academia and civil society have a more positive view. Specific suggestions from position papers shared in the public consultation by medical devices industry respondents also included the creation of standards for clinical trials e-signatures and more digitisation to assist medication management at hospitals. Real world evidence[177] and big data have not been used to their full potential, neither artificial intelligence and machine learning, though initiatives are ongoing, namely the proposed **European Health Data Space**[178].

While the **General Data Protection Regulation (GDPR) and EU Data Protection Regulation** allow the (further) processing of sensitive personal data for scientific purposes or for reasons of public interest in the area of public health, industry and public health authorities found nevertheless the coherence moderate with the general pharmaceutical legislation. In the targeted survey, 26% of industry respondents assessed it as "slightly" coherent while 24% of public authorities respondents rated it as "moderately" coherent. There is uncertainty on the extent to which private companies and universities can further process sensitive personal data for scientific purposes[179] and the application of the GDPR varies between Member States[180].

4.1.1.5 Ensure competitive functioning of the single market

The intervention reduced the administrative burden for generic medicines and the introduction of the Bolar exemption was expected to speed up market entry of generic medicines, while the other measures of this strand aimed to reduce the costs for generic medicines, improving their access. These measures were also expected to further harmonise the marketing authorisation procedure and reduce market barriers, ensuring the **competitive functioning of the single market**.

The market for generic and biosimilar medicines has increased in the evaluation period from 13% to 16% in terms of sales revenue and from 25% to 40% in sales volume[181].The total

[175] E.g requirement for marketing authorisation holders and Member States to electronically submit information on suspected adverse reactions to the EU database on adverse reactions (Eudravigilance).

[176] Procedural guidance on eSubmissions can be found in the Heads of Medicines Agencies and EMA websites: https://www.hma.eu/human-medicines/cmdh/procedural-guidance/esubmissions.html and https://esubmission.ema.europa.eu/index.htm.

[177] Flynn, Robert, et al. "Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?." Clinical Pharmacology & Therapeutics 111.1 (2022): 90-97.

[178] COM(2022) 197 final EUR-Lex - 52022PC0197 - EN - EUR-Lex (europa.eu).

[179] Dept for Digital, Culture, Media and Sport, Data a New Direction (2021), available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1022315/Data_Reform_Consultation_Document__Accessible_.pdf.

[180] NIH, Implications of GDPR for US-EU Cooperation in Biomedical Science: Observations from the US National Institutes of Health (2019). Available at: http://www.iscintelligence.com/archivos_subidos/robert_eiss_gdpr_us-eu_cooperation_in_biomedical_science_isc_gdpr_seminar_19_nov_2019.pdf.

[181] Section on access and indicator AFF-4 of Analytical report.

European biosimilar market has reached €8.8 billion in 2021[182] while the generics market was valued at €67 billion for 2021[183].

The vast majority of biosimilar medicines fall within the mandatory scope of the centralised procedure. The EU has been an early adopter of biosimilar medicines and delineated an authorisation pathway (for biosimilars) much before any other country. The biosimilar pathway is also a success according to industry, increases competition with the originator and facilitates access (of biosimilar medcines) for patients.

Generic medicines dominate the MRP and DCP (around 65% of procedures). Since 2005, between 954 and 1152 procedures were finalised every year; in 2020 around 1 600 generic products were authorised across the EU[184].

Inquiries into the **competition between originator and generic/biosimilar medicines** show that originator undertakings sometimes use various practices aiming at preventing or delaying generic entry (e.g. patent filing strategies, patent disputes and oppositions, settlement agreements with generic companies, interventions before competent authorities and life cycle strategies for follow-on products)[185]. These practices are not as such illegitimate, but in specific cases they attract the scrutiny of competition authorities[186]. While there is agreement across the various stakeholder groups – in the targeted survey and in interviews – that competition is suboptimal, many stakeholders[187] agreed that the legislation has been beneficial for increasing competition in the EU pharmaceutical sector by facilitating the market entry of generic and biosimilar medicines, particularly through the Bolar exemption.

In terms of coherence, the general pharmaceutical legislation, which seeks to safeguard public health, is in line with **EU competition legislation,** whose primary objective is protecting consumer welfare. For example, Articles 101 and 102 TFEU facilitate competition based on price (allocative efficiency). They prohibit originators from abusing dominant positions (acquired largely from exclusivity rights) to impede the subsequent entry of generic or biosimilar medicines. Merger controls (and to a lesser extent Articles 101 and 102 TFEU) also provide scope for protecting competition based on innovation (dynamic efficiency).

The EU's leading role on biosimilars

Biosimilar medicines have since 2005 an abbreviated registration process complemented by guidelines. Between 2006 and 2021, 84 biosimilar medicines were authorised in the EU[188]. The EU accounted for around 70% of the world's biosimilar medicine authorisations in the 5-year period 2006-2010 and in 2016-2020, still accounted for the largest share of authorisations (30%)[189]. In

[182] Troein et al., 2021
[183] Market Data Forecast, 2022
[184] MRFG and CMDh statistics: No Slide Title (hma.eu), CMDh statistics (hma.eu).
[185] Final Report, Pharmaceutical sector inquiry, European Commission, Competition DG available at: https://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf, COM(2019) 17 final: https://ec.europa.eu/competition/sectors/pharmaceuticals/report2019/report_en.pdf.
[186] See e.g. Commission Decision of 15 June 2005 in case COMP/AT.37507 – Generics/AstraZeneca, Commission Decision of 19 June 2013 in case COMP/AT.39226 – *Lundbeck*, Commission Decision of 9 July 2014 in case COMP/AT.39612 – *Servier*, Commission Decision of 10 December 2013 in case COMP/AT.39685 – *Fentanyl*.
[187] Based on stakeholder interviews, 62,5% of healthcare professionals (total interviewed = 8), 56% of civil society representatives (total interviewed = 16), 29% of public authorities (total interviewed = 48), 53% of industry representatives (total interviewed = 66) and 43% of academics (total interviewed = 14).
[188] GaBI, 2022
[189] Troein et al., 2021

comparison, the FDA only approved its first biosimilar medicine in 2015, and has since granted 29 approvals for biosimilar medicines with only 18 having been launched on the US market[190].

However, uptake (and access) of biosimilar medicines is not uniform across Member States. On a per capita basis, central and eastern European markets lag behind western European countries[191]. Uptake is affected by factors such as historic usage of protected brands, lack of clarity on the scientific foundation for interchangeability of biosimilars with their originators, national policies on interchangeability and lack of confidence in biosimilar medicines among healthcare professionals and patients[192]. There may be additional costs for biosimilar medicine manufacturers to develop the same relationships with prescribers, key opinion leaders and patients as originators (to encourage prescribing), and for post-launch studies to assuage healthcare professionals' concerns as regards comparability of the biosimilar medicine and the originator[193]. These factors may also influence the uptake of biosimilar medicines.

The EC has actively promoted biosimilar medicines' uptake through its Project Group on Market Access and Uptake of Biosimilars consisting of Member States, EEA countries' representatives, and other stakeholders such as patient organisations, healthcare professionals and experts. In addition, Member States have provided targets and incentives for biosimilar medicines' uptake, e.g. France has set a target of 80% biosimilar penetration by 2022[194]. About a dozen countries in Europe, including Germany, France and the UK, offer incentives to prescribe biosimilar medicines[195].

Biosimilar entry creates competition, broadening patients' access to advanced treatments at more affordable prices and alleviating healthcare costs. In Germany, the waiting time for patients with rheumatoid arthritis to be treated with a biologic has been reduced from 7.4 years to 0.3 years after the introduction of biosimilar medicines[196]. Biosimilar medicines are typically cheaper by 20% compared to originator products[197]. One study estimated the impact of biosimilar entry in terms of healthcare systems savings between 2007 and 2020 for eight EU countries (France, Germany, Italy, Poland, Romania, Spain, Sweden, and the UK), ranging from €11.8 billion to €33.4 billion[198]. Savings from biosimilar medicines are smaller compared to generic medicines at least in part because of the higher development and manufacturing costs as well as greater regulatory requirements to obtain marketing authorisation, which create barriers to market entry for competitors[199].

Generally, only one Union marketing authorisation is granted to an applicant for a specific medicinal product, however, the applicant/holder can obtain a **duplicate Union authorisation** for the same medicinal product *where there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients, or co-marketing reasons*[200]. MAHs have been making use of this exception to obtain a duplicate authorisation for the first own generic/biosimilar product on the basis that its inaugural launch into the market can improve availability because it

[190] GaBI, 2021
[191] Troein et al., 2021
[192] Druedahl et al., 2022
[193] Mestre-Ferrandiz et al., 2016
[194] Haustein et al., 2012
[195] Arad et al., Realizing the benefits of biosimilars: what the U.S. can learn from Europe, Duke MargolisCenter for Health Policy, April 2021.
[196] Guntern, 2021
[197] Chen et al., 2021
[198] Haustein et al., 2012
[199] Ferrario et al., 2020
[200] European Commission, 2019

usually increases accessibility. Still, this behaviour may have hindered competition from generic or biosimilar medicines.

4.1.2 Efficiency

4.1.2.1 Types of costs and benefits

The revision addresses several aspects in the development, production, distribution and use of medicines, some of which have anyway occurred (at least partly). The situation before and after 2004 revision is compared, taking into account general market developments, whenever appropriate. The evidence for the size of costs and benefits has been gathered from various sources: interviews, surveys and data analysis.

The 2004 revision were not accompanied by a comprehensive *ex ante* impact assessment, and as such the evaluation has sought to define the main types of direct and indirect costs and benefits, retrospectively. The following table, lists the main types of costs or benefits identified for each of the main stakeholder groups:

Actors	Type of cost / benefit	Direct impacts
Innovator industry	Pre-marketing costs (e.g. R&D)	A mixture of cost savings (reflecting improved harmonisation and centralisation) and cost increases
	Post marketing costs	Cost increases associated with the strengthening of the EU-wide pharmacovigilance system
	Market access benefits	Earlier access
	Market protection benefits	Higher protection level
Generic industry	Market access benefits	Simplified multi-country access, earlier biosimilar authorisation
	Market protection benefits	Delayed entry but more innovation creates more business opportunities for generic companies
Wholesalers	Distribution costs	Harmonisation facilitating cross-border trade resulting in lower costs
EMA	Regulatory costs	Expansion in scope of activities creating a higher volume of work, resulting in higher operating costs
NCAs	Regulatory costs	Generally higher costs, some savings due to fewer authorisation procedures nationally
Health systems: healthcare providers, patients, carers, citizens.	Quality of MPs (benefits)	Measures generally result in higher quality / efficacy of products
	Availability of MPs (benefits)	National health systems and patients have access to a larger number of innovative medicines
	Costs of MPs	Some products have longer market protection, which may result in higher prices
	Information on MPs (benefits)	More and better information available, more informed decision making by reimbursement agencies and prescribers
	Environmental impact of MPs (benefits)	Improved transparency around the environmental risks of specific products / APIs, facilitating improved environmental management

Table 2: Cost/benefit and potential direct impacts, by stakeholder group

Costs and benefits were identified and measured comparing the situation post 2004 revision with the pre 2004 situation, taking into account general market developments, when appropriate. Given the long period of time since the implementation of the 2004 revision, most stakeholders were unable to provide quantitative estimates of the costs and benefits associated with those changes. Therefore, the cost-benefit analysis relied on quantitative

estimates provided by a small number of organisations that directly experienced those changes and on limited historical data. This limited number of observations was augmented by several studies and presentations. However, data are scarce and only large estimated ranges could be identified.

Stakeholders	Cost	Benefits
Citizens and consumers, health systems	Increased pharma expenditure due to strengthened exclusivities	25-30 new innovative medicines, in total; producing 170,000-210,000 QALYs in total; which amounts to €4.8bn-€17.2bn in monetised benefits
Businesses	Additional investments in IT systems to cope with expanded data requirements on safety and manufacturing – 250M€ Higher costs due to data requirements for new and current marketing authorisations; additional costs for legal departments €50m-€100m p.a., €750m-€1,500m in total	Cost savings due to the harmonisation and streamlining of procedures associated with the introduction of the DCP and the substantial reduction in the use of the mutual recognition procedure CP: €4.8m p.a., DCP: €36m p.a. Eliminating the need for further (after the first) renewals at 5-yearly cycles €23m p.a.
EMA	Higher staff and evaluation costs for EMA €2.5m-€3.1m p.a	
NCAs	higher inspection costs for national competent authorities €8m-€25m p.a	Cost savings for national competent authorities due to streamlining / harmonisation of national authorisation procedures (switch to DCP away from MRP) €20m-€40m pa

Table 3: Summary of estimated costs and benefits

4.1.2.2 Stakeholder impact

Citizens and health care systems

Citizens expect continued patient access to new and essential medicines. The authorisation of products is an inherenet element to meet this objective, but not sufficient as the authoristaion is an intermediate step before real patient access happens. The expansion of the scope of the centralised procedure and the extension of the regulatory protection period have contributed to an increase in the number of marketing authorisations of innovative medicines in Europe. The number of newly authorised medicines increased in the period following the introduction of the revisions, with the number of applications and authorisations almost doubling in the next 10 years - from around 35 in 2005 to around 70 in 2015[201]. The same has happened in respect to the number of medicines with new active substances (NAS) increasing from around 20 peryear to around 30 per year. This growth in the number of medicines and NAS is partly a reflection of changes in the scope of the centralised procedure, but it also reflects wider trends, with increasing demand for new medicines globally and an expansion in R&D investment by pharmaceutical companies across the world[202].

Notwhitstanding the increased number and sales of generics in the EU and in the authorisations of innovative medicines, there is still an issue of access to medicines across EU countries, not all EU citizens have equal access (see Section 4.1.1.1 for more details).

[201] In 2021, EMA recommended 92 medicines for marketing authorisation. Of these, 54 had a new active substance which had never been authorised in the European Union (EU) before. (European Medicines Agency, 2021a).

[202] This OECD report reviews the important role of medicines in health systems, describes recent trends in pharmaceutical expenditure and financing, and summarises the approaches used by OECD countries to determine coverage and pricing. (OCDE, 2019).

There is no simple means by which to estimate the numbers of additional new medicines authorised and launched on the market that are attributable to the 2004 revision, however, there is a clear discontinuity in the EMA trend data with the 3-year averages declining around 10% per year across the period 2001-2005 and then growing around 20% per year from 2006-2009. The US FDA authorisation data exhibits a similar trend, but with a 3-year delay. Within the period, the EU changes from authorising 5-10 fewer products each year to authorising 5-10 more than the FDA. The trend data suggest the US regulatory system had adjusted by 2010 with the FDA once again authorising more innovative medicines annually than the EU. The two regions' 3-year averages mirrored one another through to 2016, after which there was a marked divergence in outputs between the regions with authorisations in the US growing strongly while the EU recorded a period of low or no growth in product authorisations. From this perspective, the analysis assumed the 2004 revision have led to the authorisation of an additional 25-30 innovative medicines in total across the 4-year window between 2006 and 2009.

Working with this estimate, it was assumed that those 25-30 new medicines will have been approved for sale in the EU and that each will have delivered 10 years of additional benefits to health services and patients. The analysis of IQVIA sales data for the period 2009-2021 calculated an average annual sales income of €22.7m across all innovative medicines and all EU markets. Using this average of sales, the calculated, combined EU sales for these additional products falls in the range €570m-€680m. Based on the number of additional products and EU sales, the estimation is that the 2004 revisions were associated with an additional 170 000-210 000 QALYs[203] across the period. The estimated monetary value of the 2004 revision would fall in the range €4.8bn-€17.2bn.

The **impact of the regulatory data and market protection is quite significant**, with an estimate that 1/3 of all centrally authorised innovative medicines benefit from the 10 or 11 years protection[204]. This is a sizeable reward for innovators, allowing sufficient duration to recover R&D investment and support additional investment in innovation benefiting society as a whole. In the absence of regulatory protection, some products would still have an SPC protection, but less than 10 years. And for half of the products currently benefitting from regulatory protection, there would be no protection at all, offering little to no incentive to invest in R&D, submit a market authorisation application and launch the product on various markets.

On the other hand, this **regulatory protection delays generic/biosimilar entry, and creates an increased expense to public health systems**. Although this is an expected and assumed effect of the regulatory protection that is tolerated to promote innovation, the legislation was designed with targeted features to facilitate entry of generics/biosimilars into the market (i.e. the Bolar exemption and the biosimilars regulatory pathway).

For national health technology assessment bodies and **health payers**, the introduction of the CMA proved problematic, with substantial additional costs associated with the subsequent assessment of the relative cost-effectiveness of these newly authorised medicines.

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[203] This is based on a median ICER of €33,000 / QALY which was calculated using a basket of 11 medicines and the ICERs presented in the NICE HTA assessment reports. Using the WHO guidelines on valuing a QALY (1-3 GDP/Capita) http://www.who.int/choice/cost-effectiveness/en/, as recommended in the Better Regulation Toolbox (tool #32), and using an average GDP/capita for the EU of €27,810 (Eurostat Statistics Explained, 2021).

[204] The other 2/3 has a longer protection than 10 or 11 years, thanks to patent and SPC protection, or orphan market exclusivity.

Businesses

The 2004 revisions introduced a **harmonised system of regulatory data protection for innovative medicines** (8 years of data protection, with additional 2 years of market protection + possibility of additional 1 year market protection for new indications with significant clinical benefit) that stakeholders[205] viewed positively, with the new arrangements bringing greater clarity, harmonisation and predictability as compared with the previous situation, where there was a variety of different national policies in place.

The baseline situation was defined by the pre-revision Directive 2001/83/EC, which required Member States to grant a period of six years of data exclusivity for most pharmaceuticals from the date of the first market authorisation, and 10 years for biotech and other high-tech medicinal products[206]. The Directive allowed Member States to define a period of ten years for all pharmaceuticals if they considered it was "in the interest of public health." Belgium, France, Germany, Italy, the Netherlands, Sweden, and the United Kingdom did so. The other eight Member States implemented the 6-year period as their default term, using the 10-year period selectively. The 2004 revision turned the 6-year and/or 10-year period into the 8+2 arrangements. These changes became applicable across all 15 Member States and the 13 central and eastern European countries that joined the Union after May 2004. The latter typically had no specified period of data exclusivity, prior to this. While more than half the EU would have seen an enhancement in the standard period of regulatory protection, most innovative medicines – even nationally authorised – would have been granted 10 years protection rather than 6 years.

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The interviews and surveys revealed that adjustment costs for businesses[208] mainly related to the need to invest in upgraded IT systems. Based on the data received in the survey, the estimated one-off adjustment costs are at €250 million[209].

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[205] 167 out of 173 industry respondents open public consultation considered the current data and market protection period the most important incentives for innovation.

[206] Adamini et al., 2009

[207] The other 2/3 has a longer protection than 10 or 11 years, thanks to patent and SPC protection, or orphan market exclusivity.

[208] (one off) adjustment costs relate to the changes that companies had to make in order to provide the information for the additional inspectiongs introduced with the 2004 revision.

[209] Five businesses estimated their one-off costs, which ranged from €25,000 to €15m, or 0.1-1% of annual sales. The median figure was around 0.5%. Applying this 0.5% to the EU pharma industry output in 2005 (c.

Industry also incurred ongoing additional administrative costs associated with several new measures, including, for example, the expansion in the scope of the centralised procedure[210]. The biggest additional costs however related to the post-market authorisation phase, with substantial additional reporting introduced to strengthen pharmacovigilance. Industry respondents were not able to provide specific estimates for these individual elements though. For originators, the additional costs amounted to ca. 5-10% increase in the overall companies' regulatory costs. For the generics industry, the greater detail in the regulatory dossier increased the costs associated with variations to marketing authorisations. The major drivers of the ongoing costs for the distribution industry are related to the need to control, record, and validate all the elements in storage and distribution systems. These ongoing additional costs are estimated at €200m a year or €3bn over 15 years in current prices. Adjusting this for inflation would suggest a total adjustment cost of €2bn-€2.3bn. No significant, quantifiable indirect costs for industry have been identified.

As regards benefits, there were efficiency gains for companies in the guise of faster and more consistent assessment procedures (through the CP) and increased harmonisation of the decentralised procedures. For industry, however, the most significant efficiency gain relates to the withdrawal of the obligation to renew marketing authorisations every five years. The overall estimated amount of savings is around €300m-€375m over the past 15 years.

The abolition of the 5-year renewal of marketing authorisations led to an estimated cost reduction of €23m per year, covering the MAs authorised via the centralised procedure and nationally authorised. This has resulted in an estimated reduction of around 150 renewals of EU marketing authorisations annually over the period, and 1 350 national renewals. The stakeholder consultation confirmed that these changes have benefited the generics industry in particular. This has resulted in a saving of around €6.8m p.a. in fees and staff costs for the 150 renewals of Union marketing authorisations, and around €16.2m for products authorised by Member States, where the dossiers were less complex and renewal fees are lower.

There are also small cost savings for businesses, due to faster approval procedures, through the expansion of the centralised procedure and the harmonisation of decentralised procedures (DCP). Based on the average number of new applications these savings are estimated at €40m per year across the period, with 90% of those savings being realised by the generics industry (c. €36m per year).

The revision of the legislation might have encouraged and rewarded an increase in R&D, through the extension of the regulatory protection period across all Member States, the expansion of scientific advice, the additional data protection for new indications or the introduction of new assessment procedures designed to keep pace with the evolution in medical science. Feedback from stakeholders suggests that these multifaceted changes would likely have been lost in a broader set of market pressures affecting the global research-intensive pharmaceutical industry.

€150bn according to EFPIA statistics), we arrive at an estimated gross cost of around €750m. There would have been a benefit to companies from implementing these new IT systems, and as such we have assigned a part and not all those costs to the 2004 revision. We have no feedback as to the appropriate fraction, so we have assumed one third, or €250m, as a conservative estimate of the one-off costs for EU industry adjusting to the requirements of the legislation.

[210] The revisions also included changes to the submission documents primarily the introduction of the environmental risk assessment (ERA), and the need to improve the readability of the content of the package leaflet and label, requiring greater detail on manufacturing value chains and sites.

EU statistics[211] broadly mirror the trends in the statistics for the US and other competitor regions, with no evident discontinuities in trends in the years following the implementation of the 2004 revision. The exception is biosimilar medicines, where the EU regulatory system's early response has underpinned a comparative advantage. Data show that the EU accounted for around 70% of the world's biosimilar medicine authorisations from 2006 to 2010. This 5-year period accounted for the largest share of authorisations (30%), albeit India and China have registered stronger growth and have bigger pipelines[212].

In summary, it is estimated that the overall costs of the revisions to the EU pharmaceutical industry amounts to €1bn-€1.3bn. While this is a significant sum viewed in isolation, it amounts to around 0.5% of the EU industry's c. €200bn annual economic output and less than 0.05% of the total output over the 15-year period since 2004[213].

Public authorities

The European Medicines Agency

The 2004 revision led to a substantial increase in the work of the EMA, related to the expansion in the scope of the centralised authorisation procedure, an intensification of the provision of scientific advice and greater support for a wider range of coordination and development activities with respect to the regulatory network and international cooperation. The Agency's annual expenditure increased from €96m in 2004 to €266m in 2014, reflecting in part the further enlargement of the EU (10 countries joined on 1 May 2004) and the incorporation of these countries' national competent authorities within the EMA structures, and the intensification and transfer of authorisation activities from Member States[214].

The EMA annual budget show steady year-on-year growth across the 10 years to 2014 and beyond[215]. The distribution of activities has remained broadly stable over time, split 35% on staff costs, 25% on buildings and 40% on operations. Operational expenditure (mainly consisting of expenditure for meetings (c. 4%) and evaluations [c. 35%]) for EMA increased from €39m in 2004[216] to €168m in 2020[217], while staff expenditure increased from €32m to €115m in the same period. Both types of expenditure rose much faster than inflation in these years. The increase in real terms was thus around €190m in the period 2004-2020.

This increase may be partly, attributed to the 2004 revision. In the absence of these additional EMA-led procedures, businesses would have continued to make use of national procedures. This means that the expenditure for NCA-led authorisations are lower due to expansion of the centralised procedure. It is assumed that these national savings largely mirror the extra costs for the EMA. There may be economies of scale, however, the amount to which these Member State savings and EU costs differ proved difficult to assess, as the data collection has not resulted in clear indications from stakeholders about either the savings or the costs. Given the intensification of support and coordination that accompanied the transfer of activities from the national regulators to the EMA, it is estimated that around 20-25%, or €40m-€50m, of the real-terms increase in EMA's expenditure is related to the 2004 revision. Given the substantial increase in EMA's costs over time, and the need to

[211] E.g. BERD, medicines pipeline.
[212] Troein et al., 2021
[213] EFPIA & PWC, 2019
[214] Increased activities due to the expansion of scope of the centralised procedure, new specialised frameworks on paediatric medicines and ATMPs, as well as further responsibilities on pharmacovigilance.
[215] European Medicines Agency, n.d.-b
[216] European Medicines Agency, 2005
[217] Samassa, 2021

make assumptions about attributable impacts, an average annual additional cost in the range: €2.5m-€3.1m has been put forward.

National authorities

Most NCAs provide resources to the EMA through the release of staff to work within its main committees and working parties, supporting both the assessment of applications and post-authorisation activities (e.g. variations, renewals, translations, etc.). The expansion in the scope of the work of the EMA has resulted in a reduction in activities relating to national authorisations and a switch of the work in support centralised procedures.

Only two NCAs[218] attempted to quantify the changes to their costs due to the 2004 revisions. Several other NCAs reported increases in national costs relating to the expansion of centralised activities in general and in particular the additional enforcement obligations due to the strengthened pharmacovigilance system, however, these stakeholders were not able to quantify those additional costs. Some public authorities and industry representatives[219] are of the view that they are not adequately remunerated for the services provided to the EMA. A revision of the EMA fee framework is currently ongoing and as part of it, NCAs costs are being taken into account to calculate revised, cost based fees and remuneration amounts.

Feedback from stakeholders overall, revealed a positive balance of opinion: the costs of the revisions are judged to have been proportionate to the benefits. The overall positive opinion as to the cost-effectiveness of the legislative changes, looks different across stakeholders. Industry and public authorities are strongly positive on the overall balance of costs and public health benefits, whereas health systems and – in particular – patient groups are slightly negative overall. The latter consider the legislation has been strongly beneficial to industry, with the revision offering valuable incentives that have supported investment in innovative medicines but have increased prices for those products. They are very much less positive about the balance of costs and benefits from the patient's perspective, expressing concerns about affordability, uneven access, unmet medical need, and medicines shortages. For this group, the perceived health impact is relatively small as compared with the (indirect) costs of the 2004 revision and the substantial number of remaining challenges.

4.1.2.3 Simplification and burden reduction

The preceding paragraphs have detailed three areas of simplification and burden reduction that have been achieved following the implementation of the 2004 revision:

- Cost savings for industry, especially the generics industry, due to the harmonisation and streamlining of procedures associated with the introduction of the DCP and the substantial reduction in the use of the MRP;

- Cost savings for industry, especially the generics industry, due to the switch to – as a general rule – a single renewal of a MA 5 years after the original authorisation, eliminating the need for further renewals at 5-yearly cycles; and

- Cost savings for NCAs due to the streamlining and harmonisation of national authorisation procedures (switch to DCP away from MRP).

[218] Out of twenty-seven survey replies from public authorities.

[219] Views collected from six public authorities in interviews (out of forty-eight) and from three industry represntatives in survey responses (out of one-hundred-thirteen).

Recognising the results achieved, opportunities remain for further reductions of administrative burden, e.g. streamlining of changes to marketing authorisation (variations)[220] which was also mentioned by industry and medicines authorities in stakeholder consultations. The stakeholder consultations revealed widespread concerns across stakeholders from industry and regulators over the under-exploitation of digitisation within the EU medicines regulatory system and the related problem of duplicative activities there may be areas where further harmonisation and digitisation of regulatory processes could deliver savings.

In carrying out the evaluation and the analysis of costs and benefits, elements of the general pharmaceutical legislation that posed an administrative burden or were overly complex have been identified.

The 2004 revision introduced new measures, designed to improve the **effectiveness of the regulatory system**, that brought additional costs for some stakeholder groups. From the consultations and interviews, the following elements were identified as the main sources of additional costs:

- Changes to documentation requirements, including environmental risk assessments;
- Increased transparency and harmonisation of key documents, i.e. publication of European public assessment reports (EPARs), summary of product information (SmPCs) and package leaflet;
- Harmonised application of good manufacturing practice (GMP) for active substances;
- Improved pharmacovigilance by more frequent submission of periodic safety update reports (PSURs); and
- Reinforcement of inspections and increased coordination by introducing new tools (EudraGMDP).

For **industry**, the major administrative burden relates to the additional post-market authorisation procedures that have to be followed to support a more robust pharmacovigilance system.

For **public authorities**, the major additional costs were associated with the expansion in the scope of the centralised procedure and the general intensification of the work of the EMA committees. This however is largely driven by increasing applications. There have also been challenges with the growing numbers of advanced therapy medicines and more complex products that require relatively greater scientific effort to review and often entail assessments and advice from multiple committees.

4.1.2.4 The costs of partially meeting or not meeting some of the objectives

The 2004 revision has achieved its objectives to a large extent and as such there have been no substantial costs incurred by any stakeholder groups associated with a failed or partially achieved objective.

There are challenges around access and affordability in the broadest sense, where the 2004 revision did little to improve the effectiveness of the general pharmaceutical legislation in ensuring access to medicines for all. While it was not a specific objective of the previous revisions, there are widespread concerns that medicines shortages have become a bigger

[220] COM(2021)497 final

problem over time. Shortages were seen as a large cost to public health and for day-to-day operations. Pharmacists in particular argued that the legislation lacks flexibility to allow them to handle shortages, which creates inefficiencies. It was estimated by some interviewees that pharmacists spent 6 hours every week to deal with medicine shortages, though the average in Portugal can be as high as one day per week spent on this task[221].

For public authorities and civil society organisations, the high price of medicines arising from what they perceive to be the misuse/abuse of incentives was cited as a cost to healthcare systems, in particular for small countries.

4.2 How did the EU intervention make a difference?

Evidence from literature and stakeholder consultations suggest that the objectives could not reasonably be better achieved at national level and that the EU is the appropriate level of intervention. The general pharmaceutical legislation has brought value in ensuring the quality, safety and efficacy of medicines and the functioning of the single market through common principles and regulatory approach, harmonised rules and requirements for the authorisation fo medicines[222].

Higher availability of medicines leads to better access for patients throughout the EU. It enables more competition both among innovative medicines and generic and biosimilar competitors after protection expiry. Patients thus benefit from safe, effective medicines of good quality and from higher availability of medicines across the EU (i.e. more medicines authorised irrespective of the authorisation procedure). The centralised procedure and its expanded scope have increased the availability of innovative medicines, in particular for smaller Member States[223].

Coordinated actions at EU level have benefitted industry as well. The common principles, harmonisation, centralised or coordinated assessments, authorisations and mutual recognition between Member States have led to easier interactions with medicines authorities as well as easier and faster authorisation of medicines. As an example, the decentralised procedure allows authorisation in several Member States through the same procedure without requiring a national marketing authorisation to rely upon saving at least 180 days. Stakeholder groups, including industry and public authorities, highlighted the added value of EU-level coordination and cooperation to develop best practices. The increased cooperation between Member States and between public authorities as well as the successful collaboration of EMA with NCAs has led to the optimisation of resource use for industry and medicines authorities[224].

The EU general pharmaceutical legislation provides a simplified framework for medicines that is easier to navigate in and less costly for industry than 27 national frameworks. Some industry stakeholders, in particular SMEs and generic companies, highlighted the added value of also having the decentralised procedure and mutual recognition procedure in

[221] Technopolis study 2022b.

[222] E.g. documentation requirements and assessment criteria, specific authorisation procedures, harmonised requirements for authorisation of manufacturers and distributors and for manufacturing and distribution, harmonised requirements for active substances and their manufacturing and mutual recognition of inspection outcomes.

[223] Smaller Member States would not have the resources or expertise to assess all the innovative medcines authorised through the centralised procedure.

[224] The pan-EU SPOR (Substance, Product, Organisation and Referential) data management serices was mentioned as an example of a valuable source for promoting exchange of medicinal product information across Member States.

addition to the centralised procedure allowing flexibility to get approval of medicines at national level.

For medicines authorities, the evidence shows there is EU added value in the reduction of duplication of assessments and inspections through mutual recognition and coordinated procedures[225]. The centralised procedure also allows medicines authorities to rely on the collective expertise of the Network, which is particularly important in very specialised or new fields with few available experts[226].

Among stakeholders, there was consensus that the legislation has struck the right balance between action at EU level and national action. In the targeted survey, stakeholders indicated this to be the case from a moderate to large extent (Table 4). Respondents considered that in the absence of coordinated action at EU level, it would have been difficult for Member States to put in place appropriate harmonised measures. Industry stakeholders also highlighted the EU as a global leader in establishing the first science-based regulatory framework for authorisation of high-quality, safe and effective biosimilar medicines.

Please provide your view on the balance of EU level actions and national actions arising from the legislation.	All stakeholders average score	Individual stakeholders average score					Agreement between stakeholders
		Industry	Civil Society	Public Authorities	Academic	Health Services	
To what extent has the legislation struck the right balance between action at EU level and national level?	3.3	3.2	2.8	3.37	3.7	3.3	High
To what extent has the EU intervention in the context of the COVID crisis struck the right balance between action related to the legislation at EU level and national level?	3.8	4.22	3.7	3.6	3.9	3.6	High
In the absence of EU level action, to what extent would member states have had the ability to put in place appropriate measures?	2.4	2.3	1.75	2.7	3.0	2.5	High

Table 4: Overview for the evaluation criterion 'EU added value' summarising the overall average view for all stakeholders, per stakeholder group, and the level of agreement across the stakeholder groups.
Source: Targeted survey data (Technopolis study, 2022)

Concerning **proportionality and subsidiarity** it can be argued that EU actions in the pharmaceutical area do no go beyond what is necessary to achieve the objectives of the Treaty[227]. The EU sets a general regulatory framework, allowing Member States to be involved in the assessment of innovative medicines for the EU, to authorise medicines for their own territory – through the non-centralised procedures, to be responsible for manufacturers and distributors based in their own territory and to be involved in the pharmacovigilance of medicines marketed in their territory. At the same time, the general pharmaceutical legislation fully respects the Member States' exclusive competence in the organisationof health services, including pricing and reimbursement of medicines.

During consultation activities (incl. interviews) stakeholders commonly cited the creation of the EMA as one of the biggest achievements of the legislation. Stakeholders regarded **EMA**

[225] OECD (2021), International Regulatory Co-operation, OECD Best Practice Principles for Regulatory Policy, OECD Publishing, Paris, https://doi.org/10.1787/5b28b589-en.
[226] Idem.
[227] Legislation regulating medicines is based on Articles 114 and 168(4)(c) of the Treaty on the Functioning of the European Union (TFEU). As a shared competence with Members States and in line with the principle of subsidiarity, Article 168(4)(c) of the Treaty allows the Union to set measures establishing high standards of quality and safety for medicinal products. The authorisation of medicines is fully harmonised at EU level. EU action takes advantage of the single market (Article 114) to achieve a stronger impact as regards access to safe, effective and affordable medicines, as well as the security of supply across the EU.

as a key actor in the unification and coordination of the regulatory system across the EU, which provides a valuable exchange of experience and access to a wide range of scientific and technical expertise that would not be available in one country or region alone. Thus, **the pooling and coordination of scientific resources under a common set of rules and practices** has helped foster a common understanding across Member States of high standards of medicines evaluation and approval and handling of safety concerns consistently. Stakeholders frequently pointed out that since the establishment of EMA, **transparency on how the regulatory system works and decisions are made has greatly improved** – thus building trust and consistency across the EU regulatory system. EMA publications of European public assessment reports (EPARs) and guidance documents were cited as a reason for the increased flow of transparent information. Industry stakeholders highlighted EMA's clear guidance on pre-authorisation and post-authorisation procedures for medicines as particularly valuable for facilitating regulatory processes. Moreover, EPARs have had wider impact in facilitating approval of medicines outside the EU (e.g. Africa, Asia, South America).

4.2.1 Added value of the EU intervention in the context of the COVID-19 crisis

During the COVID-19 crisis, EU action proved to be of particularly high added value. Throughout the consultations conducted, all stakeholders highlighted the right balance between the action at EU and Member States' level (Table 4).

There is consensus that EU level action **enabled quicker and concerted action** compared to what Member States would have been able to achieve independently. Stakeholders commonly cited[228] this was made possible because of **regulatory flexibilities and optimisations** enabling resources, capacities and expertise to be rapidly mobilised across EU. For example, the Commission granted a temporary derogation from certain rules for clinical trials of medicines involving GMOs, in particular the environmental risk assessment[229], amended the variation regulation to facilitate the adaptation of COVID-19 vaccines[230] and allowed labelling flexibilities, remote processes for source data verification, audits and monitoring[231]. These measures helped to accelerate the development and approval of vaccines and to coordinate equitable access to vaccines in all Member States.

The pandemic provided a good example of how the legislation enabled Member States to **work together, learn from each other and coordinate efforts**. For example, public authorities cited multinational work sharing activities such as assessments of COVID-19 vaccines as an EU value add – especially for less experienced Member States.

Stakeholders' feedback, and especially interviewed academic researchers, highlighted that the creation of an an emergency task force at EMA, EU-wide adoption of accelerated assessments and rolling review played an important role in fast approval and access to medicinal products for COVID-19. These **EU-level mechanisms prevented duplication of**

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[228] Based on the Evaluation Workshop and Interviews, 50% of healthcare professionals (n = 8), one civil society representative (total interviewed = 16), 42 % of industry representatives (total interviewed = 60) and 21% of academics (total interviewed = 14).

[229] Regulation (EU) 2020/1043.

[230] Commission Delegated Regulation (EU) 2021/756 of 24 March 2021 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.

[231] Notice to Stakeholders - Questions and Qnswers on regulatory expectations for medicinal products for human use during the covid-19 pandemic, Brussels, 30 September 2021 https://ec.europa.eu/health/system/files/2021-09/guidance_regulatory_covid19_en_0.pdf

efforts and enabled timely availability of the right expertise, which particularly benefited smaller Member States[232].

Table 5 shows that EU authorisation of COVID-19 vaccines took place only a few weeks after authorisation in the USA and earlier than in Japan.

COVID-19 vaccine name	EU (conditional marketing authorisation)	USA (Emergency Use Authorisation)	Japan (Special Approval for Emergency)
Comirnaty	21/12/2020	11/12/2020	14/02/2021
Spikevax	06/01/2021	19/12/2020	21/05/2021
Vaxzevria	29/01/2021	n/a	21/05/2021
Jcovden	11/03/2021	27/02/2021	n/a
Nuvaxovid	20/12/2021	n/a	18/04/2021

Table 5: Comparison of authorisation dates for COVID-19 vaccines in the EU, USA and Japan.
Source: COVID-19 Track Vaccines (COVID19 Vaccine Tracker, n.d.) and EMA (European Medicines Agency, n.d.-c).

Civil society stakeholders mentioned that EMA played a central role in **supporting Member States to communicate the risks and benefits of vaccines** through various activities such as public stakeholder meetings, media engagement activities and issuing regular pandemic safety updates with accompanying visuals to explain regulatory concepts[233]. This helped build public confidence in COVID-19 vaccines and uptake by European citizens.

There was consensus across stakeholders that EU-level cooperation was very important for **quick coordinated action to ensure medicines supply chains continued to function** during the pandemic. Health services highlighted the creation of the EU Executive Steering Group on Shortages of Medicines as an important enabler for the **increased collaboration and data sharing** across Member States to prevent and mitigate supply shortages[234] Furthermore, EU-level guidelines on the optimal and rational supply of medicines to avoid shortages during the COVID-19 outbreak[235] and the reinforcement of EMA's mandate[236] were cited as being valuable to Member States. These guidelines helped promote cooperation between Member States, thus preventing stockpiling and encouraging sharing of essential medicines during the pandemic. Moreover, the guidelines to establish 'green lanes' were seen[237] as instrumental in facilitating the cooperation between Member States to order to prevent shortages across the EU.

[232] For example, industry highlighted the EU added value of leveraging and consolidating scientific expertise across EU to provide rapid interactive scientific advice. This promoted use of best methods and study designs for developing COVID-19 medicinal products. Thus, ensuring the development of high-quality, safe, and effective vaccines for European citizens.
[233] Cavaleri et al., 2021
[234] This steering group, along with other ad hoc structures and processes established during the pandemic, has been codified in Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices, PE/76/2021/REV/1, OJ L 20, 31.1.2022, p. 1
[235] Communication from the Commission Guidelines on the optimal and rational supply of medicines to avoid shortages during the COVID-19 outbreak 2020/C 116 I/01, OJ C, C/116, 08.04.2020, p. 1, CELEX: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020XC0408(03))
[236] Regulation (EU) 2022/123
[237] Based on interviews, views expressed by one civil society representative and one healthcare professional.

4.3 Is the intervention still relevant?

The general pharmaceutical legislation has delivered positively on the four main objectives of the 2004 revision, as the analysis shows in section 4.1. Despite the progress made, these objectives remain highly relevant today.

4.3.1 Ensure quality, safety and efficacy of medicines

The EU has a recognised robust regulatory framework to authorise safe, efficacious medicines of high quality. The framework has responded well to the need to incentivise development of **innovative medicines.** However, it has been less relevant to ensure development and authorisation of medicines addressing unmet medical needs and antimicrobial resistance (see Section 4.1.1.4) [238].

Scientific and technological developments challenge the current framework with new products combining medicines with technologies regulated under other frameworks, e.g. medical devices with articifical intelligence, creating uncertainty about the applicable framework. Another area where the current framework is not adapted to concerns the new platform technologies[239]. Stakeholders from industry, civil society, healthcare professionals and public authorities are therefore calling for adaptations.

Despite the introduction in 2004 of a requirement for environmental risk assessment in the application for marketing authorisation, the environmental impact of medicines continues to be a relevant concern in the EU, as residues of medicines are detected in the environment[240]. According to the public authorities the relevance of the environmental risk assessment is low to moderate in minimising the environmental impacts. The general pharmaceutical legislation cannot stand alone in this respect and the environmental impact has to be addressed also through measures on waste and chemicals.

4.3.2 Enable access to medicines

While the EU regulatory framework has responded well to the need to make medicines available in the Member States through a robust and flexible authorisation system, the general pharmaceutical legislation has limitations to ensure that authorised medicines are launched in the Member States and thus in ensuring equitable access to all citizens across the EU. Accelerated assessment, conditional marketing authorisation and compassionate use programmes contribute to earlier access to medicines. However, external factors such as national decisions on pricing and reimbursement and market size, are of higher relevance when it comes to access to medicines.

An important aspect in terms of access to medicines and on which political focus[241] has increased in recent years is the **affordability of medicines**. The EU pharmaceutical

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[238] E.g. there are only currently 43 antimicrobials in development and in the evaluation period 25 new antimicrobials have been authorised in the EU, cf. case study 1 on AMR (Technopolis study report 2022).

[239] When a certain process /method is used to manufacture specific individualised treatments, i.e. adjustments to the medicine are made based on the characteristics of the patient or the causing pathogen.

[240] Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee European Union Strategic Approach to Pharmaceuticals in the Environment COM/2019/128 final.

[241] As demonstrated by the Council conclusions on strengthening the balance in the pharmaceutical systems in the European Union and its Member States (OJ C, C/269, 23.07.2016, p. 31, CELEX: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52016XG0723(03)).

legislation has limitations in delivering on affordability of medicines, as its scope is the authorisation of medicines. Factors outside EU competence, such as a Member State's health budget and negotiating power, have greater influence. Still, the legislation impacts on costs of development, authorisation, manufacture, distribution and supervision of medicines as well as on generic and biosimilar competition and hence on the affordability of medicines. As the analysis shows[242], the 2004 revision reduced some administrative costs. However, overall costs for the pharmaceutical industry and for healthcare systems were not reduced, Although the revision has facilitated competition from generic and biosimilar medicines, leading to cheaper medicines.

In the evaluation period, the evidence shows that the number of shortages has increased and there has been an increased reporting of shortages (see Section 4.1.1.2). The current framework was not specifically designed to mitigate or prevent shortages and rather focuses on notifying supply disruptions; it is thus not surprising that the majority of stakeholders rated the relevance of the legislation in maintaining security of supply of medicines as low.

Stakeholders representing civil society, academia, health services and public authorities find access, affordability and shortages among the areas least addressed by the general pharmaceutical legislation; more than half of the respondants in these stakeholder groups found that the legislation is not at all or slightly relevant in ensuring access to affordable medicines and 80% of health service respondents found that the legislation is not at all or slightly relevant in maintaining security of supply of medicines in the EU.

4.3.3 Ensure the competitive functioning of the EU internal market

The general pharmaceutical legislation is relevant to the functioning of the EU internal market. The full harmonisation of authorisation and post-authorisation requirements, including regulatory protection periods, provides a level-playing field for all actors. It provides measures to ensure competition such as the pathways for market authorisation, including for generic, biosimilar and over-the-counter medicines, though the time of competition from generic or biosimilar medicines is also governed by patent and supplementary protection certificates. Importantly, the actual market launch of products depends on businesses decisions and on national pricing and reimbursement schemes.

4.3.4 Ensure attractiveness in the global context

The 2004 revision further ensured a coherent and attractive regulatory system for developing pharmaceuticals in light of scientific and technological developments and the EU enlargement.

The USA has the largest share of the global market for pharmaceuticals, more than three times the size of the EU market, the second largest. A 2021 comparison of six regulatory agencies - US, EU, Japan, Canada, Switzerland, Australia - found that all new active substances (NAS) authorised by the six agencies are first submitted to the FDA (USA) and on average only a few days later to the EU (with the EU being the second choice jurisdiction)[243]. Submissions to the other agencies occurred 63-150 days later on average compared to the US.

[242] See Annex 13.
[243] CIRS, 2021

The **time needed for the assessment of the marketing authorisation application** is another important factor for regulatory attractiveness. Figure 16 presents additional results[244]. Data from 2011 to 2020 shows that the FDA had the shortest median approval time overall (273 days in the first five year period falling to 242 in 2026-2020). In 2020, the median approval time in the EU was 182 days greater than in the US. These results suggest that shorter approval times may result from more NAS going through expedited processes in the US than in the EU.

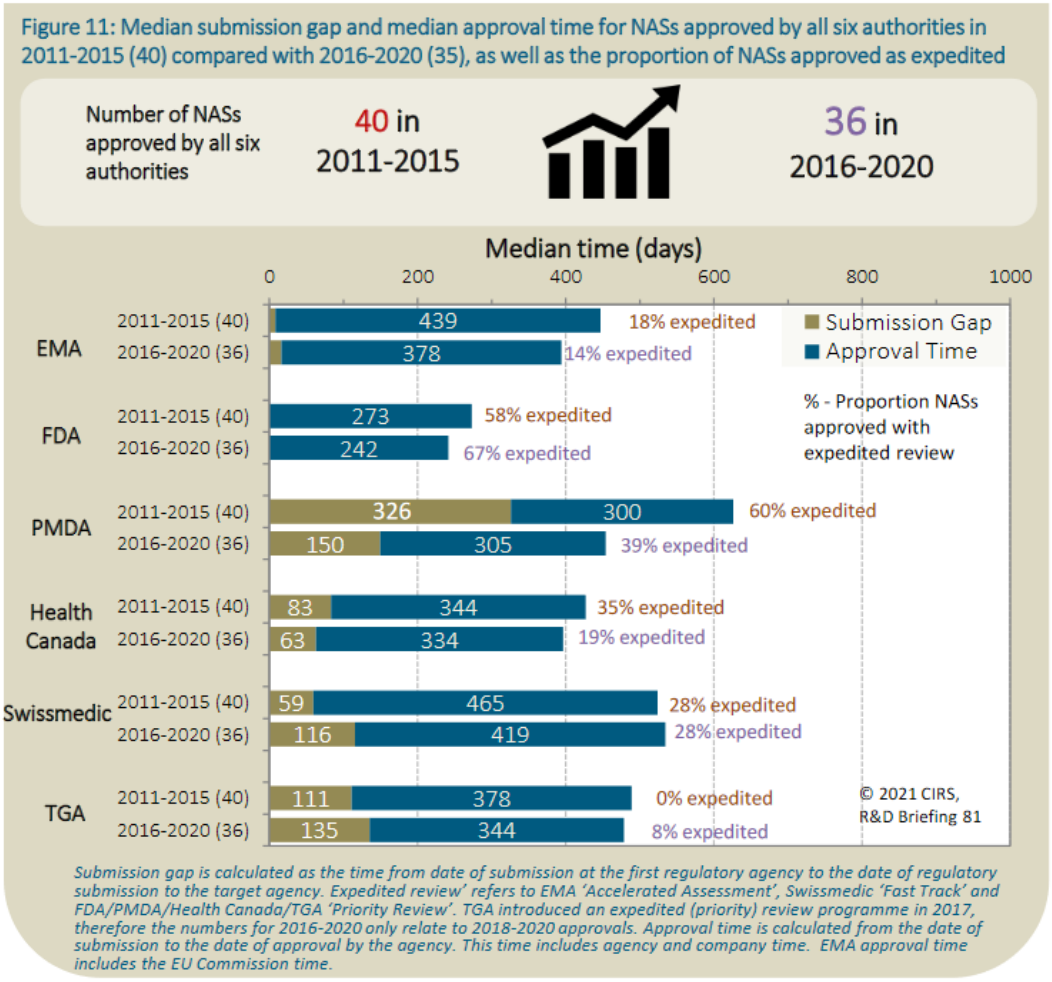

Figure 16**:** New active substance median approval time for six regulatory authorities in 2011-2020

Source: Centre for Innovation in Regulatory Science annual analysis of new active substance approvals by the EMA, FDA, the Japan Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, Swissmedic and the Australian Therapeutic Goods Administration (TGA). Approval TMP by the agency. This time includes agency and company time. EMA approval time includes EC time. N1 = median approval time for products approved in 2020; (N2) = median time from submission to the end of scientific assessment for products approved in 2020.

Several industry participants[245] (including those in the EU) in the stakeholder consultations (interviews and survey) confirmed that the FDA is a preferred jurisdiction for developers. This can be due to differing data requirements for filing, greater opportunity for direct

[244] Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time. N1 = median approval time for products approved in 2020; N2 = median time from submission to the end of scientific assessment for products approved in 2020.

[245] Views of nineteen industry representatives (out of the sixty interviewed and the one hundred and thirteen industry replies to the survey).

interaction on scientific advice and need to interact with multiple EMA committees (e.g. up to five bodies[246] for ATMPs targeting rare diseases). In addition, some lack of coordination between the EMA committees CHMP, PDCO, COMP and CAT, has been identified[247].

It was a common view in the consultations that complexities also arise from the links between the general pharmaceutical legislation and other EU legislation. it can make the EU less attractive for developers, in particular for SMEs and companies that are not familiar with the EU system. For example, public authorities and industry interviewees observed that medical devices, clinical trials and medicines are regulated by different regulations and implemented by different competent authorities, making it difficult to coordinate approaches and navigate the system. In Japan and the USA, separate regulations also apply to these areas, but the same competent authority is in charge of them.

The targeted survey showed a high agreement among industry, public authorities and health service stakeholders that the current legislation has provided an attractive and robust authorisation system for medicines[248]. In particular, the centralised assessment system (CP route) allowing developers to access the EU market on the basis of a single marketing authorisation (MA), increases the EU's attractiveness as as market and location for pharmaceutical development and manufacturing. According to industry interviewees, the EU has also been a global leader in setting up a process for licensing biosimilars, which encourages innovation and filing in the EU compared to other jurisdictions. Besides the market size, there are several factors influencing developers' strategies as to when and where they apply for MA. These include the level of regulatory flexibility or specific local epidemiological situations. In terms of **pharmaceutical R&D**, the EU has a strong second position globally (after the US), especially together with the UK and Switzerland. The EU's biopharmaceutical industry R&D expenditure has continuously grown in the last decades and only US firms spend more in comparison. Between 2005 and 2019, employment in the EU pharmaceutical industry increased from 636 763 in 2005 to 795 000 (estimated), and employment in pharmaceutical R&D increased from 100 636 to 118 000 (estimated)[249].

Figure 17 presents a time-series analysis of medicines approved in the EU either developed in the EU or elsewhere. It suggests that the legislation and the 2004 revision had a positive impact on the relative attractiveness of the EU. A trend analysis on the number of EU approved medicines - novel, new molecular entities; and all products, including biosimilars and other generics - was carried out to understand whether the reformed regulatory environment in the EU following the implementation of the 2004 revisions had provided an advantage to pharmaceutical companies based in the EU as compared to their competitors located elsewhere and looking to sell into Europe.

The analysis[250] did not support the hypothesis that the 2004 revision (expansion of the CP, greater harmonisation of processes and procedures, etc.) might have given advantage and

[246] COMP, CAT, SAWP, CHMP and PRAC.
[247] SWD(2020) 163 final.
[248] See Appendix B: Targeted survey overview - areas where the current legislation has been effective.
[249] EFPIA. (2021). The Pharmaceutical Industry in Figures. www.efpia.eu. For pharmaceutical industry data includes Iceland (since 2017), Turkey (since 2011), Croatia and Lithuania (since 2010), Bulgaria, Estonia and Hungary (since 2009), Czech Republic (since 2008), Cyprus (since 2007), Latvia, Romania & Slovakia (since 2005), Malta, Poland and Slovenia (since 2004); For pharmaceutical R&D Data includes Iceland (since 2017), Greece & Lithuania (since 2013), Bulgaria and Turkey (since 2012), Poland (since 2010), Czech Republic, Estonia and Hungary (since 2009), Romania (since 2005) and Slovenia (since 2004) Croatia, Cyprus, Latvia, Malta, Serbia, Slovakia: data not available.
[250] See Annex 13.

boost the competitiveness for EU industry in comparison with international competitors. However, the analysis (ran for all competing regions) suggests that any additional burden that may have been introduced by the 2004 revision, such as ERAs and improved pharmacovigilance and manufacturing practices, did not disadvantage EU-based pharmaceutical companies when compared with their international competitors, either within the EU or when exporting to other regions. The stakeholder consultations with industry suggest that overall, the various revisions resulted in a net increase total regulatory costs, estimated at 5-10% of regulatory costs. The analysis found a small increase in the average number of annual approvals pre and post implementation for EU origin medicines and medicines that originated with businesses located outside the EU. This does not rule out the possibility that the regulatory environment improved, to the benefit of both EU and non-EU industry.

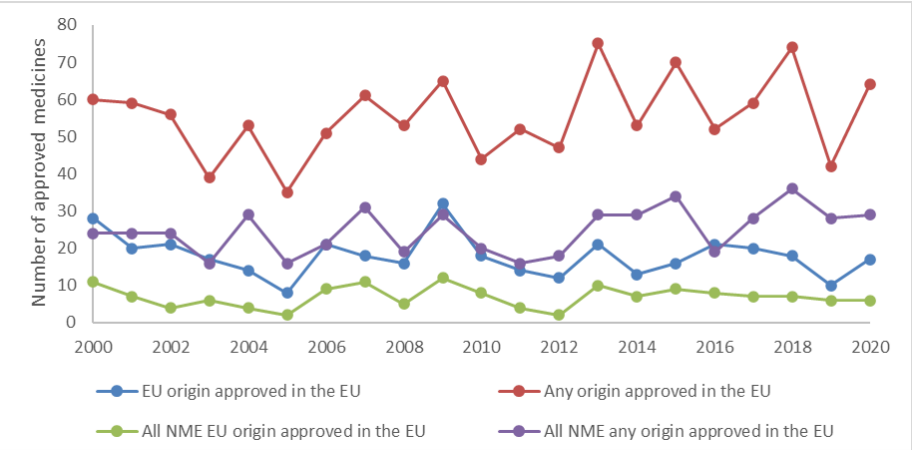

Figure 17: EU-origin medicines and any-origin medicines approved in the EU, split by all medicinal products and new active substances only
Source: Pharmaprojects, 2000-2020, from Pharma Intelligence study team analysis.

The landscape for **pharmaceutical manufacturing** has also changed in last decades. Production of less complex products, such as small chemical molecules and traditional vaccines, has moved to the Asian continent, in particular to China and India for off-patent medicinal products[251]. In the EU, small and large companies have shifted production focus to more complex, biological products (e.g. cell-based products), which require high-tech infrastructure, skilled work force and sophisticated processes. This has led to some companies offering contract manufacturing services as alternatives to in-house manufacturing and consolidated the EU as an important location for high-tech pharmaceutical manufacturers.

The EU has a large trade surplus in pharmaceutical products and is a leading exporter in developed markets. Between 2010 and 2019, there was a 78% increase in the value of EU27 exports of pharmaceutical products to other EU27 countries and third countries[252]. While the overall figures are positive for the EU, there is no obvious effect of the 2004 revision on the EU pharmaceutical industry's trade data. Other factors such as stable political and business environment, availability of skilled workers and existing infrastructure also play a role in EU's competitiveness, while high manufacturing standards and robust enforcement of good manufacturing practices increase the quality of EU produced medicines, which contributes to investments in manufacturing.

[251] Progenerika, 2020
[252] Guinea & Espés, 2021

The EU's manufacturing capacity for exporting vaccines: COVID-19

The Comirnaty mRNA vaccine is an example of the EU's manufacturing capacity underpinning a global leading role in exporting high-tech vaccines. BioNTech, the German biotechnology company that developed the technology behind Comirnarty, partnered up with Pfizer, headquartered in the US with production facilities in the EU, to advance and scale-up human clinical testing and manufacturing capacity. By March 2021, after receiving conditional marketing authorisation from the Commission in December 2020[253], the BioNTech/Pfizer collaboration had already produced over 70 million vaccine doses in Germany and Belgium, positioning the EU in the second place in manufacturing of COVID-19 mRNA vaccines, only behind the US.

Through the export authorisation mechanism, the EU became the global leader in vaccines exports in 2021, supplying to the UK, Canada, Mexico, Japan, and many other countries. As of March 2022, the EU had nearly 40% of the global share of vaccine exports, as outlined below.

Table 6 - Total number of vaccine doses exported by producing economy

Producing economy	Number of doses (million)	Share of world exports	Exports as share of total supply
European Union	2,276.20	39.70%	64.80%
China	1,869.10	32.60%	32.10%
United States of America	859.1	15%	58.40%
Korea, Republic of	235.8	4.10%	91.10%
India	134.7	2.30%	5.70%
Russian Federation	100.2	1.70%	35.80%
South Africa	91.2	1.60%	87.00%
Japan	67	1.20%	99.80%
Other	105.9	1.80%	

Source: World Trade Organization. WTO-IMF Covid-19 Vaccine Trade Tracker.

Alongside measures to simulate innovation in medicines and to harmonise requirements and coordinate assessments within the EU regulatory system, the **simplification and reduction of administrative burden** linked to the authorisation and monitoring of medicines and companies in the EU contributes to the attractiveness of this framework in a global context. Although authorisations were granted in the EU after those in US, many innovative medicines were authorised[254], regardless of where they were developed. In this respect, the general pharmaceutical legislation remains relevant, though external factors, such as the global development of medicines or market size play an equally important role in the attractiveness of the EU as a medicines market.

[253] Product information for Comirnaty, Union Register of medicinal products for human use https://ec.europa.eu/health/documents/community-register/html/h1528.htm.

[254] Around 60-80 medicines are authorised through the centralised procedure every year, see section 4.1.1.1, Figure 1, though not all of these are innovative; in 2020, positive EMA opinion was given for 39 new active substances, 22 for medicines for children and 3 for ATMPs, cf. EMA Annual Report 2020.

4.3.5 Megatrends

It has almost been 20 years since the last comprehensive revision of the general pharmaceutical legislation and its provisions are not future-proofed. The 14 megatrends identified by the EC Joint Research Centre[255] should be considered in terms of their impacts on the legislation. Out of these 14 megatrends, four trends are likely to strongly shape the future of health in Europe and thus to impact all concerned stakeholders.

Megatrend 1 and 4: Shifting health challenges, climate change and environmental degradation. This overarching topic includes trends ranging from the digitalisation of society to demographic changes or environmental challenges. Even though science and technology enable us to live longer, the rise of new diseases due to anthropogenic causes and demographic changes will create a new burden for public health. The COVID-19 crisis best pictures this situation. The impact of changing climate patterns on public health is another example. It is therefore crucial to create a more agile and flexible legislative framework ready to adapt to future challenges and to simultaneously maintain its objectives in terms of research and innovation.

Megatrend 2: Accelerating technological change and hyperconnectivity. Increasing technological developments are changing the way we live, but also the nature and speed of new discoveries. In the field of public health, there are new ways to generate health data at individual level to develop more personalised treatments based on patients' needs and genetic profile. Technological changes are fundamental in the area of research and innovation to maintain scientific developments, especially in areas of unmet need. There is also great potential in connecting datasets and using advanced analytics. Administrative burden and inefficient procedures could be improved through the use of technological tools.

Megatrend 3: Increasing demographic imbalances. The global population is growing and age structures becoming more imbalanced. Especially in Europe, population is ageing and birth rates are declining. This shift recalls the fundamental need to guarantee a high level of health protection for the people of Europe, particularly through quick access to innovative, safe and efficacious products and increased market surveillance.

5 WHAT ARE THE CONCLUSIONS AND LESSONS LEARNED?

5.1 Conclusions

New, innovative medicines are essential for providing new opportunities to treat or prevent diseases. The EU pharmaceutical legislation has established a framework that encourages the development of such medicines, while ensuring high standards of quality, safety and efficacy, and enabling the internal market to function smoothly.

The evaluation shows that the general pharmaceutical legislation is a successful EU intervention. It achieved progress on its high level objectives. The needs, problems and the initial objectives of the legislation and of its revision remain relevant.

The EU general pharmaceutical legislation has set up a robust and flexible authorisation system which benefits from harmonised processes through the centralised procedure for innovative medicines requiring pooled European scientific expertise. In parallel, it allowed for the co-existence with decentralised procedures at national level, available for smaller

[255] The Megatrends Hub | Knowledge for policy (europa.eu).

companies and generic companies with distinct business models. In addition, post-marketing monitoring and reinforced inspections of manufacturing and distribution created a consistent system along the lifecycle of medicines. The system designed at EU level has allowed for safe, efficacious and high quality medicines.

The system includes a predictable incentives framework (8+2 years of regulatory protection period) that has kept Europe an attractive market for medicine developers and has allowed innovative medicines to be available to the different national health systems. However, innovative medicines may not always be accessible to patients and their benefits may not commensurate with their costs for healthcare systems. In addition, the analysis shows that the protection period directly influences market entry of generic and biosimilar medicines (in cases where no longer protection period apply due to patents), affecting affordability of medicines and Member States' health budgets. The Bolar exemption has allowed quicker generic entry, but since the implementation of the exemption varies, so do the benefits. The creation of an authorisation pathway for biosimilars in Europe before any other jurisdictions, has made Europe a leader in this space, allowing the launch of biosimilar medicines on the EU market and thereby increasing access for patients, choice for health services and providing cost savings for national health system. Yet, there is room for further improving the uptake of biosimilar medicines across Member States.

It is important to note however that the increased number of innovative medicines does not lead to equitable access to those across Member States. The legislation was not able to steer market launch decisions of companies and access to medicines primarily in smaller Member States and those with lower per capita healthcare budgets. Access thus remains a real problem for many across the EU. There are however clear limitiations what the general pharmaceutical legislation can achieve, as companies make commercial decisions on market launch and pricing and reimbursement remains within the remit of the Member States.

The European pharmaceutical industry sector remains second behind the US even though revenues have increased. Similarly, R&D investment has increased in absolute terms but not as fast as in the US or China recently. The US remains the jurisdiction of choice for filing marketing authorisation applications for new active substances but the EU is the second destination for filing and most substances are being authorised in the EU less than 1 year after the FDA.

The legislation is well-framed, internally coherent and has clear EU added value. However, its coherence with other legislation has become a challenge in a fast-changing EU regulatory landscape. Emergence of new technologies and borderline cases (that potentially sit between two or more legislations) cause inconsistencies and uncertainties such as the coverage of GMO requirements, environmental challenges and new manufacturing methods.

Overall efficiency was challenging to assess quantitatively. Most stakeholders were unable to provide quantitative estimates of the costs and benefits associated with the 2004 revision. Where available, data is scarce and much of the relevant data is not available in literature. There were cost savings associated with the harmonisation and streamling of procedures (for industry and NCAs) and through switching to a single MA renewal after 5 years. Age-standardised mortality rates have improved in all EU countries in the period since 2007[256], albeit with significant variations in improvements across Member States and the regulatory system will have been an important contributor, by driving innovation in new medicines as well as ensuring the safety, quality and efficacy of medicines. Based on additional products coming on the market and EU sales, it was estimated that the 2004 revision were associated

[256] Santos et al., 2020

with an additional 170 000-210 000 QALYs across the evaluation period (based on a median ICER of €33 000 / QALY) and total additional public health benefits monetised at €4.8bn-€17.2bn. With the upper bound of additional costs estimated at €1.8bn, the 2004 revisions have delivered a positive overall social return.

5.2 Lessons learned

The objectives of the general pharmaceutical legislation remain valid. As shown in the analysis, the last review of the general pharmaceutical framework in 2004 provided an appropriate regulatory framework for ensuring access to high quality, safe and efficacious medicines to all Member States. Furthermore, the introduction of the accelerated assessment procedure and the conditional marketing authorisation procedure facilitated faster authorisation and access to medicines of major public health interest, therapeutic innovation and targeting unmet medical needs.

The evaluation findings indicate that while the legislation has been overall flexible to accommodate innovation, it has not been successful in specific areas. These were related to a lack of adequate incentives for innovation by SMEs, academic/industry collaborations, innovation to address areas of UMN and antimicrobial innovation. The reasons are manifold (e.g. market failure, complexity in disease pathologies, knowledge gaps in molecular and physiological underpinnings of diseases, high risk R&D).

Alongside the initial objectives which remain relevant, new objectives will need to be considered in the legislation and new approaches are needed to address the remaining challenges. There is limited readiness and adaptability of the legislation to respond to technological developments, for example, in new manufacturing methods, and rapidly increasing presence of digitisation in new tools generating (real world evidence) evidence for regulatory decision-making and for the development of medicines.

Continued relevance also involves providing targeted incentives to the development of medicines that respond to high unmet medical needs, for example for therapies against antimicrobial resistant infections. AMR has become an issue of greater public health concern requiring further action. The recognition of the increasingly complex and advanced therapies as medicines within the legislation is also important to ensure continued relevance of the legislation to permit authorisation of those products in a streamlined manner for the benefit of patients.

Not all objectives have been fully met through the 2004 revision of the legislation, notably the aim to ensure equitable access to medicines for patients in all EU Member States has had the least success. Affordability was not among the objectives of the 2004 revision of the general pharmaceutical legislation. Furthermore, pricing and reimbursement decisions are a national competence. However, in the past years, the costs of medicines for health systems continue to rise affecting patient access and country differences in terms of availability of medicines are of great concern. The impact of the new HTA Regulation adopted in 2022 has yet to be seen but it is expected to improve the availability innovative health technologies through joint clinical assessments, joint scientific consultations and voluntary cooperation.

As regards the implementation of the legislation at national level, differences have been noted across Member States in the implementation of Directive 2001/83/EC. Examples include in particular the implementation of the "Bolar" provision, the hospital exemption, the assessments of medicines containing or consisting of genetically-modified organisms (GMOs) and the provisions related to medicines shortages.

Improved coherence with other specialised health legislations is required to remove uncertainty and improve consistency of interpretation. In addition, improved coherence with other wider EU legislations is required to reduce tensions and improve synergies, increasing the likelihood of positive impact in terms of public health, environmental sustainability, digitalisation, etc. This will ensure a systemic fit of the general pharmaceutical legislation in the wider EU policy framework.

Several lessons have been learned from the recent experience of medicine developers and public authorities having acted under the pressure of the ongoing COVID-19 pandemic. It also highlighted factors causing shortages such as over-reliance on one or very few foreign suppliers for some essential APIs. The actions taken during the pandemic have shown that there is room for flexibility to adapt regulatory processes and accelerate product development and authorisation processes, including the use of remote processes for source data verification, virtual audits and monitoring. This would reduce administrative burden for developers and release capacity for regulatory authorities. Collaboration between industry and regulators during the pandemic on the development of COVID-19 vaccines and therapeutics as well as on stocks and shortages demonstrated that different interests can be usefully aligned. EMA has also adapted to respond to the scientific, regulatory and operational challenges which can serve as a blueprint not only for future emergencies but for a more fit for purpose system. It is however noted that EMA and the network of national competent authorities have limited resources and its expertise and capacity need to be expanded in order to progress complex dossiers at pace and keep up global attractiveness, and do so without compromising safety, efficacy and quality of authorised medicines.

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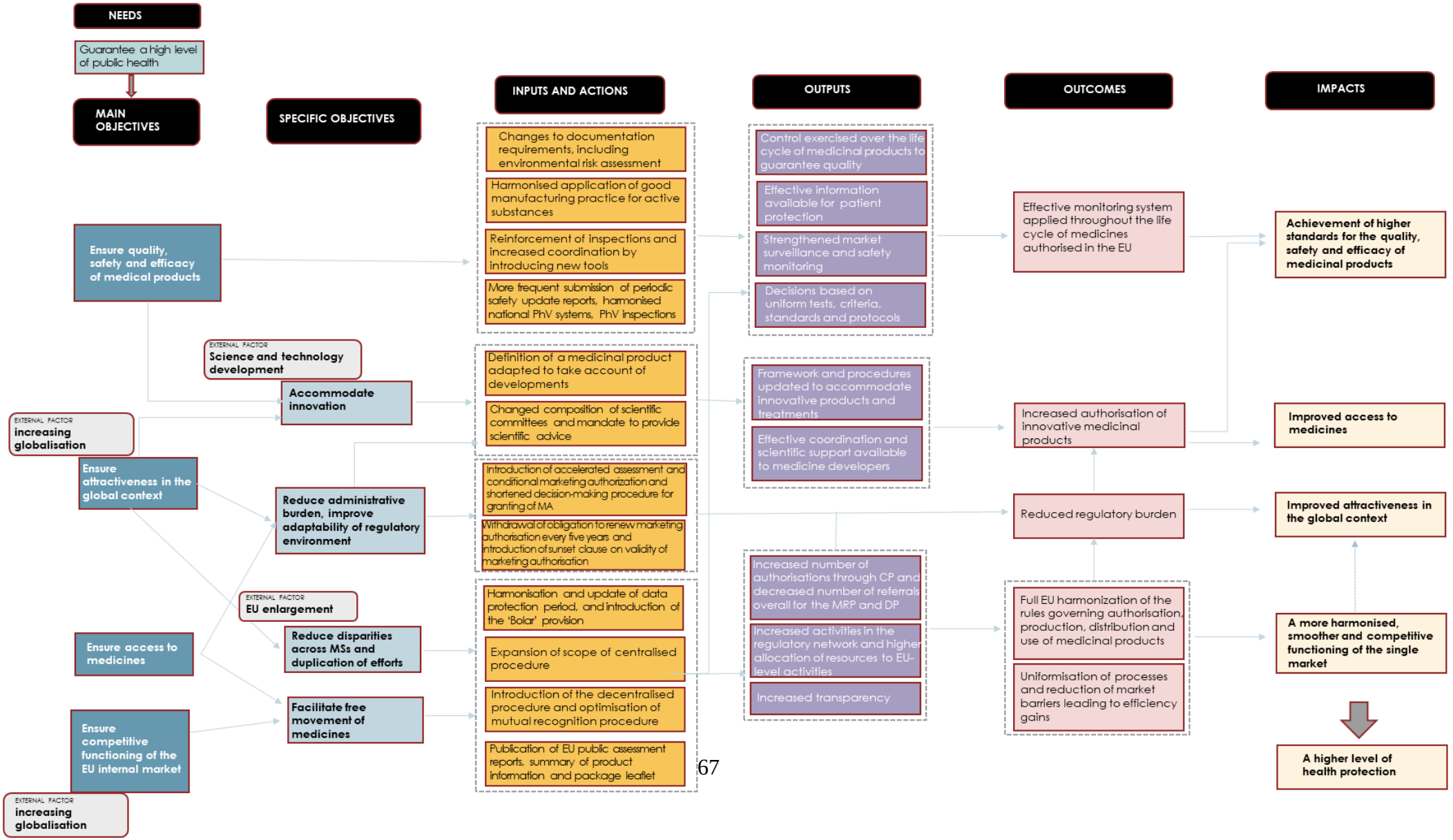
7 APPENDIX A: INTERVENTION LOGIC



8 APPENDIX B: TARGETED SURVEY OVERVIEW – AREAS WHERE THE LEGISLATION HAS BEEN EFFECTIVE

To what extent has the legislation been effective in contributing to the following objectives?	All stakeholders average score	Individual stakeholders average score					Agreement between stakeholders	Ranked Effectiveness
		Industry	Civil Society	Public Authorities	Academic	Health Services		
Safeguard public health	3.7	4.4	3.5	4.0	3.5	3.3	Low	most effective
Provide an attractive and robust authorisation system for medicines	3.8	3.9		3.8		3.8	High	most effective
Provide resources and expertise to ensure timely assessment and authorisation of medicines at all times	3.44	3.3		3.5			High	
Enable timely access to medicines for patients and health systems	2.9	3.2	2.8	3.1	2.7	2.8	High	
Enable access to affordable medicines for patients and health systems	2.4	3.0	2.0	2.3	2.1	2.7	Low	least effective
Minimise inefficiencies and administrative burden of regulatory procedures	2.8	2.3		3.0		3.1	Low	
Provide harmonised measures for an improved functioning of the internal market for medicines	2.9	2.7	2.60	3.5	2.8	2.8	Med	
Ensure quality of medicines including through manufacturing rules and oversight of manufacturing and supply chain	3.9	4.4	3.7	4.2	3.9	3.5	Low	most effective
Enhance the security of supply of medicines and address shortages	2.3	2.9	1.80	2.4		2.0	Low	least effective
Provide clear and appropriate responsibilities to all actors throughout the lifecycle of medicines, including post-marketing obligations and oversight	3.6	3.6		3.7			High	
Ensure a competitive EU market for medicines	2.8	3.1	2.2	3.0			High	
Improve competitiveness of EU pharmaceutical industry on the global market	2.7	2.4		3.1			Low	
Facilitate generic/biosimilar product entry to markets	3.3	3.6	2.7	3.3	3.3	3.44	High	
Enable progress in science, technology and digitisation for the development of high quality, safe and effective medicines	3.2	3.0	3.0	3.2	3.1	3.6	High	
Accommodate innovation for the development of complex and combination medicinal products	3.0	2.9	2.7	3.2	2.9	3.3	High	
Accommodate innovation for medicine manufacturing	3.1	3.2		3.2	2.9	8	High	
Attract pharmaceutical developers from outside the EU	2.7	2.7					High	
Reduce the environmental footprint of medicines	2.5	3.1	2.2	2.3			Low	least effective

9 APPENDIX C: EVALUATION MATRIX

An evaluation matrix was developed to provide a framework for answering the evaluation questions. The matrix cross-references evaluation questions to the relevant judgement criteria, indicators and data sources. The indicators aim to compare periods before and after the 2004 revision of the general pharmaceutical legislation was implemented.

The indicators followed by a star (*) are explained in details in the analytical report (Annex 10). These cover parameters and areas such as new marketing authorisations (number, type of medicine and approval times), access and affordability (medicine prices), clinical trials, medicine shortages in Member States (number and cause) and non-compliance with good manufacturing procedure (GMP).

Evaluation question	***Sub-questions***	***Judgement Criteria***	***Indicator***	***Data sources***
EFFECTIVENESS				
1. To what extent have the actions envisaged by the general pharmaceutical legislation contributed to achieving the following objectives?	1.a. To safeguard public health.	***For all Effectiveness questions:*** Degree to which quantitative indicators show positive trend over time. This is corroborated with qualitative information (where available).	Number of innovative medicines*; Number of medicines authorised*; Time from start of Phase1 to completion of Phase 3 clinical trials*; Sales volumes of antibiotics*; Adverse reaction data trends (EudraVigilance).	Desk research; Mini case studies; Stakeholder views including targeted survey, interviews and stakeholder workshops.
	1.b. To build an attractive and robust authorisation system for medicines.		Number of USA-origin medicines approved in the USA, of Japan-origin medicines approved in Japan, of Switzerland-origin medicines approved in Switzerland*; Number of USA-, Japan-, Switzerland- medicines approved in the EU*; Transition success rate (%) of candidates	Desk research; Mini case studies; Stakeholder views including targeted survey, interviews and stakeholder workshops.

Evaluation question	*Sub-questions*	*Judgement Criteria*	*Indicator*	*Data sources*
			from Phase 3 to approval*; Speed of approval for authorised medicines*; EMA assessment times including accelerated assessments.*	
	1.c. To give patient timely access to medicines.		Number of approved medicines with zero sales volume in EU countries*; Time from authorisation to non-zero sales volume reported for authorised medicines in individual EU countries*; Number of market withdrawals*; Time from market authorisation to market withdrawal*.	Desk research; Mini case studies; Stakeholder views including interviews and stakeholder workshops.
	1.d. To minimise inefficiencies and administrative burden of regulatory procedures.		Number of lead and co-lead assessments by national regulatory authorities (rapporteurs and co-rapporteurs)*; EMA assessment times including accelerated assessments*.	Desk research; Stakeholder views including targeted survey, interviews and stakeholder workshops.
	1.e. To provide harmonised measures for an improved functioning of internal market for medicines.		Number of medicines authorised*; Number of lead and co-lead assessments by national regulatory authorities (rapporteurs and co-rapporteurs)*; Employment in the pharmaceutical industry*; GVA contribution of the pharmaceutical industry*; Revenue generated by pharma	Desk research.

Evaluation question	*Sub-questions*	*Judgement Criteria*	*Indicator*	*Data sources*
			companies*.	
	1.f. To ensure the quality of medicines including through manufacturing rules and supply chain oversight.		Change of root cause reported for medicines*; Number of non-compliance of GMP, stratified by countries*.	Literature review; Mini-case studies; Stakeholder views including targeted survey, interviews and stakeholder workshops.
	1.g. To create an integrated lifecycle model with clear and appropriate responsibilities including post-marketing obligations and oversight.		Number of medicines authorised*.	Mini-case studies; Stakeholder views including targeted survey, interviews and stakeholder workshops.
	1.h. To create a competitive market for medicines in the EU, including taking into account market effects impacting on affordability.		Number of EU-origin medicines approved in the EU*; Number of USA-, Japan-, Switzerland origin medicines approved in the EU*; Volumes and values of EU import/export of APIs, vaccines, finished pharmaceutical products and antibiotics*; Net price of selected group of medicines (e.g., representative sample or essential medicines list) in individual countries*; Rate of generics/biosimilars entry and uptake*; Average price discount (%) of generics/biosimilars over originator*; Number of authorised medicines per class, therapeutic area*; Number of pipeline products per class, therapeutic area*; Sales volume	Desk research; Mini-case studies; Stakeholder views including stakeholder workshops.

Evaluation question	*Sub-questions*	*Judgement Criteria*	*Indicator*	*Data sources*
			of antibiotics*.	
	1.i. To make it easier to place generic/biosimilar products on the market.		Rate of generics/biosimilars entry and uptake*; Time to entry after IP protection expires*.	Desk research; Stakeholder views including targeted survey and interviews.
	1.j. To enable innovation for the development of high quality, safe and effective medicines in a way that harnesses the benefits of digitisation and emerging science and technology.		Number of antibiotics approved per year*; Number of antibiotic medicine candidates in the R&D pipelines*; Number of candidates entering Phase 1 clinical trials*; Transition success rate (%) of candidates from Phase 1 to Phase 2 to Phase 3 to clinical trials to approval*; Number of clinical trials with digital end points, real world data, complex trial design.	Literature review; Desk research; Mini cases studies; Stakeholder views including targeted survey, interviews, stakeholder workshop.
	1.k. To ensure openness to cutting-edge products and integrated therapies.		Number of medicines authorised*.	Desk research; Mini cases studies; Stakeholder views including targeted survey, interviews.
	1.l. To improve competitiveness of EU pharmaceutical industry on the global market.		Number of EU-origin medicines approved in one or more non-EU countries*; Value of medicine exports EU to USA and USA to EU; EU to Japan and Japan to EU; EU to Switzerland and Switzerland to EU*; Revenue generated by pharma companies*; Volumes and values of EU import/export	Literature review; Desk research; Stakeholder views including stakeholder workshop.

Evaluation question	*Sub-questions*	*Judgement Criteria*	*Indicator*	*Data sources*
			of APIs, vaccines, finished pharmaceutical products and antibiotics*.	
	1.m. To enhance the security of supply of medicines and address shortages.		Trend of shortage duration for medicines in shortage*; Trend of volume drop for medicines in shortage (critical, severe, moderate)*; Number of third-country API sites, stratified by geography*; Number of EU-registered API sites, stratified by MS*.	Desk research; Mini case studies; Stakeholder views including stakeholder workshop.
	1.n. To reduce the environmental footprint of medicines.		Concentrations of pharmaceutical residues in the environment*; Emission intensity/absolute emissions of GHG by the pharmaceutical industry*.	Literature review; Desk research.
2. How do the achieved results and impacts compare with the expected ones?	2.a. To what extent the results of the legislation meet the need of stakeholders?		Comparison of available indicators with stakeholder views.	Desk research; Stakeholder views including targeted survey, interviews, stakeholder workshop.
3. Which were the key contributing and hindering factors in achieving the intended objectives?	3. a To what extent has the type of legislative act, i.e. a Directive, been a contributing or hindering factor in achieving the intended objectives?		Comparison of available indicators with stakeholder views.	Desk research; Stakeholder views including targeted survey, interviews, stakeholder workshop.
	3.b. To what extent has Directive 2001/83/EC been transposed by Member States in a way that allows the effective		Qualitative evidence based on expert legal opinion and stakeholder views.	Desk research; Stakeholder views and expert legal opinion including targeted survey,

Evaluation question	*Sub-questions*	*Judgement Criteria*	*Indicator*	*Data sources*
	implementation; which are the factors hampering the implementation; to what extent are these factors influenced by regional and national conditions? Are there any unexpected or unintended effects that occurred and which drove or hindered progress?			interviews.
4. To what extent is the general pharmaceutical legislation relevant to position the EU regulatory system in an international context, including the attractiveness of the EU system for developers compared to other jurisdictions?	4.a. To what extent non-EU based sponsors conduct trials in the EU? To what extent non-EU based sponsors apply for marketing authorisation in the EU?		Number of USA-, Japan-, Switzerland-origin medicines approved in the EU*; Number of clinical trials performed in different geographies*; Overall Likelihood of Approval (LOA) from Phase 1*; Time from start of Phase1 to completion of Phase 3 clinical trials*.	Desk research; Stakeholder view including targeted survey, interviews.
EFFICIENCY				
5. What have been the main costs (e.g. implementation costs, authorisation costs, life cycle management, staff time etc.) to implement and apply the general pharmaceutical legislation for the different actors concerned (e.g. Commission, Member States, industry, patients, researchers, etc.)? What were the factors driving these costs?	5.a. What have been the main costs (per stakeholder category) implications of the legislation?	The implications of the legislation can be monetised in an attributable way.	Cost per product development and implementation steps.	Literature review; Stakeholder view including targeted survey and stakeholder workshops.
	5.b. What have been the cost drivers?	Views on relevant drivers and their contribution to overall costs.	Top cost elements.	Literature review; Stakeholder view including targeted survey, interviews, stakeholder workshops.
6. What social, environmental and economic benefits has the general pharmaceutical legislation achieved for the different stakeholders and what is the corresponding monetised value, where possible and	6.a. What have been the social benefits of the legislation?	Degree to which quantitative indicators show favourable trend over time and this is corroborated with qualitative	Net price of selected group of medicines (e.g., representative sample or essential medicines list) in individual countries*; Ratio of net price of medicines	Desk research; Mini case studies; Stakeholder view including interviews.

Evaluation question	*Sub-questions*	*Judgement Criteria*	*Indicator*	*Data sources*
relevant to estimate?		information (where available)	to GDP per capita in individual countries*; Expenditure on medicines in total healthcare spending in individual countries; Rate of generics/biosimilars entry and uptake*; Change in unmet healthcare needs.	
	6.b. What have been the economic benefits of the legislation?	Degree to which quantitative indicators lead to favourable trend over time	Employment in the pharmaceutical industry*; GVA contribution of the pharmaceutical industry*; Revenue generated by pharma companies*; Foreign direct investment in the pharmaceutical sector.	Desk research.
	6.c.. What have been the environmental benefits of the legislation?		Concentrations of pharmaceutical residues in the environment*; Emission intensity/absolute emissions of GHG by the pharmaceutical industry*; Residues of pharmaceuticals in the environment and emissions from manufacturing plants.	Literature review; desk research.
7. To what extent were the general pharmaceutical legislation's costs proportionate to its benefits (i.e. positive outcomes)?	7.a. What is the scale of the significant and monetisable costs and benefits, applying the principle of proportionate analysis? What is the ratio of those significant costs and benefits? What is the balance of those	The extent to which the model result in positive outcomes	Partial cost benefit analysis considering monetisable costs and benefits and accompanying multi-criteria analysis to assess the balance when including non-monetisable aspects.	Literature review; Desk research; Stakeholder view including targeted survey, interviews, stakeholder workshop.

Evaluation question	*Sub-questions*	*Judgement Criteria*	*Indicator*	*Data sources*
	costs and benefits when including non-monetisable aspects?			
8. What have been the costs of partially meeting or not meeting some of the objectives and requirements of the general pharmaceutical legislation?	8.a. What share of the total costs can be attributed reasonably to each of the specific objectives of the legislation? What is the scale / value of the benefits associated with each specific objective and attributable to the legislation? What have been the total costs of meeting each of these specific objectives, jointly and severally?	The cost and benefit items can be attributed to objectives and these can be aggregated	Cost-Benefit model integrating the share of costs and value of benefits for each objective and jointly.	Literature review; desk research; Stakeholder view including targeted survey, interviews, stakeholder workshop.
9. Which elements of the general pharmaceutical legislation pose an administrative burden or are overly complex? What are the administrative costs for the different actors? Which provisions could be further simplified?	9.a. Which are the burdensome or complex aspects of the legislation?	The degree to which stakeholders can point to attributable administrative burden.	Top 5 'burdens' overall and by key stakeholder group.	Literature review; Stakeholder view including targeted survey.
	9.b. What is the level of costs corresponding to these aspects?	The degree to which administrative burden can be quantified by stakeholders.	Median value of costs associated with the principal direct costs for each key stakeholder group	Literature review; Desk research; Stakeholder view including targeted survey.
COHERENCE				
10. To what extent has the general pharmaceutical legislation responded to the needs and problems concerning medicines for the 2004 revision?	10.a To what extent definition of new therapies and new forms of administration routes enabled innovation?	Degree to which quantitative indicators show favourable trend over time and this is corroborated with qualitative information (where available).	Speed of approval for authorised medicines*; Number of authorised medicines per class, therapeutic area*; Number of pipeline products per class, therapeutic area*.	Desk research; Stakeholder view including targeted survey, interviews.

Evaluation question	*Sub-questions*	*Judgement Criteria*	*Indicator*	*Data sources*
	10.b. To what extent the new pathway for biosimilars responded to the needs?		Rate of generics/biosimilars entry and uptake*; Time to entry after IP protection expires*; Average price discount (%) of generics/biosimilars over originator*.	Desk research;, Stakeholder view including targeted survey, interviews.
11. To what extent are the general pharmaceutical legislation's objectives and required actions relevant today to address the current needs and problems and expected scientific and technological developments related to medicinal products in the EU?	11.a. How have the needs and problems identified for the 2004 revision evolved since then?	Degree to which quantitative indicators show identifiable trend over time.	Overall Likelihood of Approval (LOA) from Phase 1*; Number of grants and value of grant funding by country and/or funding body*; Amount of private R&D investment in the sector*; Number of medicines authorised*; Speed of approval for authorised medicines*; Share of EU population with access to medicines sold on the market*; Net price of selected group of medicines (e.g., representative sample or essential medicines list) in individual countries*; Ratio of net price of medicines to GDP per capita in individual countries*; Expenditure on medicines in total healthcare spending in individual countries*.	Desk research; Stakeholder view including stakeholder workshop.
	11.b. What are the current needs and problems related to the use of medicinal products and how will they evolve (e.g. fulfilling unmet medical need, access to affordable medicines, security	Views on relevant needs and problems corroborating quantitative trends of indicators	Analysis of the current level of indicator available from the comparative analysis of the European pharmaceutical legislation and contrast those	Desk research; Stakeholder view including targeted survey, interviews, stakeholder workshop.

Evaluation question	*Sub-questions*	*Judgement Criteria*	*Indicator*	*Data sources*
	of the supply chain, adaptation of the regulatory framework to scientific and technological developments)?		with stakeholder view.	
12. To what extent is the general pharmaceutical legislation relevant to health crises resilience and responsiveness? What are the lessons learned from the COVID-19 pandemic?	12.a. To what extent is the general pharmaceutical legislation relevant to health crises resilience and responsiveness?	The degree to which stakeholders and experts can point to relevant examples.	Examples of application of the legislation during crises management and response.	Literature review; Mini case studies; Stakeholder view including, interviews, stakeholder workshop.
	12.b. What are the lessons learned from the COVID-19 pandemic?	The degree to which stakeholders can articulate learnings.	Qualitative assessment based on stakeholder view.	Literature review; Stakeholder view including interviews, stakeholder workshop.
COHERENCE				
13. To what extent is the general pharmaceutical legislation coherent internally? Have the different elements of the legislation have operated together to achieve all the objectives of the legislation in a coherent way? Which are the reasons for the perceived tensions between innovation, access and affordability and which are the factors influencing them? ***(Internal coherence)***	13.a. To what extent is the EU legislation coherent and different elements operate in synergy to achieve all of its objectives? Are there tensions between the objectives linked to innovations, access and affordability of medicines? If yes, what are those? How could these be resolved?	The degree to which (positive or negative) interdependencies of the elements of the general pharmaceutical legislations can be identified and where needed resolved.	Qualitative assessment based on expert legal opinion (analysis of potential overlaps, contradictions, or other inconsistencies between its provisions/requirements; analysis of whether its provisions adequately fulfil its objectives) and stakeholder view on issues and solutions (especially Member State authorities in charge of the implementation and enforcements of this legislation at national level).	Literature review; Mini case studies; Stakeholder view including interviews, stakeholder workshop.

Evaluation question	*Sub-questions*	*Judgement Criteria*	*Indicator*	*Data sources*
14. The general pharmaceutical legislation has strong links with lex specialis pharmaceutical legislations. To what extent has the general pharmaceutical legislation created an effective and coherent link with the specialised pharmaceutical frameworks that is not hampered by undue complexity? ***(external coherence I)***	14.a. Are there overlaps, inconsistencies or ambiguities between the legislation and lex specialis pharmaceutical legislations? Is there unnecessary complexity in the system due to the way the legislation is drafted there? Are there ways the legislations could be better streamlined?	The degree to which interdependencies of the general pharmaceutical legislations and specialised pharmaceutical frameworks can be identified and where needed resolved	Qualitative assessment based on axpert legal opinion (analysis of potential inconsistencies between the general pharmaceutical legislation and the *lex specialis* pharmaceutical laws of core obligations using a table of comparison and possible legal solutions).	Literature review; Mini case studies; Stakeholder view including interviews, stakeholder workshop.
15. To which extent is the general pharmaceutical legislation dependent on the implementation of the linked legislation in achieving its objectives? In particular, the link with the non-pharmaceutical legislations and non-pharmaceutical policies should be explored. ***(external coherence II)***	15.a What are the potential links between the pharmaceutical legislation and other EU legislations and policies along the pharmaceutical chain (e.g. development, placing on the market, use, waste management and/or emissions in the environment)? To what extent is the intervention coherent with international obligations? including the SDGs? Are these other legislations (designed at different times with different purpose under different competencies) essential for the pharmaceutical legislation achieve all of its objectives? Do these other legislations	The degree to which (positive or negative) interdependencies of the general pharmaceutical legislations and other EU legislations can be identified and their effects assessed	Qualitative assessment based on expert legal opinion. Note: An in-depth legal analysis is not feasible, however, there is already a vast amount of literature available which would guide the evaluation, meaning a legal analysis would only be needed to debunk or prove a specific inconsistency.	Literature review, Stakeholder view including interviews, stakeholder workshop.

Evaluation question	*Sub-questions*	*Judgement Criteria*	*Indicator*	*Data sources*
	hinder the pharmaceutical legislation to achieve any of its objectives?			
EU ADDED-VALUE				
16. What has been the added value resulting from the EU intervention in the legislation of pharmaceuticals compared to what could have been achieved at international, national or regional level without such intervention?	16.a. What has been the added value of the EU legislation compared to international actions alone? compared to EU national actions alone? compared to EU regional actions alone?	The degree to which additional value can be identified as a result of the implementation of the general pharmaceutical legislation	Qualitative assessment based on expert legal opinion and stakeholder view.	Literature review; Stakeholder view including interviews, stakeholder workshop.
17. To which extent did the general pharmaceutical legislation strike the right balance between action at EU level and national action? Is it a proportionate response to the problem?	17.a To what extent has the EU legislation been applied in a balanced and proportionate way to problems arising?	The problems and related national/EU actions can be assessed along the same metric/scale and their relationship assessed.	Number of MA via the CP versus MRP or DCP*; Number of lead and co-lead assessments by national regulatory authorities (rapporteurs and co-rapporteurs)*.	Literature review; Desk research, Stakeholder view including interviews, stakeholder workshop.
18. What has been the added value resulting from the EU intervention in the context of the COVID crisis (e.g. providing strategic priorities for action, a common framework for action, etc.)?	18.a. In what way has the EU intervention added value to the COVID response?	The degree to which added value through quantitative indicators can be attributed to EU action and corroborated by qualitative information for the ongoing crisis.	Number of clinical trials conducted and number of medicines authorised relevant for COVID medicine (therapeutic categorisation)*	Literature review; Desk research; Mini case studies; Stakeholder view including interviews, stakeholder workshop.
19. To which extent did this EU intervention strike the right balance between action at EU level and national action? Is it a proportionate response to the pandemic?	19.a. To what extent has the EU intervened in a balanced and proportionate way with respect to national actions during the	The degree to which EU actions and national actions can be disentangled.	Qualitative assessment based on expert legal opinion and stakeholder view.	Literature review; Mini case studies; Stakeholder view and expert legal opinion including interviews, stakeholder workshop.

Evaluation question	*Sub-questions*	*Judgement Criteria*	*Indicator*	*Data sources*
	COVID crisis?			

10 APPENDIX D: OVERVIEW OF BENEFITS AND COSTS

Table 22 Overview of costs and benefits identified in the evaluation

		Citizens/Consumers		Businesses		Administrations		Society	
		Quantitative	Comment	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment
Costs and Benefits of 2004 revision of Pharmaceutical Legislation (millions of Euro)									
Direct costs									
Direct Compliance costs (adjustment costs)	**one-off**			€250m	Additional investments in IT systems to cope with expanded data requirements on safety and manufacturing, estimated at 0.1-1% of sales. Using the 0.5% median value gives a gross figure of €750m for the EU industry overall. However, the new iT systems have provided wider benefits / productivity gains, so the attributable cost is assumed to be lower (1/3 of gross costs)				
Direct compliance costs (adjustment costs)	**recurrent**			€50m-€100m p.a., €750m-€1,500m in total	Higher costs due to data requirements for new and current marketing authorisations; additional costs for legal departments				
Enforcement costs: (costs associated with activities linked to the implementation of an initiative such as monitoring, inspections and adjudication/litigation)	**recurrent**					EMA: €2.5m-€3.1m p.a., NCAs: €8m-€25m p.a.	Higher staff and evaluation costs for EMA; higher inspection costs for national competent authorities		
Direct benefits									
Health impacts	**recurrent**	25-30 new innovative medicines, in total; producing 170,000-210,000 QALYs in total; which amounts to €4.8bn-€17.2bn in monetised benefits, using WHO guidelines	The additional number of new products has been estimated based on a comparison between EMA and FDA authorisations over time; the QALYs are based on estimated average EU						

		Citizens/Consumers		Businesses		Administrations		Society	
		Quantitative	Comment	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment
		on valuing QALYs	income and a median ICER						
Compliance costs: lower costs marketing authorisations	**recurrent**			CP: €4.8m p.a., DCP: €36m p.a.	Cost savings due to the harmonisation and streamlining of procedures associated with the introduction of the DCP and the substantial reduction in the use of the mutual recognition procedure				
Compliance costs: Lower costs marketing authorisations (lower regulatory costs)	**recurrent**			€23m p.a.	MA holders benefited from the switch to a single renewal of a MA 5 years after the original notice of authorisation, eliminating the need for further renewals at 5-yearly cycles, and removing the need for renewals by generics companies				
Enforcement	**recurrent**					€20m-€40m pa	Cost savings for national competent authorities due to streamlining / harmonisation of national authorisation procedures (switch to DCP away from MRP)		
Environmental damage	**recurrent**							0	The 2004 revision has not contributed to reducing the environmental footprint.

Table 6 Simplification and burden reduction (savings already achieved)

	Citizens/Consumers/Workers		Businesses		Administrations		Society	
	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment
Title[257]*: (i) direct compliance cost savings (for example adjustment cost savings, administrative cost savings, savings from regulatory charges)*								
Recurrent savings (MAHs)			CP: €4.8m p.a., DCP: €36m p.a.	Cost savings due to the harmonisation and streamlining of procedures associated with the introduction of the DCP and the substantial reduction in the use of the mutual recognition procedure				
Recurrent savings (MAHs)			€23m p.a.	MA holders benefited from the switch to a single renewal of a MA 5 years after the original notice of authorisation, eliminating the need for further renewals at 5-yearly cycles, and removing the need for renewals by generics companies				
Recurrent savings (enforcement)					€20m-€40m pa	Cost savings for national competent authorities due to streamlining / harmonisation of		

[257] Each simplification/saving should be included on a separate line.

						national authorisation procedures (switch to DCP away from MRP)		

PART II: <u>Potential</u> simplification and burden reduction (savings)

*Identify further potential simplification and savings **that could be achieved** with a view to make the initiative more effective and efficient without prejudice to its policy objectives[258].*

	Citizens/Consumers/Workers		Businesses		Administrations		[Other…] _ specify	
	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment
Description: Our evaluation consultations revealed widespread concerns across industry and regulators about the under-exploitation of digitalisation within the EU pharma regulatory system and the related problem of duplicative activity. As such, there may be areas where further harmonisation and digitalisation of regulatory processes could deliver savings, however, these are contingent on future revisions and operational enhancements being implemented. As an aside, we note that the EMA strategy indicates there are >80 people working on digital transformation and its annual financial accounts show it is investing €5m-€15m a year in new ICT systems. The wider literature on ICT productivity suggests that a 10% increase in ICT investment should produce a productivity gain of around 0.6%[259]							
Recurrent (MAHs)			€9.6m p.a.	There are opportunities for substantial further digitalisation across the EU pharma regulatory system to increase efficiency and duplicative activity				
Recurrent (EMA)					€2.1m p.a.	There are opportunities for substantial further digitalisation across the EU pharma regulatory system to		

[258] This assessment is without prejudice to a possible future Impact Assessment.

[259] https://www.sciencedirect.com/science/article/abs/pii/S0167624513000036.

						increase efficiency and duplicative activity		
Recurrent (NCAs)					€12m p.a.	There are opportunities for substantial further digitalisation across the EU pharma regulatory system to increase efficiency and duplicative activity		