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

Evaluation Report

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LEGAL NOTICE

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GLOSSARY

Term or acronym	*Meaning or definition*
ADR	Adverse drug reaction
AMR	Antimicrobial resistance
API	Active Pharmaceutical Ingredient
ATC	Anatomical Therapeutic Chemical code
ATMP	Advanced therapy medicinal product
BSSD	Basic Safety and Standards Directive
BTC	Blood, tissue and cell
CHMP	Committee for Medicinal Products for Human Use
CMA	Conditional marketing authorisation
CMC	Chemistry, Manufacturing and Control
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures
CMO	Contract Manufacturing Organisations
CP	Centralised authorisation procedure
DCP	Decentralised authorisation procedure
EEA	European Economic Area
EFTA	European Free Trade Association
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
GDP	Good Distribution Practices
GMP	Good Manufacturing Practices
GDPR	General Data Protection Regulation
GMO	Genetically modified organism
HTA	Health Technology Assessment
ICSR	Individual case safety reports
IP	Intellectual property
MAH	Marketing authorisation holder
MRP	Mutual recognition procedure
MS	Member State
NAS	New active substances

NCA	National Competent Authority
OPC	Open public consultation
PDMP	Plasma Derived Medicinal Product
PRAC	Pharmacovigilance Risk Assessment Committee
SDG	Sustainable Development Goal
SME	Small and medium enterprises
SPC	Supplementary Protection Certificate

ABSTRACT

The most recent comprehensive revision of the EU general pharmaceuticals legislation took place in 2004. In the intervening decades, the global pharmaceutical sector, technological approaches and societal focus have changed. The new Pharmaceutical Strategy for Europe provides a framework for new developments as part of the Commission's vision to build a stronger European Health Union. This strategy calls for an evaluation of the performance of the current regulatory system and targeted revision of the general pharmaceutical legislation. The report summarises data and analyses to support the evaluation of the legislation, notably Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation (EC) 726/2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency.

The study followed the Better Regulation guidelines, to develop an intervention logic and a baseline; assess the effectiveness, efficiency, relevance, coherence and EU added value of the legislation; consider lessons learnt from the COVID-19 pandemic in relation to the functioning of the pharmaceutical system; and draw conclusions on the evidence gathered to support future policy decisions.

EXECUTIVE SUMMARY

Study scope and objectives

The study in support of the evaluation focussed on Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation (EC) No 726/2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency, i.e., the general pharmaceutical legislation. The relevant time period for the evaluation is following the completion of the comprehensive revision of the legislation in 2004, from the year 2005 until end of 2020, and covers relevant trends and developments for the development, authorisation, manufacturing, supply, and monitoring of medicines. The years between 2000-2005 served as a baseline for the evaluation. The geographical scope of the evaluation was the European Economic Area, however comparisons with the other jurisdictions such as the US, Australia, Canada, Israel, China, Japan and South Korea were also made where relevant and feasible.

The goals of the study were specifically:

1. To assess, in line with the Better Regulation guidelines, the effectiveness, efficiency, relevance, coherence and EU added value of the legislation;
2. To assess the performance of the legislation during the COVID-19 crisis in relation to the functioning of the pharmaceutical system and consider the lessons learnt from the pandemic;
3. To draw conclusions on the evidence gathered to support future policy decisions.

Methodological approaches and limitations

A mixed quantitative and qualitative approach was applied to collect and analyse data in the study. It included peer-reviewed literature and policy document review to gather existing knowledge base and served as a source of facts and figures; secondary data analysis, including statistical, econometric and trend analysis. In addition, case studies were developed that focus on specific issues and illustrate linkages and mechanisms behind trends observed in the data. Finally, extensive stakeholder consultations were conducted and resulting primary data was analysed from the feedback for the consultation on the Roadmap/Inception Impact Assessment and public consultation, targeted surveys, interviews and an evaluation workshop for stakeholders. Stakeholder groups consulted included public authorities, civil society and patient organisations, healthcare professionals and their associations, academic and public research organisations/experts and industry.

There have been a number of limitations that affect the robustness of findings. First, effects are linked to a complex multi-factorial evidence base and stakeholders were often unable to break down observed effects to drivers. This was particularly the case for providing quantitative information linked to the costs and benefits (efficiency) of the legislation. Second, the broad scope of the general pharmaceutical legislation inherently linked it to a large number of specialised pharmaceutical legislations and other more general EU rules and laws that have been added and periodically amended over the years. These confounding external factors influenced primarily the relevance, effectiveness and efficiency of the legislation. In addition, many businesses operate globally with functional teams that comply with and report to authorities in multiple jurisdictions and therefore they were not able to isolate the effects of the EU legislation. Third, due to the extended time period in scope for 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 legislative revision. Further, quantitative data definition and data collection approaches changed over time making it challenging to conduct a continuous trend analysis.

Background to the intervention

The overarching need of a general pharmaceutical legislation was to guarantee a high level of public health throughout Europe. This meant that safe, high quality and effective medicines needed to be available and accessible to patients regardless of the member state in which they resided. The 2004 revision of the general pharmaceutical legislation envisioned four main, high-level objectives:

1. Ensure quality, safety and efficacy of medicinal products. This means a robust authorisation system, surveillance and supervision are in place along the entire medicinal product lifecycle, including post-authorisation monitoring and pharmacovigilance procedures.

2. Ensure access to medicines. Health protection can only be effective if patients have equitable access to medicinal products as early as possible after authorisation.
3. Ensure competitive functioning of the EU internal market. Competition across medicine developers is expected to bring ever more innovative and effective medicines to meet the needs of patients in all member states (both original branded forms and those that are no longer under patent protection, i.e., generic versions).
4. Ensure attractiveness in the global context. Medicine development is a global endeavour, and it is important that Europe has a legislative framework that is globally attractive to medicine developers.

More specifically, these high-level objectives were expected to be achieved through a number of more specific objectives which were mutually reinforcing a more systemic view:

Accommodate innovation. This means that the legislative system is ready for the new scientific and technological developments that underpin innovative and effective products. Here innovation comprises not only new molecular entities but also adding value (follow-on innovation), repurposing existing medicines and developing biosimilar products.

Reduce administrative burden, improve adaptability of regulatory environment. This specific objective responds directly to the need for all medicine developers (including generic manufacturers) to navigate the regulatory landscape with minimum administrative burden (cost and time) and, as noted above, accommodate new scientific and technological developments.

Reduce disparities and duplication of efforts. Historically, European countries had differing rules and processes that added complexity and resulted in duplicated efforts. Harmonisation and standardisation were promoted to reduce duplication, improve certainty and transparency to allow a level playing field for medicine developers across European MSs and transparent information access to patients.

Facilitate free movement of medicinal products. According to the concept of the internal EU single market, products should be traded freely across the Union. This objective aims to facilitate free trade for medicinal products through greater harmonisation of processes.

Baseline

In the increasingly globalised environment and pharmaceutical practices in the 1990s, the European pharmaceutical sector was losing competitiveness to the US. Fragmented EU member state policies did not result in the level of scientific interaction between industry and public or private research organisations that would have been necessary for industry to successfully exploit the latest scientific results. European pharmaceutical companies struggled to advance in innovative areas such as biotechnology. In addition, European companies tended to operate exclusively in their protected national markets which did not provide strong incentives to adopt innovation and globalised business strategies.

The European pharmaceutical system had two major routes to authorise medicines since 1995: the historic national authorisation route (and the related mutual recognition procedure, MRP) and a centralised route via the (now named) European Medicines Agency. Nevertheless, the MRP system was seen as less successful in achieving harmonisation as some Concerned Member States continued to evaluate marketing authorisation applications, sometimes raising concerns that were unaligned with the recognition principle. Regulatory data protection periods differed under the two approval systems and across national systems, which led to differences in availability of innovative products on national markets and lowering pharmaceutical companies' willingness to invest in incremental research.

The continued EU enlargement also contributed to the need to establish an integrated environment for pharmaceuticals, as differences across the new member states would have amplified the problems of fragmentation and disparity.

Evaluation findings

Effectiveness

The legislation has been most effective with regard to the objective of safeguarding public health and least effective in terms of ensuring access to medicines and addressing medicine shortages,

according to overall stakeholder opinion. Industry identified two areas where the legislation was deemed the least effective: minimising inefficiencies and administrative burden of regulatory procedures; and improved global competitiveness of the EU pharmaceutical industry.

Quality, safety and efficacy of medicinal products

One of the major enablers for achieving this objective is the centralised procedure (CP), which has allowed effective and robust authorisation of medicines at EU level, together with decentralised procedure/mutual recognition procedure (DCP/MRP), pre-authorisation scientific advice and other services provided by EMA. These achievements have improved quality standards and have ensured safe and efficacious medicines are available to the EU population.

Stakeholder consultations also highlighted some areas for improvement, including the assessment of microbiome products, GMOs and environmental risk as well as better accommodation of bedside and decentralised manufacturing in the legislation or related guidance.

Attractiveness in the global context

The 2004 revision was an important step forward in ensuring a coherent and attractive regulatory system for developing pharmaceuticals, in response to increased scientific and technological complexity of medicinal products and EU enlargement. The centralised procedure was remarked that allows developers to make the first steps to EU market access in an integrated fashion, which increases the EU's attractiveness as both market and location for pharmaceutical development and manufacturing. The EU has also been a global leader in setting up a process for licensing biosimilars, which encourages innovation and submitting market application in the EU.

Nevertheless, the USA remains the largest global market for pharmaceuticals, more than twice the size of the EU market which has the second largest share of the global market. Several industry participants confirmed that the USA remains the preferred jurisdiction for developers to file innovations. Reasons for these preferences include differing data requirements, greater opportunity for direct interaction on scientific advice and the need to interact with multiple EMA committees in complex cases. New active substances authorised by all agencies are largely submitted to the US FDA first and followed by submission to the EU. However, the proportion of US FDA-authorised substances not authorised by EMA decreased over time, which shows that the EU system is globally attractive. In particular, the legislation has proven flexible enough to accommodate many developments and innovations in the pharmaceutical sector. There has been a growth in the number of innovative medicines, including technologically innovative medicines (e.g. ATMPs) and those addressing unmet medical needs (e.g. through PRIME and conditional marketing authorisation routes).

There are areas where the legislation has not been fully able to accommodate emerging technological developments as readily, such as combination products/borderline cases with medical devices or substances of human origin, digitalisation and new manufacturing methods. It was a common view in the consultations that one of the reasons for this problem is the lack of coherence in certain areas of the EU regulatory system, which can make it less attractive for developers, in particular for SMEs.

Access to medicines

The 2004 revisions expanded the scope of the centralised procedure and harmonised other procedures and rules to improve access to medicines across the EU. Access however remains uneven across the EU, even for medicinal products that have been approved through the EMA's centralised procedure. Perhaps it is not surprising as access involves multiple criteria[1], some of which are outside the scope of the EU legislation. The data for total assessment times by EMA show a notable improvement between 2005-2010, which then increased gradually over the following period. In comparing the EMA and FDA assessment times, EMA average assessment times are shorter than those of the FDA for the period up until 2015, beyond which the situation reversed.

[1] Access is defined by fulfilment of the following criteria: 1) a medicine has been (conditionally or fully) approved for marketing in the country, 2) has been placed on the market by the marketing authorisation folder, and 3) is made available to patients as part of (partially) reimbursed care.

Stakeholders reported inefficiencies related to differing interpretation and implementation of the legislation and other relevant regulations and directives at the MS level which has led to delayed and unequal access across Member States.

Affordability

The affordability of medicines is an important factor for national health systems and patients, and it also has relevance to the profitability of the pharmaceutical industry. It is remarked that pricing and reimbursement decisions are based on national assessments of cost-effectiveness and thus in the remit of national authorities. Nevertheless, beyond intellectual property protection (conferred by patents and supplementary protection certificates), regulatory protection (i.e., data exclusivity and market protection) are also granted at the EU level to incentivise and reward pharmaceutical innovation. While the regulatory protection periods are now harmonised in the EU, the multiple possible protections can create a complex system.

An analysis of a sample of products of EU4 countries (France, Germany, Italy and Spain) with protection expiry between 2016-2024 shows that two thirds of the products are protected by intellectual property rights from generic competition, while one third of the products are protected by regulatory protection.

Medicine prices vary significantly between EU member states, and pharmaceutical spending is the third biggest cost element in healthcare spending at roughly 1.5% of the EU's GDP. Average spending on pharmaceuticals however remained stable in the EU over the last 20 years at about 20%. Spending levels and trends also depend on therapeutic areas; spending on oncology products increased fastest, while spending on cardiovascular products decreased over the same period. Understanding spending in hospital settings is more complex, however, there are indications that pharmaceutical spending in hospital settings has been rising faster.

Our analysis of top selling medicinal product sales data indicates that branded product prices drop on average by one third of the price level prior to generic entry. This is the highest level of decrease among comparator countries, and similar to that in Australia and Korea. The discount of the corresponding generic products (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%.

Medicine shortages

Medicine shortages is a key issue impacting on access to medicines and ultimately public health. Health professionals noted that the current legislation has not been effective in addressing the issues of the medicine shortages as evidenced by rising shortage notifications over the last 10 years. However, there may be other factors contributing to the increase, for example, there are more countries tracking and reporting shortages, and or doing so more effectively. The dominance of notifications due to 'quality and manufacturing' issues can be seen as an example of the legislation having been successful in increasing the observance of manufacturing standards. The implication is that, while the legislation has helped in creating more insight into the scale and the prevalence of medicine shortages, it has not yet been able to address sufficiently the reasons behind the shortages occurring or to alleviate their impact. Stakeholders, particularly industry and NCAs, report that generic medicines are particularly at risk of shortages, given the higher relative fragility of their supply chains.

Accommodating innovation

The legislation has provided a regulatory system which has facilitated innovation across the product lifecycle according to stakeholder interviews. 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 for accommodating innovation.

Some of the shortcomings stakeholders pointed to include addressing and supporting generic and biosimilar innovation, unmet medical needs, and development of antimicrobials. Stakeholder groups concurred that digitalisation and emerging science and technology developments have not been adequately integrated in the current regulatory system. Most stakeholders agreed that the legislation and related guidelines do not provide sufficient clarity for companies and national regulators when it comes to combination 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.

Competitiveness of EU pharmaceutical industry

The ever-increasing need for innovation in the pharmaceutical sector has led to an increase in total R&D expenditure in the EU, doubling since 2000 to more than €40bn in 2019, albeit no significant change can be attributed specifically to the implementation of the 2004 revisions of the legislation. The EU has a strong second position globally, especially together with its close neighbours, the UK and Switzerland, that are part of the European biopharmaceutical innovation ecosystem through cross-country collaborations and movement of skilled professionals and capital. Nevertheless, R&D investment in the EU has remained significantly lower that than in the US (€74 billion in 2019).

Competitive functioning of the EU internal market

There are differing views among stakeholders as to what the internal EU market for pharmaceuticals is. Some stakeholders (e.g. civil society, healthcare professionals and public authorities) disputed the idea that there is a single EU market for medicines. Their view is that there are multiple national/regional markets in practice. It is also worth noting that markets can only be understood for individual therapeutic areas as there is no competition across therapeutic areas. There is agreement across the various stakeholder groups that competition is suboptimal.

Nonetheless, many stakeholders agreed that the legislation has been beneficial for increasing competition in the pharmaceutical sector of the EU by facilitating generics and biosimilar entry in the market, particularly through the Bolar exemption.

The EU has been an early adopter of biosimilars and delineated an authorisation pathway for biosimilars much before any other country. The biosimilar pathways are seen as success increasing competition with the originator and facilitate access of biosimilars to patients.

Efficiency

Most stakeholders were unable to provide quantitative estimates of the costs and benefits associated with the 2004 revisions of the legislation. This limited number of observations was augmented by data from studies, where possible, and we have therefore provide large ranges for the monetary estimates of costs and benefits.

The 2004 revision is likely to have resulted in a net increase in regulatory costs to society on the order of €1.1bn-€1.8bn (over 15 years). The higher costs are the result of the higher standards set and the associated additional compliance and regulatory costs. There have also been benefit gains in terms of reduced costs for MAHs, the EMA and NCAs, which sum to €1.2bn-€1.5bn, largely offsetting the additional costs of increased information requirements and pharmacovigilance activities.

The 2004 revision is also widely believed to have resulted in more innovative medicinal products and a higher quality regulatory system, which is likely to have resulted in a positive health impact for patients treated with such products, which would otherwise not have been available, or would have been available later in time. We have estimated this additional health impact at 25-30 new innovative medicines, in total; which amounts to €4.8bn-€17.2bn in monetised benefits, using WHO guidelines on valuing QALYs. The valuation of health impacts is widely accepted to be deeply challenging and was carried out at an aggregate level, however, even working with the lower bound estimate of health impacts and cost savings (€6bn) and the upper bound of the estimated additional costs (€1.8bn), the 2004 revisions have delivered a positive overall social return.

This economic analysis resonates with feedback from stakeholders overall, where the overall balance of opinion is positive: 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 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 revisions 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 needs, and medicines shortages.

Coherence

In terms of internal coherence, the legal analysis and literature review on the legislation has identified overlaps, contradictions, or other inconsistencies within or between the Directive and the Regulation.

There are several in-built mechanisms to ensure an adequate articulation between the general pharmaceutical legislation and the specialised pharmaceutical frameworks. Nevertheless, some potential issues of coherence were identified, for example due to differing national rules on the conduct of trials with children may still delay the completion of a paediatric investigation plan (Paediatric Regulation) and for orphan medicinal products, generic competitors can only submit an application for marketing authorisation at the end of the 10-year protection period (Orphan Regulation).

There are several pieces of legislation not included in the specialised pharmaceutical legislation whose implementation can impact on several objectives of the general pharmaceutical legislation. Specific points were identified in linked legislations on health matters, including in the EMA fees Regulation, BTC legislation, Medical Devices Regulation, Health Technology Assessment Regulation, Cross-border healthcare Directive, GMO (Genetically Modified Organisms) legislation. Additional aspects were analysed in linked legislations not directly linked to the health sector, namely, SPC legislation, Unitary Patent protection, Data protection laws, drug precursor legislation, REACH Regulation, Environmental Quality Standard Directive, and EU Competition law.

In terms of coherence in implementing parts of the legislation, two key issues have been identified. First, the interpretation and timing of implementation of the 'Bolar' provision by member states. Second, the implementation and practice of hospital exemption that shows variations in the ways quality, safety and efficacy standards are implemented and controlled across member states for ATMPs.

How did the EU intervention make a difference?

The legislation provided a robust framework enabling harmonisation of regulations, incentives, standards, administrative requirements, and procedures for pharmaceuticals across the EU, according to stakeholders. These centralised and coordinated harmonisation measures across the medicine lifecycle simplified the regulatory system for medicine developers and reduced duplication of efforts across member states.

Within interviews, stakeholders commonly cited the creation of the European Medicines Agency (EMA) as one of the biggest achievements of the legislation. Stakeholders regarded EMA as a key actor in the unification and coordination of the regulatory system across the EU. The centralised procedure has been particularly valuable for smaller member states without the necessary resources and expertise to establish their own systems. The pooling and coordination of scientific resources under a common set of rules and practices has helped foster a common understanding across MSs on how medicinal products are evaluated and approved to a high standard and dealing with safety concerns in a consistent way. Industry stakeholders pointed to increased cooperation between member states and public authorities and highlighted successful collaboration of EMA with national competent authorities that has led to the optimisation of their resource use.

Furthermore, 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.

EU action during COVID-19 crisis was a particularly value added intervention. EU level action enabled quicker and concerted action compared to what MSs would have been able to achieve independently. Stakeholders commonly cited this was made possible because of regulatory flexibilities and optimisations enabling resources, capacities, expertise, and IT capabilities to be rapidly mobilised across EU.

There was consensus that the legislation has struck the right balance between action at EU level and national action and highlighted the added value of EU-level coordination and cooperation to develop best practices.

Is the intervention still relevant?

The objectives of the general pharmaceutical legislation remain valid after 15 years despite the introduction of multiple specialised legislations and several amendments of those. However, the legislation has limited provisions, mandate and specific action available to ensure that authorised medicines are launched in all member states and thus ensure equitable access to those for citizens across the EU. Therefore, the relevance of the legislation to equitable access to medicines is low.

Looking into the future, new objectives would need to be considered for the legislation to remain relevant in the face of the megatrends identified by the EU's Joint Research Centre. This includes the readiness and adaptability of the legislation to respond to technological developments and rapidly increasing presence of digitalisation in new tools generating regulatory evidence and medicinal products preventing, diagnosing and targeting diseases. Continued relevance also involves providing targeted incentives to the development of those medicinal products that respond to high unmet medical needs, for example for therapies against antimicrobial resistant infections.

The recognition of the increasingly complex and advanced therapies as medicinal products within the legislation is also important to ensure continued relevance of the legislation to permit authorisation of those products in a streamlined manner for all manufacturers, small to large, commercial or otherwise.

Conclusions

The general pharmaceutical legislation is a successful EU intervention in the sense that it achieved all four high level objectives to some extent. The objective to ensure quality, safety and efficacy of medicinal products was achieved to the largest extent, while that of ensuring access to medicines was achieved to a limited extent. The objectives of ensuring competitive functioning of the EU internal market and attractiveness in a global context were achieved to a moderate extent. With the needs and problems that the 2004 revisions were addressing still remaining relevant, the objectives of the legislation and its revision also continue to remain relevant for the future.

A robust and flexible authorisation system was developed in Europe taking advantage of harmonised processes through the centralised procedure for innovative medicines requiring pooled European scientific expertise; while decentralised procedures at national level available for smaller companies and generic producers 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. These elements contributed strongly to the stated objective of ensuring quality, safety and efficacy of medical products in Europe.

The system includes a predictable incentives framework (8+2 years of regulatory data and market protection period) that has kept Europe an attractive market for medicine developers and allowed innovative medicines to be available to national health systems. However, this does delay market entry of generic products, affecting affordability of medicines and national health budgets. On the other hand, the Bolar exemption has allowed quicker generics entry, but since the implementation of the exemption varies, the benefits are also variable. The creation of a delineated authorisation pathway for biosimilars in Europe before any other jurisdictions, has made Europe a leader in this space, allowing the launch of biosimilars 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 biosimilars across EU member states.

It is important to note however that the availability of innovative medicines does not lead to equitable access to those across member states, another stated objective of the legislation. In effect, the relevance of the legislation is rather limited with regard to access, as companies make decisions on market launch while national health systems retain clear responsibility over providing their chosen healthcare provision (including medicinal products) to their population and likewise for the decision to pay for those. Nevertheless, 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 to guarantee a high level of public health.

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 USA or Japan. The US remains the jurisdiction of choice for filing marketing authorisation

applications for new active substances, but the EU has the second destination for filing and more substances are being authorised by the EMA less than 1 year after the FDA.

The legislation is well-framed, internally coherent and has clear EU added value. However, external coherence has become a challenge in a changing EU regulatory landscape. Emergence of new technologies and borderline cases (that potentially sit between two or more legislations) cause inconsistencies/uncertainties such as the coverage of GMO requirements, environmental challenges and new manufacturing methods along with definition of products e.g. ATMPs, radiopharmaceuticals and medical devices.

Lessons learned

The objectives of the general pharmaceutical legislation remain valid after 15 years. As discussed, not all objectives have been fully met through the 2004 revisions of the legislation and new approaches are needed to address those challenges. However, these are complex issues that the legislation in itself may not be able to solve effectively.

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 between legislations, increasing the likelihood of impact in terms of public health, environmental sustainability, digitalisation, etc. This will ensure a more systemic fit of the general pharmaceutical legislation in the wider EU policy framework.

Looking into the future, new objectives will need to be considered for the legislation to continue to remain relevant. This includes the readiness and adaptability of the legislation to respond to technological developments, e.g., in new manufacturing methods, and rapidly increasing presence of digitalisation in new tools generating (real world) regulatory evidence and medicinal products preventing, diagnosing and targeting diseases. Continued relevance also involves providing targeted incentives to the development of those medicinal products that respond to high unmet medical needs, for example for therapies against antimicrobial resistant infections. The recognition of the increasingly complex and advanced therapies as medicinal products within the legislation is also important to ensure continued relevance of the legislation to permit authorisation of those products in a streamlined manner for all manufacturers.

Many 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 has demonstrated that there is room for flexibility to adapt regulatory processes and accelerate product development and authorisation processes, including use of remote processes for source data verification, virtual audits and monitoring. This would reduce administrative burden on medicine developers and release capacity for regulatory authorities. EMA has also adapted its governance model 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 as safety and efficacy of increasingly complex and advanced therapies will need to be assessed. It is however noted that EMA has limited resources and its expertise and capacity need to be expanded in order to progress complex dossiers at pace and keep up with the US FDA, where relevant, and do so without compromising safety and quality of authorised medicines.

The pandemic also highlighted factors causing shortages such as over-reliance on one single or very few foreign suppliers for some essential APIs. This might be mitigated through diversification of suppliers. Collaboration between industry and regulators (especially EMA) during the pandemic on stocks and shortages, to provide scientific advice and to generally expedite the medicine development process demonstrated that different interests can be usefully aligned. This however needs to happen under public scrutiny and transparency.

1 INTRODUCTION

This is the final report for "The study in support of the evaluation and impact assessment of the EU general pharmaceutical legislation" that was commissioned by the Directorate-General for Health and Food Safety and was carried out by Technopolis Group with support of Ecorys BV, Milieu Law & Policy Consulting, Utrecht University (Centre for Pharmaceutical Policy and Regulation & Innovation Studies Group) and Informa Pharma Custom Intelligence.

This report first elaborates the purpose and scope of the evaluation along with the methodological approach and its limitations. Next, it provides a background to the intervention and how the situation evolved over time. It then provides the findings of the evaluation first summarised as a high-level narrative before providing responses to individual evaluation questions per evaluation criterion. Finally, we describe the key conclusions from the evaluation.

1.1 Purpose and scope of the evaluation

The evaluation focussed on Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation (EC) No 726/2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency, i.e., the general pharmaceutical legislation (in the following "legislation"). The goals of this study were specifically:

- To assess, in line with the Better Regulation guidelines, the effectiveness, efficiency, relevance, coherence and EU added value of the legislation;
- To assess the performance of the legislation during the COVID-19 crisis and consider the changed circumstances and the lessons learnt from the pandemic in relation to the functioning of the pharmaceutical system;
- To draw conclusions on the evidence gathered to support future policy decisions.

1.2 Scope of the evaluation

The evaluation covers the core of the legal scope of the general pharmaceutical legislation and it includes aspects of the specialised product groups, i.e., advanced therapy medicinal products, medicines for children and medicines for rare diseases, insofar these are covered by the general pharmaceutical legislation. The specialised pharmaceutical legislations themselves were not in scope for the evaluation.

The evaluation only partially assessed the following provisions (i.e., in relation to the objectives of the evaluation) that have been recently added to the corpus of the general pharmaceutical legislation due to their relative novelty:

- Amending Directive 2010/84/EU and 2012/26/EU: Pharmacovigilance;
- Amending Regulation (EU) No 1235/2010 and 1027/2012: Pharmacovigilance;
- Amending Directive 2011/62/EU Falsified medicinal products, with exception of the provisions relating to active pharmaceutical ingredients (APIs) and brokering of medicinal products.

The relevant time period for the evaluation is from the year 2005 until end of 2020. This is because 2004 marked a significant amendment to the legislation[2], with implementation starting in the following year. The 15-year period for the evaluation was used to illustrate trends and developments over time that were relevant for the development, authorisation, manufacturing, supply, and monitoring of medicines. However, the evaluation covered all key aspects and developments that are relevant to the current performance of the EU legislation, including elements that had not been directly addressed by the legislative changes in 2004. The years between 2000-2005 leading up to the implementation of the revised legislation served as a baseline for the evaluation.

The geographical scope of the evaluation was the European Economic Area, i.e., EU28 and three EFTA states, however comparisons with the other jurisdictions such as the US, Australia, Canada, Israel, China, Japan and South Korea were made where relevant and feasible (e.g., in the comparative legal analysis and quantitative secondary data analysis).

[2] Official Journal of the European Union publication date of 30 April 2004.

1.3 Methodological approaches and limitations

The evaluation assessed the general pharmaceutical legislation based on the five overarching evaluation criteria of effectiveness, efficiency, coherence, relevance and EU added value. To that end, a layered list of evaluation questions was drafted per evaluation criterion using the Commission's list from the Terms of Reference as a starting point. An evaluation matrix was developed to provide a framework for answering the evaluation questions (see Annex II). The matrix cross-references evaluation questions to the relevant judgement criteria, list of indicators and analytical approaches i.e., methods/tasks.

In terms of **methodology**, a mixed quantitative and qualitative approach was applied drawing on multiple methods (see Annex I). It included peer-reviewed literature and policy document review to gather existing knowledge base and served as a source of facts and figures; secondary data analysis of over 50 macro indicators relevant to industrial & economic competitiveness, through research & innovation, to access, affordability and single market effects, including statistical, econometric and trend analysis in the EU, compared to data from other jurisdictions. This information is available in the Analytical report. In addition, case studies were developed that focus on specific issues and illustrate linkages and mechanisms behind trends observed in the data. Finally, extensive stakeholder consultations were conducted and resulting primary data was analysed from the feedback for the consultation on the Roadmap/Inception Impact Assessment and public consultation, targeted surveys, interviews and an evaluation workshop for stakeholders. Stakeholder groups included public authorities, civil society and patient organisations, healthcare professionals and their associations, academic and public research organisations/experts and industry.

There have been a number of **limitations** that affect the robustness of findings. First, effects are linked to a complex multi-factorial evidence base and stakeholders were often unable to break down observed effects to drivers of those effects and link those to specific legislative measures in scope. This was particularly the case for providing quantitative information linked to the costs and benefits (efficiency) of the legislation.

Second, the broad scope of the general pharmaceutical legislation inherently linked it to a large number of specialised pharmaceutical legislations and other more general EU rules and laws that have been added and periodically amended over the years in scope of the evaluation. These confounding external factors influenced primarily the relevance, effectiveness and efficiency of the legislation. In many cases, stakeholders provided information more directly attributable to these other legislations rather than to the legislation in scope for the evaluation. In addition, many businesses operate globally with functional teams that comply with and report to authorities in multiple jurisdictions and therefore they were not able to isolate the effects of the EU legislation.

Third, due to the extended time period in scope for 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 legislative revision. Staff turnover in organisations over time and limited institutional memory also contributed to limitations in data collection. Many businesses underwent business development activities including acquisitions, mergers, initiation of new research areas or discontinued development programmes, which all result in apparent changes not attributable to the legislation.

Fourth, some stakeholder groups (especially the civil society and public authorities) found it challenging to mobilise internal resources to provide information, data and evidence across all evaluation dimensions and data collection channels during the data collection period of the study. It should also be noted that stakeholder consultation took place during an intense wave of the coronavirus pandemic in Europe. To make sure that views from across the stakeholder groups were included, the study team used a purposive sampling frame for interviews and workshops to allow good coverage of different member states (MSs) and stakeholder types (e.g., a spread across associations and individual companies, generics companies and originators, large pharma and SMEs in industry; national competent authorities [NCAs] and payers among public authorities, etc.). To mitigate response rate bias for the targeted survey and open public consultations, results were presented by stakeholder group or weighted in calculations.

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. Moreover, data collection and indicators are not uniform across all countries. As such, the extent to which

robust analysis and interpretation is possible especially for comparisons across different jurisdictions and even MSs is limited depending on the comparability and (un)availability of data. The difference-in-difference statistical approach was used as part of the mitigation measures for this problem where possible.

As a result of the limitations described above, both qualitative and quantitative data collected during the evaluation show large variations of quality across stakeholder groups. Extensive data cleaning and data verification were applied to ascertain that data provided meet the inclusion criteria of the study (i.e., the answer is relevant to the question posed). Much of the quality data collected are linked to more recent years and therefore direct attribution of these effects to the 2004 revision of the legislation remains limited. In terms of qualitative data collected through open questions in the targeted survey and open public consultation (OPC) as well as interviews, data quality and quantity were affected by a variety of factors including the number and nature of topics covered, time available for responses (e.g., 90 minutes for interviews) and domain expertise of respondents. Moreover, stakeholder groups were not homogenous but comprised a variety of different stakeholder types. Therefore, it was not possible to determine the consensus view or explanation for some topic areas.

2 BACKGROUND TO THE INTERVENTION

2.1 Description of the intervention and its objectives

An intervention logic for the 2004 revision of the legislation was not formally developed in 2001 when the legislative review of the general pharmaceutical legislation was initiated. This legislative review was a formal requirement of Article 71 of Regulation (EEC) No 2309/93 to analyse the achievements of Regulation (EEC) No 2309/93 and Directive 75/319/EEC, Chapter III.

However, a robust evaluation requires an intervention logic describing the objectives and impact pathways envisioned for the intervention. An intervention logic was therefore developed as part of the current study building on the draft model provided in the Terms of Reference. It is important to emphasise that an intervention logic shows how the intervention was expected to work by the legislators when it was introduced and not how it worked in practice, which is the subject of this evaluation. A diagram depicting the intervention logic i.e., the relationship between the objectives, actions, results and impacts of the intervention is shown in Figure 1.

The overarching need of a general pharmaceutical legislation was to **guarantee a high level of public health throughout Europe**. This meant that safe, high quality and effective medicines needed to be available and accessible to patients regardless of the MS in which they resided. This was particularly relevant as the European Union continued the enlargement process beyond 2004. Moreover, the revision recognised that development of medicinal products was a scientifically and technologically complex, highly regulated, time-consuming and expensive endeavour that required a globally attractive legal system to ensure the competitiveness of the pharmaceutical sector and internal market for medicines in Europe.

The 2004 revision of the general pharmaceutical legislation envisioned four main, high-level objectives:

1. **Ensure quality, safety and efficacy of medicinal products**. This means a robust authorisation system, surveillance and supervision are in place along the entire medicinal product lifecycle, including post-authorisation monitoring and pharmacovigilance procedures.
2. **Ensure access to medicines**. Health protection can only be effective if patients have equitable access to medicinal products as early as possible after authorisation.
3. **Ensure competitive functioning of the EU internal market.** Competition across medicine developers is expected to bring ever more innovative and effective medicines to meet the needs of patients in all Member States. This objective also considers a system where medicines that are no longer under patent protection (off-patent medicines) can be available in generic as well as the original branded forms so that there is a price competition benefitting national health systems.
4. **Ensure attractiveness in the global context.** Medicine development is a global endeavour, and it is important that Europe has a legislative framework that is globally attractive to medicine developers.

More specifically, these high-level objectives were expected to be achieved through a number of more specific objectives which were mutually reinforcing a more systemic view:

Accommodate innovation. This means that the legislative system is ready for the new scientific and technological developments that underpin innovative and effective products. Here innovation comprises not only new molecular entities but also adding value (follow-on innovation), repurposing existing medicines and developing biosimilar products. In other words, the legislation presents no roadblocks to innovation, rather, it is flexible and adaptable enough to enable new advances in medicinal products in a competitive environment.

Reduce administrative burden, improve adaptability of regulatory environment. This specific objective responds directly to the need for all medicine developers (including generic manufacturers) to navigate the regulatory landscape with minimum administrative burden (cost and time) and, as noted above, accommodate new scientific and technological developments. Therefore, rationalisation and simplification of the system was foreseen as far as possible to improve the legislation's overall consistency and visibility, the transparency of procedures and decision-making.

Reduce disparities and duplication of efforts. Historically, European countries had differing rules and processes that added complexity and resulted in duplicated efforts. Harmonisation and standardisation were promoted to reduce duplication, improve certainty and transparency to allow a level playing field for medicine developers across European MSs and transparent information access to patients. With the EU enlargement processes, this element received a particular focus.

Facilitate free movement of medicinal products. According to the concept of the internal EU single market, products should be traded freely across the Union. This objective aims to facilitate free trade for medicinal products through greater harmonisation of processes.

Regarding the broader policy context, the United Nation's Sustainable Development Goals (SDGs) were established in 2015 to succeed the Millennium Development Goals, as a global development framework to achieve better and more sustainable future for all. Although coming after the EU general pharmaceutical legislation was enshrined, the SDGs, in particular SDG Goal 3 of ensuring good health and well-being at all ages, SDG Goal 9 of building a resilient industrial infrastructure to foster innovation, and SDG Goal 10 of reducing inequality within and among countries, are consistent with the objectives of the general pharmaceutical legislation.

Multiple, interdependent impact pathways mediated by inputs and actions were foreseen in a complex pharmaceutical sector and health system for the four main objectives. These were expected to eventually lead to a higher level of health protection across Europe. The four key impact pathways are described below.

Impact pathway 1: Higher standards for the quality, safety and efficacy of medicinal products

A number of **actions** foreseen in the 2004 revision of the legislation were expected to lead to the achievement of higher standards for safe, efficacious and quality medicines: Changed documentary requirements, including environmental risk assessment (ERA); Harmonised application of good manufacturing practice for active substances; Reinforced inspections and increased coordination by introducing new tools; and more frequent submission of periodic safety update reports, harmonised national pharmacovigilance systems and inspections.

These actions were collectively expected to lead to the immediate results (or **outputs**): Quality control exercised over the life cycle of medicinal products; Strengthened market surveillance and safety monitoring; Effective information available for patient protection; and Decisions based on harmonised criteria, standards and protocols. Longer term these outputs should lead to the **outcome** that an effective monitoring system be in place in the EU covering the full lifecycle of medicines, which would ultimately enable the availability of efficacious, safe and high-quality medicines (**impact)**.

In addition, additional actions foreseen to accommodate innovation such as adaptation of the definition of a medicinal product, changes in the composition of EMA scientific committees and their mandate to provide scientific advice were also expected to contribute to this impact dimension, through outputs such as updated frameworks and procedures to accommodate new innovations and more effective coordination of advice and scientific support available to medicine developers. These outputs would promote the outcome of increased level of authorisation of innovative medicinal products, contributing to the impact of improving availability of medicines with a high level of safety, efficacy and quality in the EU.

Impact pathway 2: Improved access to medicines

The **actions** foreseen in the legislation to accommodate new scientific and technological developments in medicinal products included firstly the adaptation of the definition of medicinal product in the legal text taking account of these developments. Secondly, the composition of the various EMA committees was to be modified to reflect the ever more complex need to provide scientific advice to medicine developers. Pooling scientific expertise from MSs to guarantee a higher level of public health protection was one of the key aims of the revision (European Commission, 2002a). The 2004 revisions also introduced extra data protection periods for new indications for old medicines (repurposing). These actions taken together were expected to lead to the following **outputs**: updated frameworks and procedures to accommodate innovative products and treatments as well as effective coordination and scientific support available to medicine developers. These outputs, along with a reduced regulatory burden achieved from streamlined and harmonised authorisation processes, were expected to lead to a positive **outcome** which is an increased number of innovative medicinal products being authorised. Ultimately, the legislators foresaw that with increased number of authorised innovative products (partly through accelerated assessment and conditional marketing authorisation), patient access to medicines would improve (**impact**). However, it should be noted that while authorisation may be the first step in driving access of innovative medicines to patients, the EU does not have authority to ensure marketing in the different countries. Market launch in a Member State is a decision of the marketing authorisation holder (MAH). Access to patients in MSs is also down to

pricing and reimbursement decisions at the national and regional level by health technology assessment (HTA) bodies and healthcare payers based on cost-effectiveness considerations.

Impact pathway 3: A more harmonised, smoother and competitive functioning of the single market.

It was recognised that Europe needed to do more to remove barriers and harmonise processes to ensure that the internal market for medicinal products functions effectively and is competitive, and that patients have access to both originator and generic medicines as soon as intellectual property rights and regulatory protection periods allow. Therefore, a number of **actions** were initiated in the 2004 revision of the legislation. Data protection periods varied across the Union and this element was updated and harmonised (standard 8+2 years of regulatory protection was introduced across the EU), and the so-called 'Bolar' provision was introduced for research purposes wherein generic medicine manufacturers could have earlier sight of the regulatory data dossier so that R&D could be initiated to facilitate launch of generic products as soon as the 8+2 regulatory protection lapsed (Day 1 launch) (CMS, 2007).

In terms of medicine authorisation, the scope of the centralised procedure (CP) was expanded and a new decentralised authorisation procedure (DP) was introduced to help optimise procedures to obtain national marketing authorisations. This meant expanding EMA's central role in medicine authorisation, and at the same time, reducing the potential for direct referral to the Committee for Medicinal Products for Human Use (CHMP). A co-ordination group for mutual recognition procedure (MRP) and DP (Coordination Group for Mutual Recognition and Decentralised Procedures – Human, CMDh) was established with an explicit mandate to help to reconcile disagreements between Member States.

The harmonisation of data protection, introduction of the 'Bolar' provision, expansion of the scope of the CP and introduction of the DP were expected to act synergistically, leading to an increased number of authorisations through the centralised procedure and to a decreased number of referrals from the MRP and DP to EMA (**outputs**). It was also expected that therefore a greater amount of resources would be re-allocated to EU level activities from Member States, creating efficiencies.

In addition, regulators were mandated to make more information available to the public about medicinal products, including assessment reports prepared by national competent authorities and EU public assessment reports produced by EMA, the summary of product information and package leaflets (action). The new information provisions were meant to enhance transparency (output).

In the longer term, all the outputs were expected to contribute to **outcomes** that represent improved efficiency such as full harmonisation of the rules governing authorisation, production, distribution and use of medicinal products, and more generally uniformisation of processes and reduction of existing market barriers. Indirectly, these outcomes could be expected to contribute to other impact dimensions, including improving access to medicines across Europe through enabling authorisation of a greater number of innovative medicinal products (Impact Pathway 2) and improving the attractiveness of the EU market in the global context by reducing the regulatory burden (Impact Pathway 4).

Impact pathway 4: Improved attractiveness in the global context

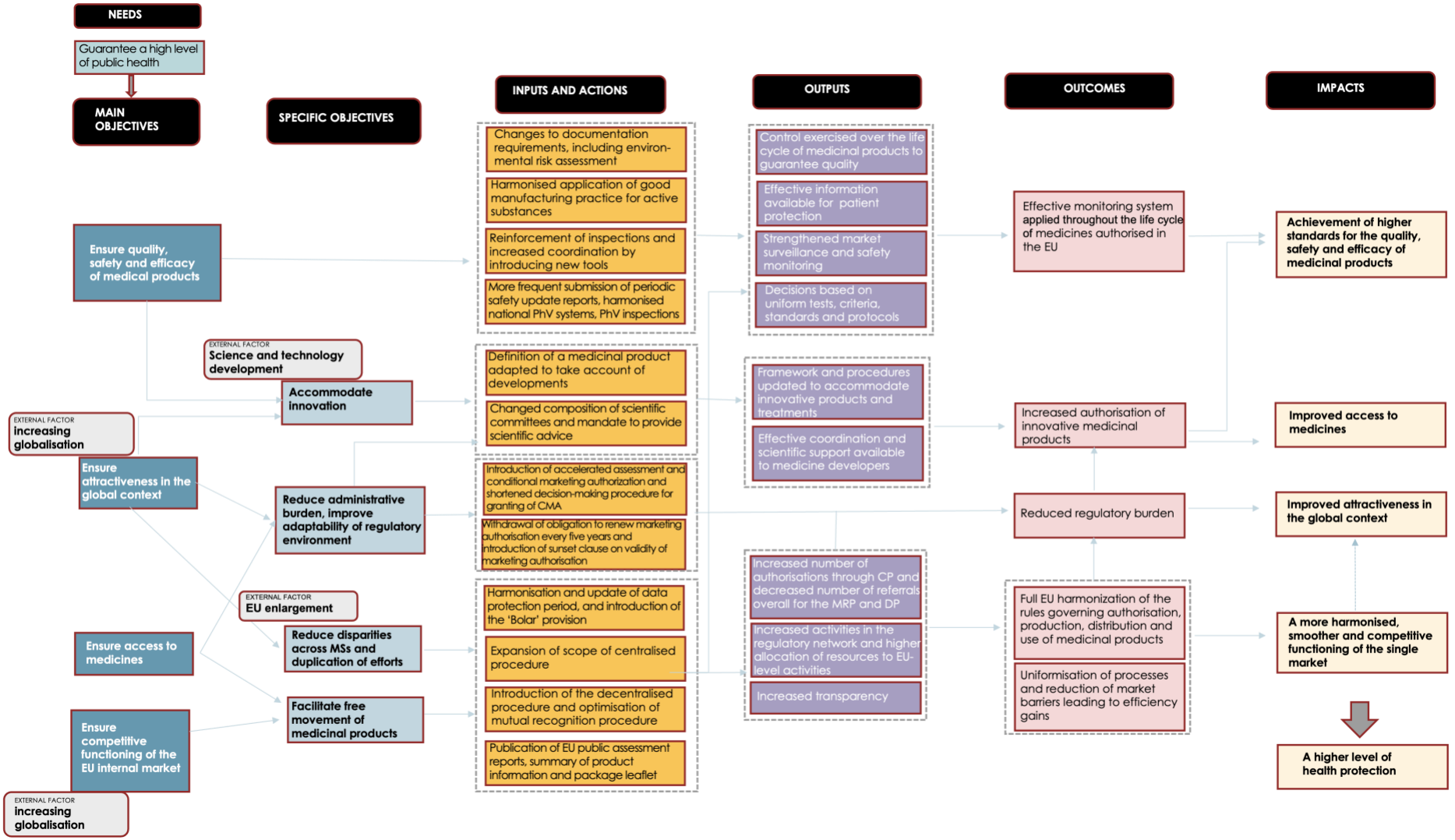
As discussed earlier, medicine development is a global endeavour and the revision put forward several **actions** to improve the EU's attractiveness for medicine developers. One such action is the withdrawal of the obligation to renew marketing authorisation every five years after the first renewal and introduction of a sunset clause on the validity of marketing authorisation. This action was intended to streamline processes and decrease the burden on marketing authorisation holders (MAHs). Another action undertaken as part of the revision was the introduction of accelerated assessment and the conditional marketing authorisation with a shortened decision-making procedure for the latter. This latter action was intended to facilitate faster decision-making processes to allow earlier access to innovative medicines for patients (European Commission, 2002b). Together, both actions were envisaged to reduce the regulatory burden for applicants (**outcome**), leading to the **impact** that overall attractiveness of Europe to medicine developers globally would be improved.

It should be noted that there are potential tensions or counterbalancing acts between objectives, i.e., reducing unnecessary burden while maintaining high regulatory standards; not hindering the

development of the pharmaceutical industry and achieving innovation while also ensuring access to medicines including generics and biosimilars. And therefore, several assumptions underpin the impact pathways as follows:

- Increased number of authorisations of innovative medicinal products leads to improved access to effective medicines in Member States;
- Accelerated assessment and conditional marketing authorisation lead to earlier access to effective medicines;
- Unnecessary administrative burden can be identified and reduced in such a way that it does not interfere with the robustness of authorisation processes;
- Health systems are in a position to administer innovative treatments, i.e., that the necessary skills, knowledge, infrastructure and resources are present, so the legislation contributes to public health protection;
- Innovative and generic product development continues to represent a commercial opportunity for the developer under the updated framework and procedures, i.e., that the market opportunity exceeds the cost and risk of medicine development, authorisation and maintaining the product on the market;
- External factors are aligned with the general pharmaceutical legislation in a way that these do not hinder the emergence of intended impacts.

Figure 1. Intervention logic of the 2004 revision of the general pharmaceutical legislation



2.2 Baseline: points of comparison

The Commission did not conduct a formal impact assessment for the revision of the general pharmaceutical legislation as it was not yet part of the standard procedure for adopting a legislative proposal. Therefore, the baseline has been reconstructed as far as possible based on available data, including by reference to the relevant explanatory memoranda for the changes and the audit of the procedures and operations of the European Agency for the Evaluation of Medicinal Products (CMS Cameron McKenna & Andersen Consulting, 2000; European Commission, 2002a, 2002b).

In Section 4, the changes and trends from 2005, when the revision was implemented, until the end of 2020 have been compared to the situation from 2000 to 2004 depending on availability of data (both qualitative and quantitative). In addition, the situation in the EU has been compared to other jurisdictions such as the US, Japan, Switzerland, Australia and Canada mainly in terms of the nature and burden of regulatory processes (including comparative legal analysis) as well as global competitiveness of the pharmaceutical sector. The key indicators used for the comparisons are indicated in the evaluation matrix (Annex II) and have been populated in the Analytical report. These cover parameters and areas such as new marketing authorisations (number, type of medicine and approval times), access and affordability (medicine price levels), clinical trials, medicine shortages in MSs (number and cause) and non-compliance with good manufacturing procedure (GMP).

Prior to the revision of the legislation (the baseline situation for the evaluation), the environment for pharmaceuticals was undergoing major changes with the enlargement of the EU and increasing globalisation of regulatory practices.

The pharmaceutical sector in the EU was not as competitive as that in the US in the 1990s. While scientific research was successfully organised in the US through smooth interaction between industry and public or private research organisations, fragmented EU MS policies did not result in the same level of interaction necessary for industry to successfully exploit the latest scientific results (Gambardella et al., 2000). Further, the fragmented nature of the European market for pharmaceuticals contributed to declining competitiveness, due to divergent public interventions and regulatory environment at national and regional levels (Gambardella et al., 2000).

European companies struggled to advance in innovative areas such as biotechnology and thus the European pharmaceutical sector was losing competitiveness. There were several reasons for this, including the lack of ability to organise innovation systems, higher labour intensity coupled with lower R&D value added activities, overall leading to a comparative disadvantage in selling their medicinal products in Europe (Gambardella et al., 2000). The restructuring of the health care system and consequently the demand for new pharmaceuticals in the USA benefited the technologically advanced, vertically specialised domestic pharmaceutical industry. European pharmaceutical companies tended to operate exclusively in their protected national markets which did not provide strong incentives to adopt innovation and globalised business strategies.

The continued enlargement of the European Union contributed to the need to establish an integrated environment for pharmaceuticals, as differences across the new Member States would amplify the problems of fragmentation and disparity. The legislative revisions thus had to be undertaken with enlargement in mind such that the adaptations to regulatory procedures would remain fit for purpose for expansion beyond the 15 EU Member States in 2002, and could accommodate scientific debates and take effective decisions with more countries involved (European Commission, 2002a). An integrated environment with harmonised systems and incentives at the EU level was regarded important to enhance EU-wide competition, improve efficiency of European companies, develop innovative medicinal products and reduce reliance on non-EU products to safeguard public health.

As noted above, the early 2000s was also a time of ever-increasing globalisation of regulatory practices and scientific and technical criteria for evaluating medicinal products across the world's three major pharmaceutical regions of the time – Europe, North America and Japan (European Commission, 2002a). This was a departure from the situation in 1995 when the new authorisation procedures (see below) were first introduced, and therefore the Commission had to consider the globalisation aspect in the 2004 revision to ensure international competitiveness of the EU regulatory system for medicines, as well as that the revised system was more modern, effective and lasting. By 2002, the Commission and Member States were actively involved, through their participation in

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in the international discussions on technical and scientific requirements in the field of human medicinal products.

The European pharmaceutical system had two major routes to authorise medicines since 1995: the historic national authorisation route (and the related mutual recognition procedure, MRP) and a centralised route (CP) via the European Agency for the Evaluation of Medicinal Products, now named European Medicines Agency (EMA). The introduction of the centralised procedure allowed applicants to apply for marketing authorisation at EU level and place medicinal products on the market in all EU countries after regulatory assessment carried out by the EMA.

According to an evaluation of the EU authorisation processes of medicinal products conducted in 2000, both the CP and the MRP systems provided complementary benefits and contributed to a harmonised and efficient regulatory environment for medicinal products in Europe (CMS Cameron McKenna & Andersen Consulting, 2000). Nevertheless, the MRP system was seen as less successful in achieving harmonisation as some Concerned Member States continued to evaluate marketing authorisation applications, sometimes raising concerns that were unaligned with the recognition principle. It was pointed out that general supervisory and management support was lacking in this system and arbitration was not an efficient mechanism for companies. However, MRP was considered particularly flexible and met the commercial needs of smaller companies as they could get prompt access to major EU markets through the Reference Member State of their choice for first application.

The CP created conditions in which a single scientific evaluation of the highest standard could provide companies rapid access to markets for their innovative products. While this was the result of cooperation of EMA and Member State authorities, overall responsibility resided with EMA. It was however a challenge to maintain the breadth and depth of regulatory expertise at the EMA in the face of emerging technologies used by the pharmaceutical industry. While the EMA was effectively coordinating Member States' scientific expertise, it was suggested that specialist groupings with particular expertise needed to be created within the Committee for Proprietary Medicinal Products (CPMP), now known as the CHMP.

The early evaluation in 2000 attempted to compare cost-benefits of the two authorisation systems but it was not possible to measure cost efficiencies for applicants and the evaluation could not demonstrate economies of scale of the CPs with respect to MRPs. While the former was expected to suit the needs of larger companies, the latter would meet the needs of many smaller companies more efficiently. It suggested that while CPs helped harmonise standards and decision making, resource requirements actually increased through funding the EMA and involvement of national authorities in every assessment activity.

Regulatory data protection periods differed under the two approval systems and across national systems, which was believed to lead to differences in availability of innovative products on national markets and lowering pharmaceutical companies' willingness to invest in incremental research. Before the revision, MSs provided 6 or 10 years of data exclusivity, except for biotechnological and high-technology medicinal products which had 10 years of data protection (Adamini et al., 2009). Austria, Denmark, Greece, Finland, Ireland, Luxembourg, Portugal and Spain applied a data exclusivity period of 6 years.

It is important to remember that the organisation, provision and financing of healthcare is the responsibility of individual MSs in Europe. Consequently, MSs negotiate prices of medicines with suppliers (through payers) and make decisions on which medicines are reimbursed. This means that access to medicines can depend on a country's buying power. While this may reflect different historical social values and level of wealth across Europe, it hindered the creation of a unified European market with a lack of economies of scale and potential for competition, and even created inconsistencies, inefficient use of resources, and possibly uneven standard of medical care (Danzon, 1997).

3 HOW HAS THE SITUATION EVOLVED OVER TIME?

3.1 Implementation of the legislation

The negative trends observed in the EU life sciences sector in the 1990s regarding pharmaceutical R&D investment and competitiveness of the industry vis-à-vis global markets (Danzon, 1997) and the risk of exacerbation of a fragmented EU pharmaceutical regulatory system with further enlargement of the market with new Member States prompted the European Commission to devise a number of measures to reverse these trends. The 2004 revision of the legislation was delivered through two main legal instruments: the Directive 2001/83/EC and Regulation (EC) No 726/2004. These instruments have provided a comprehensive platform for the regulation of the lifecycle of medicinal products from development and authorisation to post-marketing monitoring and inspections of manufacturing and distribution. Even though several Member States were delayed with their national legislation to implement the changes to the Directive 2001/83/EC, the actual use of the new measures was not substantially delayed.

Some differences have been noted across MSs in the implementation of parts of the legislation. One area is the interpretation and implementation of the 'Bolar' provision by MSs. Individual MSs have transposed Directive 2004/27/EC into law at different times (mostly between 2005 and 2007), but the text adopted in each country can allow for different interpretations of the Provision (CMS, 2007). For example, in Spain the Provision can only be used for 'experimental' purposes and no commercialisation activity in preparation for market launch is allowed. On the other hand, in the Netherlands, generic manufacturers can prepare both regulatory procedures and production under the 'Bolar' exemption to enable Day 1 product launch. Another area of inconsistency across MSs is hospital exemption[3]. A recent study on how hospital exemption has been implemented in seven European countries showed great variations in the ways quality, safety and efficacy standards are implemented and controlled across EU MSs for ATMPs, which draws concern around potential impact on public health (Hills et al., 2020). Assessment of medicines containing or consisting of genetic-modified organisms (GMOs) is also complex and varies across the EU (e.g., assessment of their environmental safety) according to civil society organisations, industry and public authority stakeholders (public consultation and interviews). On occasion, this can lead to delays in clinical trials and authorisation of GMO-containing medicinal products according to industry stakeholders. The variations exist in the Contained Use versus Deliberate Release classification, risk classifications for the same GMOs (within Contained Use), and data requirements (content and format) (Beattie, 2021; Lambot et al., 2021).

3.2 Intellectual property and regulatory protection of pharmaceuticals in the EU

Protecting intellectual property (IP) is deemed necessary to drive innovation so that return on investment to research and development can be realised. There are multiple ways to incentivise and reward pharmaceutical innovation which is a long, expensive and risky process. Patent provides the basic protection and incentive to pursue innovation taking a novel concept to industrial application by excluding others from exploiting the invention for 20 years from filing date. Secondary patents are also known in pharmaceuticals and usually filed for improved variants of the basic product, new therapeutic indications, or new combinations. Since the commercialisation may take place late in the patent protection period, the EU introduced supplementary protection certificates (SPCs) in 1992 to offset part of the lost patent term. The combined IP protection period from marketing authorisation is limited to a maximum of 15 years.

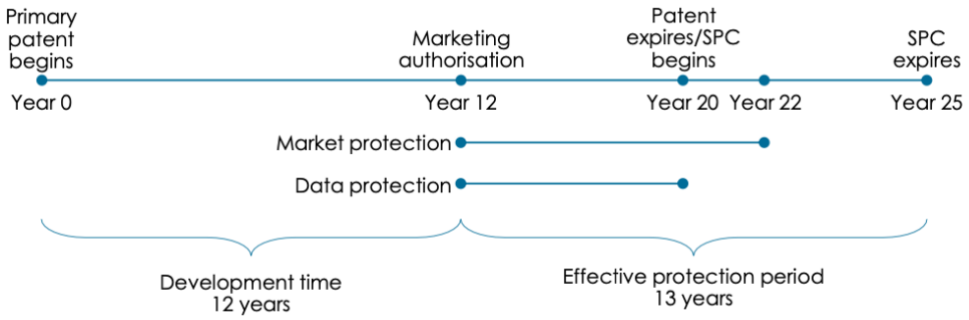
There is another protection type that is linked to the proprietary data that medicine developers collect on the quality, safety and efficacy of the product for the purpose of marketing authorisation. This data exclusivity or regulatory data protection period was standardised at 8 years in the revised pharmaceutical legislations. This means that a generic or biosimilar medicine developer can only refer to this data supporting their marketing authorisation after this period. There is also a market protection period that extends beyond the data protection period and in the EU it is an additional 2-year period when the generic version of the product cannot be placed on the market. The new

[3] 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.

harmonised regulatory protection period has applied to new marketing authorisations for which applications were submitted on 30 October 2005 onwards.

There are additional incentives and rewards in the EU, including an additional year of market protection in case a new therapeutic indication for a protected product brings significant clinical benefit; 10-year of market exclusivity for orphan medicinal products, protecting those from competition from similar medicinal products; and an extension of 6 months of SPCs to reward paediatric investigations of medicinal products, and if the investigation concerns an orphan product, the orphan market exclusivity may be extended to 12 years.

Figure 2 Intellectual property and regulatory protection periods in the EU



Source: Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (Copenhagen Economics, 2018)

The multiple possible protections can create a complex system and it is useful to focus on the expiry date of the last measure in place that protects the innovator medicinal product from generic competition in the EU markets. This may be SPC expiry or the regulatory protection expiry. A sample of 223 products in EU4 countries (France, Germany, Italy and Spain) with protection expiry between 2016-2024 shows that IP rights are the last to expire for about two thirds of the products in the basket (152), while regulatory protection is the 'last line of defence' for one third of the products (81). Similar results were obtained in a recent study (Copenhagen Economics, 2018) that found that 32-40% of products are protected by market protection. The same study found that pharmaceutical incentives and rewards in the EU are the most attractive when compared to Canada, China, India, Japan and the United States with regard to the basic regulatory protection periods (Table 1).

Table 1 Basic regulatory protection periods for pharmaceuticals globally

Country	Protection	Duration
Australia	New Chemical Entity + Market Protection	5 years
Canada	New Chemical Entity + Market Protection	6+2 years
Europe	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

3.3 A regulatory framework to support innovation and access to medicines

Since the revisions in 2004, the European Commission has worked to balance competition and affordable access to medicine (Vancell, 2012). It has introduced or proposed legislative changes that are aimed at directing more innovation to areas of unmet need whilst placing greater obligations on product developers to ensure affordability and availability of products that benefit from innovation incentives. The regulatory framework for assessment and authorisation of medicines is underpinned by the aspiration to accelerate access. Meanwhile, efforts to improve cooperation and coordination between Member States in areas such as joint assessment and procurement have increased (de Jongh et al., 2021).

Antimicrobial resistance (AMR) is one specific area of unmet medical need where significant effort is made to stimulate innovation of new medicinal products. However, the pharmaceutical industry continues to experience headwind to address this challenge owing to scientific challenges and the limited financial incentive available to meet the cost of clinical development (Theuretzbacher et al., 2020).

The role of the EMA was reinforced through restructuring as well as introduction of new scientific committees and a mandate to provide scientific advice. The EMA's position has been further consolidated through its central coordinating role in the European medicines regulatory network within the new harmonised regulatory system. The mandatory scope of the centralised procedure for marketing authorisation has been gradually extended to new active substances that treat a number of conditions, including cancer, diabetes, neurodegenerative, viral and autoimmune diseases; medicines that are derived from biotechnology processes (e.g., based on genetic engineering, monoclonal antibodies), advanced-therapy products derived from blood, tissue and cells, and orphan medicinal products. There is also the opportunity for new active substances to use the centralised procedure which are outside the mandatory scope, including chemical, biological and radiopharmaceutical substances; and those that represent major scientific and technical innovation where authorisation would be of public interest.

As a result, the great majority of new, innovative medicines now pass through the centralised procedure and not the national authorisation procedures (MRP/DCP). Total central 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 making up about half of all central authorisations (ACC-1.1, Analytical report, 2022). When comparing central authorisations of new active substances in the EU with equivalent figures in the US (ACC-1.2, Analytical report, 2022), it shows annual authorisations in the two jurisdictions within a small margin between 2006-2016, however, with a new gap opening up in recent years, and US FDA now authorising more new molecular entities. The majority of new active substances were authorised first by the US FDA over the entire period 2001-2020 (53 to 75%), however the proportion of substances authorised less than 1 year earlier by the US FDA than EMA is increasing (from around 40% in 2001-2005 to 55% in 2016-2020; ACC-1.6, Analytical report, 2022).

It should be noted that the vast majority of product approvals continue to take place at the national level through MRP/DCP procedures (usually over 1000 products per year). However, currently, almost all medicinal products containing a new active substance are submitted through the centralised procedure. For instance, only 2 new active substances were approved via MRP/DCP from 2016 to 2020.[4] 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 products following the MRP (ACC-1.3, Analytical report, 2022). Statistics from the CMDh and its precursor, the Mutual Recognition Facilitation Group (1995–2005), show a similar trend. In 2001, 423 MRPs were finalised rising to 954 in 2005. The DCP overtook the MRP in 2008 when 734 DCPs and 411 MRPs were finalised. In 2020, 856 DCPs were finalised covering 1793 products and 296 MRPs finalised covering 569 products. Note that the vast majority of the procedures concern generic medicines: 799 procedures in 2020 related to generics or other abridged applications.

[4] Heads of Medicines Agencies: Statistics (hma.eu)

3.4 Global position of the EU pharmaceutical industry

As regards external factors, it is important to note that in the past 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 (Statista, 2021). The US is the largest market for pharmaceutical products, accounting for about 47% of the global market in 2021, followed by the EU market, the second largest, accounting for 19%. Revenue generated by pharmaceutical companies in the EU has increased over time and was approximately €200 billion in 2020 (IEC-10, Analytical report, 2022).

In the future, the global market for medicines is expected to continue to grow with a compound annual growth rate of up to 6% through to 2025 (Aitken et al., 2021), with a total market size of around US$1.6 trillion (€1.5 trillion, excluding COVID-19 vaccines). The market growth is driven by an increasing number of newly developed medicines, by emerging new markets and by rising prices in key markets (Aitken et al., 2021; Statista, 2021). A US$35 billion (€33 billion) increase of expenditure is forecast for Europe, mainly on biosimilars and generics. In particular, the immunology and oncology sectors are expected to grow up to 12% compound annual growth rate globally by 2025, with hundreds of new therapies and treatments being developed.

Increasing revenues and high profitability attract investment into developing new medicines, and in 2020, the total global spending on pharmaceutical R&D was US$198 billion (€188 billion) (Statista, 2021). The total number of products in active development globally in 2021 exceeded 6,000, up 68% over the 2016 level (IQVIA, 2022). 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[5], suggesting truly innovative pharmaceuticals emerging and not simply follow-on products (IQVIA, 2022).

The strongly growing global market has been an opportunity for the EU's world class pharmaceutical industry to evolve and capture a significant share of the increase. There has been an increase in total R&D expenditure, as captured by the EU R&D Scoreboard, doubling from around €20bn in 2000 to more than €40bn in 2019, albeit no significant change could be attributed to the implementation of the legislation (RI-8, Analytical report, 2022). The highest and most persistent growth in R&D investment in EU companies that operate in pharmaceuticals and biotechnology took place in 2011-2016. On the other hand, 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).

While US firms show a lead 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 medicinal products between 2000-2020, EU exports have increased five-fold and with €215bn worth of exports, medicinal products 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.

The value of EU28 imports as well as exports from and to non-EU countries has grown consistently between 2000 and 2020 for vaccines, finished pharmaceutical products and APIs (IEC-13.2, IEC-13.3 and IEC-13.4; Analytical report, 2022). Despite the fact that the EU imports large quantities of cheap generic medicines, vaccines and APIs from outside the EU, for example, from India and China, exports are greater than imports, except for APIs for which values are almost equal. The trade figures are the highest with the USA, exports significantly higher (€80bn in 2020) than imports (€20bn in 2020) and looking at a basket of six developed economies, the EU is by far the biggest provider of their imported medicines (Erixon & Guinea, 2020).

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 (IEC-11, Analytical report, 2022). Nevertheless, the lower growth rates in Europe are correlated with a marked reduction in profits during 2016-2020. This

[5] Defined as a new and unique mechanism of action to treat a particular medical condition

period of decline in Europe was not observed in Switzerland or Japan, but Canadian companies reported negative profits during the same period.

3.4.1 Medicine prices

The affordability of medicines is an important factor for national health systems and patients, and it also has relevance to the profitability of the pharmaceutical industry. Medicine prices vary significantly between EU Member States. One study found an almost 11-fold difference between Interferone-beta prices in Germany (€1451) and Croatia (€133) (Zaprutko et al., 2017). For a sample of medicinal products, the same study showed that prices were the highest in Germany and cheapest in different EU countries but not in the poorest ones, such as Bulgaria or Romania. The medicines analysed were considered unaffordable for many EU citizens.

In the EU, average spending on pharmaceuticals as a percentage of health spending stood between 17–21% during the last 20 years (AFF-3, Analytical report, 2022). While this share was higher in 2003-2007, it has decreased slightly in the last 12 years. This figure is in line with the findings of a recent report by the IQVIA Institute highlighting that pharmaceutical spending has been growing more slowly than health spending in the recent period in most countries (Aitken et al., 2021).[6] The same report indicates that pharmaceutical spending is around €200bn in the EU, equal to roughly 1.5% of the EU's GDP.

Using net price data trends for all medicines sold in various markets between 2002-2020 (AFF-1.1, Analytical report, 2022), the average normalised price level (or cost to payers) is increasing steadily in all markets, with the EU being at an intermediate price level. Prices in Europe reached five times their 2002 level by 2020, and it is higher compared to Australia and Korea, similar to Japan, Canada or Switzerland, but significantly lower than the USA, where pharmaceutical prices increased rapidly since 2009. When focussing on medicinal products with total sales exceeding €10m, the trends remain similar but price level increases in Europe are relatively lower than comparators, with Korea being the only exception. When focussing on medicines with the highest unit prices, the trend remains similar, however when focussing on the relatively cheaper medicinal products, the price levels remain relatively constant (about 10% nominal increase on average) over the entire period between 2002-2020 (AFF-1.3 and AFF-1.4, Analytical report, 2022). This is below GDP growth of these countries with low price medicines' real prices declining further. We looked at the share of generics in the total sales value of pharmaceuticals and it remains at 15% with a rather modest growth over the period in Europe (AFF-4.2, Analytical report, 2022). The comparable value (i.e., share of generics in total sales) in the USA is 8% and in Korea 35%. When looking at the volumes of generics sales as a share of total medicine consumption, it was highest in the USA, reaching 70% of total consumption by 2020 from a baseline of 30% in 2002. The EU and most other comparators also experienced a rise in the share of generics, but at a lower growth rate. The share of generics in total consumption in the EU reached around 50% by 2020, up from approximately 25% in 2002. These results suggest that the price differential between branded and generic products is lower in Europe compared to the USA since generics account for a greater proportion of the total pharmaceutical sales value despite a lower proportion in total consumption. This is corroborated by an analysis of IQVIA MIDAS sales data, where the average generics price discount in the EU slowly rose from about 13% in 2002 to about 30% since 2011 (AFF-6, Analytical report, 2022). The evolution in the USA is, in comparison, much more dynamic. The discount on generics in the USA averaged 25% before 2012 and has risen to around 75% in 2020. Thus, a generic product in the USA on average costs only a quarter of its branded originator, compared to about 70% in the EU. The evolution of generics price discounts also seems more favourable in Canada and Japan compared to the EU, while Australia and Switzerland exhibit similar levels as the EU. On the other hand, generics entry has substantially decreased prices of branded medicines in the EU (up to around 60% lower by 2020) in contrast to countries like Australia, Japan, Canada, and particularly the USA, where branded products' prices *increase* after generic entry (AFF-6, Analytical report, 2022).

With regard to biosimilars, estimates suggest that global sales topped US$15 billion (€14 billion) in 2020, representing a compound annual growth rate of 56% since 2015 (McKinsey, 2021). The USA lags behind the EU in both biosimilar approvals and uptake, with the EU being the first to develop

[6] Spending inclusive of all products and locations where they can be delivered (retail, hospitals) and are reported after discounts and rebates received by payers

guidelines for the approval of biosimilars via an abbreviated registration process during 2005-2006 (GaBI, 2021).

Taking the quantitative analysis of how the situation evolved together with stakeholder feedback, it appears that the European pharmaceutical sector is in a stronger position than in the early 2000s, owing to a multitude of contextual factors (including the global environment) and cannot be solely attributed to the 2004 revision. The sector however did not manage to keep pace with changes in the USA both in terms of regulatory speed and flexibility and supporting innovation, developing novel medicines. It is important to point out that the two regions have markedly different systems for comparative cost-effectiveness assessment of medicines and ultimate pricing and reimbursement decisions. Moreover, as the data above shows the growth of the pharmaceutical market in the US is likely to be largely due to an increase in prices rather than increase in patient numbers per se. On the other hand, the EU has become a global hub in high-value manufacturing, and its pharmaceutical spending follows a more sustainable path and medicines are more affordable.

4 EVALUATION FINDINGS

4.1 To what extent was the intervention successful and why?

4.1.1 Effectiveness

This section of the evaluation report considers the effectiveness of the legislation, exploring the extent to which the actions implemented contributed to achieving its overarching and specific objectives and elaborating how the achieved results and impacts compare with the expected ones as per the intervention logic and impact pathways.

The targeted surveys provided an overview as to the extent to which stakeholders feel the legislation has been effective in terms of achieving its objectives. Stakeholder opinion across groups suggests that the legislation has been most effective regarding the objective of safeguarding public health and least effective in terms of ensuring access to medicines and addressing medicine shortages (see Figure 3).

There was good agreement across stakeholder groups on the most effective areas with only health services ranking "safeguarding public health" outside their top three and including "enabling progress in science, technology and digitisation" instead.

The areas related to access to medicines were areas where the legislation was deemed least effective by stakeholders. Enabling access to affordable medicines and enhancing security of supply of medicines were scored low by most stakeholder groups except for industry. Industry identified two different areas as the least effective. These were:

- Minimising inefficiencies and administrative burden of regulatory procedures;
- Improved global competitiveness of the EU pharmaceutical industry.

Overall, areas related to the other two main objectives: (1) ensure attractiveness in the global context and (2) ensure competitive functioning of the EU internal market were judged by survey respondents as effective to a moderate extent. Exceptions included industry which judged global competitiveness as one of the least effective areas (as discussed above) and civil society which scored "ensure a competitive EU market for medicines" very low on the effectiveness scale, with the view that legislation has not led to adequate competition in terms of either choice or prices.

Figure 3 Score of effectiveness of various areas of the current legislation

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		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

Source: Targeted stakeholder survey analysis

4.1.1.1 Ensure quality, safety and efficacy of medicinal products

There is consensus across all stakeholders from the different consultation methods that the **legislation has provided a good framework for safeguarding public health**, and it has been highly successful in addressing this objective. For example, the majority opinion in the targeted survey indicates that the legislation has been most effective in areas that fall under the objective of ensuring quality, safety and efficacy of medicinal products (see Figure 33) such as:

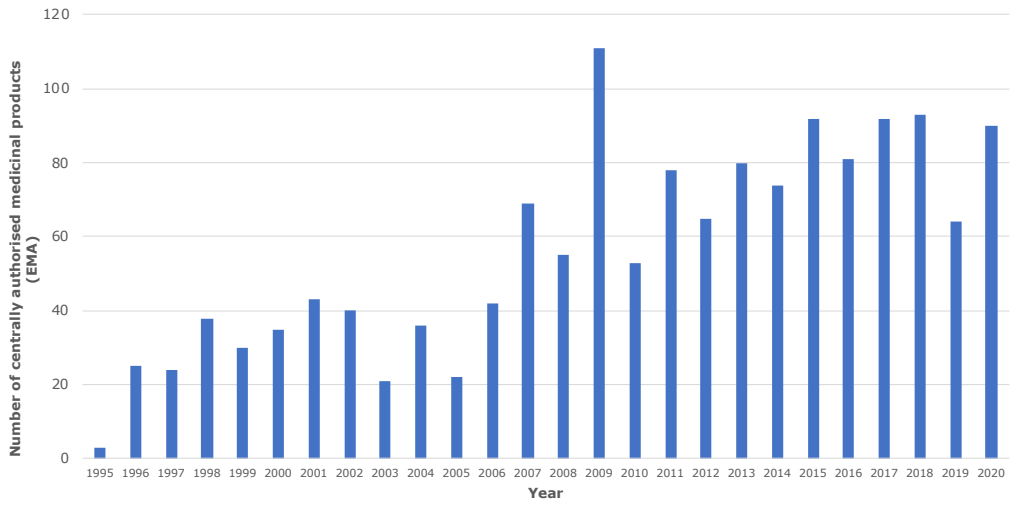
- Ensuring quality of medicines including through manufacturing rules and oversight of the manufacturing and supply chain;
- Provide an attractive and robust authorisation system for medicines;
- Provide resources and expertise to ensure timely assessment and authorisation of medicines at all times;
- Provide clear and appropriate responsibilities to all actors throughout the lifecycle of medicines.

The one area that may be linked to this objective and which scored low among stakeholders in the targeted survey and hence was deemed to be an area where the legislation had been least effective is the objective of reducing the environmental footprint of medicines.

According to interviewees across all stakeholder groups, one of the **major enablers for achieving this objective is the centralised procedure** (CP), which has allowed effective and robust authorisation of medicines at EU level. In general, stakeholders were highly positive in interviews about how the general pharmaceutical legislation has delivered a robust authorisation system for medicines. CP, decentralised procedure/mutual recognition procedure (DCP/MRP), pre-authorisation scientific advice and other services provided by EMA, accelerated assessment and streamlining of processes were cited as key achievements. These achievements have improved quality standards and have ensured safe and efficacious medicines are available to the EU population.

Figure 4 presents a time-series analysis of the total number of medicinal products that were granted a marketing authorisation under the EU centralised procedure per year (1995-2020). It underlines the feedback from our consultation on the effectiveness of the changes implemented in 2005, with a clear increase in the use of the centralised procedure over time, with the annual number of authorisations more than doubling on average. However, this may also be linked to the expansion of the scope of the centralised procedure.

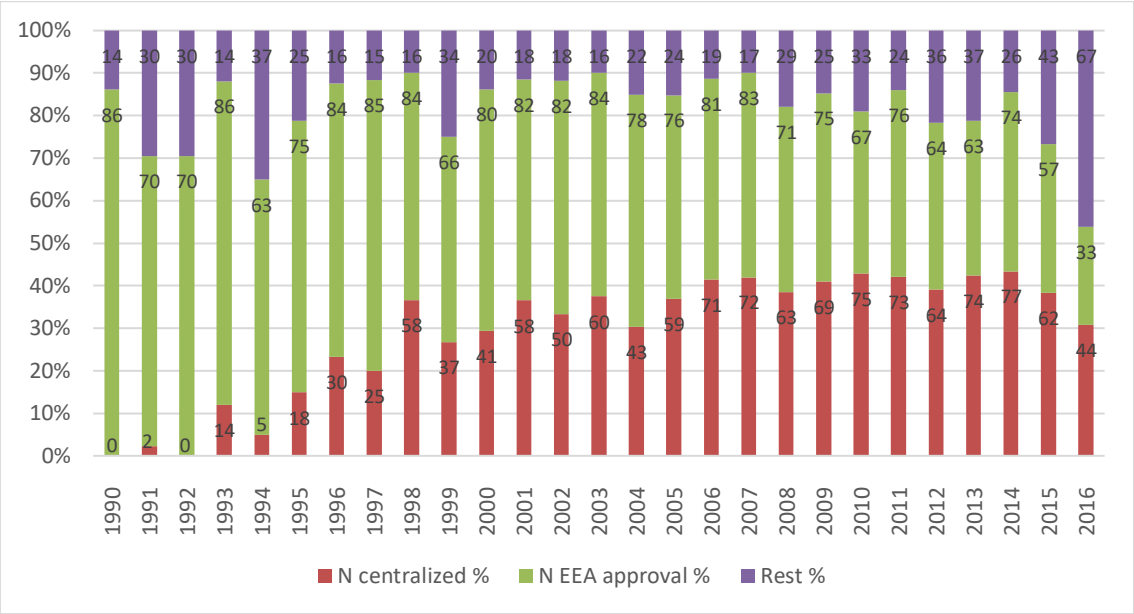
Figure 4 Number of medicinal products authorised through the EU centralised procedure (annual, 1995-2020)



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

Kyle (2019) reported the approval outcomes for new chemical entities (NCEs) that were introduced somewhere in the world from 1990 through to mid-2016. Figure 5 shows the share of NCEs that used the EMA's centralised procedure and the share that were launched somewhere in the EEA (N EEA approval), both relative to the number of NCEs first launched in each year. It is worth noting that since 2005 consistently a higher share of NCEs that were launched in the EEA used the centralised procedure compared to the previous years. This data supports the conclusion that the centralised procedure is the preferred route for authorisation of NCEs.

Figure 5 New chemical entities (NCEs) that were introduced somewhere in the world from 1990 through mid-2016



Source: Source: Kyle (2019), using data from IQVIA-MIDAS and EMA

Civil society and health services actors highlighted in interviews that there has been a significant improvement in the EMA's engagement, involvement and consultation with different stakeholders (including patients) and the scientific advice it provides, which has benefited patient safety. Better quality and safety of product manufacturing enabled by the 2004 changes to the legislation were also commented on by several stakeholders in interviews. This has been exemplified by EMA's role in coordinating regulatory action to reduce the risk of nitrosamine impurities in medicines described in the short case study box below.

The EudraGMDP database, which is the Community database on manufacturing, import and wholesale-distribution authorisations, and good manufacturing (GMP) and good-distribution-practice (GDP) certificates, shows that the number of third country registered API sites has almost doubled every year since 2019 (MI-1; Analytical report, 2022). By 2021, there were 6209 API sites registered in third countries (with links to companies with a main site registered in the EU). On the other hand, the number of API sites registered in the EU has seen a steady growth since 2013, although it almost doubled in 2021 when there were 1269 registered API sites (MI-2, Analytical report, 2022).

Regulatory action on nitrosamine impurities

Nitrosamines are a group of chemical substances that are classified as probable human carcinogens. In 2018, regulators were alerted to high level of nitrosamine impurities, N-nitrosodimethylamine (NDMA), in blood pressure medicines called 'sartans' that were produced by one API manufacturer. The discovery of this, triggered the EC to mandate the EMA to launch a review into all sartan medicines to assess the impact on the benefit-risk of these medicines to patients, which was later extended to other categories of medicines including ranitidine medicines. Based on the conclusions of the review, EMA set a temporary limit for nitrosamine impurities in medicines within a transition period of two years. Consequently, sartans and ranitidine medicines that were found to contain unacceptable levels of NDMA 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 nitrosamines coming through manufacturing into medicines. The review was published in 2020 and identified several root causes leading to the presence of nitrosamines in medicines based on which several recommendations were made to reduce the risk of nitrosamine impurities in medicines (European Medicines Agency, 2020a). An implementation plan was agreed in 2021 outlining how the European medicines regulatory network will work to implement the recommendations for all medicines authorised in the EU (European Medicines Agency, 2020b). 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, this poses challenges for some API manufacturers in complying with the new requirements, which could lead to medicines shortages. To mitigate the risk of critical medicines being recalled if they do not meet the limit, the EMA has established a centralised benefit-risk assessment where higher limits may be accepted in order that these medicines continue to be available to patients. The case of nitrosamine impurities in medicines demonstrates the effectiveness of the EU regulatory framework to rapidly respond and adapt to new safety issues for medicines and thus ensure patient safety.

The stakeholder consultations also highlighted some areas for improvement, for instance, around the assessment of microbiome products, GMOs and environmental risk as well as better accommodation of bedside and decentralised manufacturing in the legislation or related guidance.

With regard to microbiome products, the European medicines agencies regulatory network strategy to 2025 confirms that there is a need for appropriate regulatory pathways for microbiome products (HMA & European Medicines Agency, 2020). There is no international harmonisation for microbiome products either (Cordaillat-Simmons et al., 2020) and there is a need to consider new regulatory approaches according to interviewed academic stakeholders.

Stakeholders' concerns regarding GMO requirements related to the safety of medicines are mirrored in the Commission's study on new genomic technologies (European Commission, 2021). Stakeholders were of the view that the GMO legislation needs to be updated to reflect changes in scientific understanding of GMOs and aligned with requirements under the general pharmaceutical legislation. For example, no environmental or biosafety risks are associated with non-replicating viral vectors or GM human cells, as these do not duplicate and cannot survive in the environment, and hence environmental safety requirements should be adapted accordingly.

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 of the stakeholders suggested exploring a more explicit role for ERAs in benefit-risk analyses during the assessment process, or even in pharmacovigilance (Technopolis, 2022a). In interviews, there were varied opinions on how well the legislation has performed in addressing pharmacovigilance. There was difference of opinion between and within the different stakeholder groups on this aspect. For instance, some stakeholders (from the public authorities, civil society, healthcare professionals and industry) felt that pharmacovigilance has substantially enabled maintenance of safety and quality of medicines. On the other hand, several stakeholders (healthcare professionals, industry) stated

that the new pharmacovigilance requirements have considerably increased the resource burden with little added value. However, they did not provide examples or data to further elaborate their view.

Interviews with stakeholders also highlighted issues with bedside and decentralised manufacturing. Concerns were expressed that these medicines may be excluded from the scope of the legislation falling under the category of magistral preparations (Pharmacy exemption) where there is less regulatory oversight, thus jeopardising quality and safety of these medicines (Technopolis, 2022b).

Another aspect highlighted in the public consultation and interviews by individual academics and NCAs was the potential need for further improvements to efficacy assessments as exemplified by the case of oncology medicines as described in the short case study box below.

Efficacy of approved oncology medicines

Davis et al. (2017) reported that of the 48 cancer medicines recommended for approval by the EMA between 2009 and 2013 for 68 indications, most (37 indications) entered the market without evidence of benefit on survival or quality of life.[7] A minimum of 3.3 years after market entry, there was still no conclusive evidence that these medicines either extended or improved life, and when survival gains were observed over existing treatment options or placebo, they were often marginal (Davis et al., 2017). Similar observations have been made regarding cancer therapeutics that received accelerated approval from the FDA by December 2020, with post-approval trials showing negative results for 10 cancer medicines across 18 indications (Gyawali et al., 2021). Thus, there is a view that the benefit of many new cancer treatments is not proportionate to their prices (Schnog et al., 2021). A study from 2021 shows that launch prices and post-launch price changes of patented anticancer medicines do not correlate with their clinical benefit (Vokinger et al., 2021). In such a situation, it may become difficult for payers to justify spending large share of their budgets on medicines with accelerated approval that cannot clearly demonstrate proven benefit on patient-centred outcomes (e.g., quality of life and survival). This concern, namely that innovative medicines may not always provide patient benefit commensurate with their costs, was also raised in the stakeholder consultations (public consultation and interviews) by a small number of national competent authorities, payers and academics (latter providing the particular example of cancer medicines).

Clinical trial design (lack of patient-reported outcomes, use of surrogate endpoints and single-arm randomised controlled trials, underrepresentation of minorities and older patients in trial populations), bias in data publication (to show greater clinical effects, non-publication or delayed publication of negative studies) and limited post-approval data for medicines that have been approved through expedited pathways are some of the factors that may lead to medicines with limited clinical benefit being approved (Gyawali et al., 2021).

4.1.1.2 Ensure attractiveness in the global context

The 2004 revision of the legislation was deemed an important step forward in ensuring a coherent and attractive regulatory system for developing pharmaceuticals in light of increased scientific and technological complexity of medicinal products and EU enlargement. Indeed, in the targeted survey, there was a high agreement among industry, public authority and health service stakeholders that the current legislation had provided an attractive and robust authorisation system for medicines (see Figure 3). In particular, the centralised procedure via the EMA allows developers to make the first steps to EU market access in an integrated fashion, which increases the EU's attractiveness as both market and location for pharmaceutical development and manufacturing. The EU has also been a global leader in setting up a process for licensing biosimilars, which encourages innovation and submitting market application in the EU compared to other jurisdictions according to industry interviewees in stakeholder consultations.

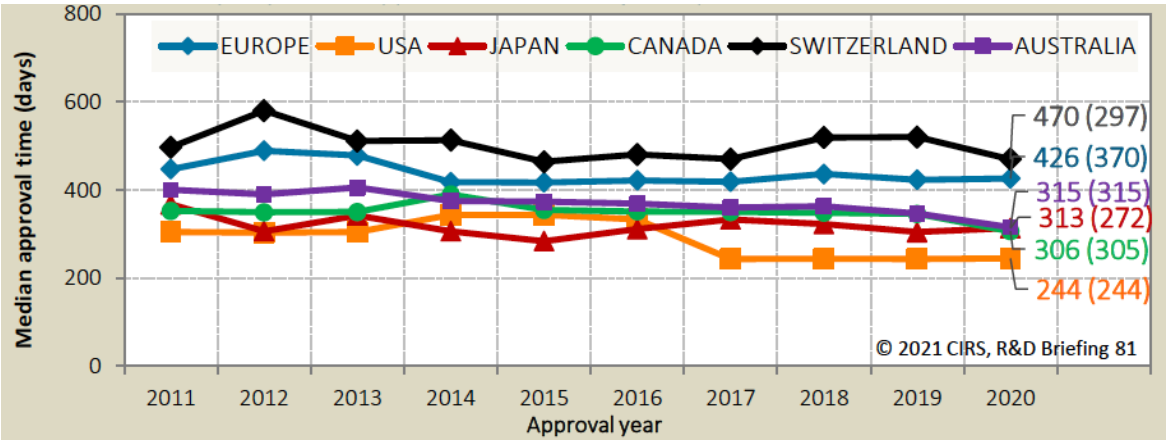
Yet, there are several factors influencing developers' strategies in relation to when and to which regulatory agencies they apply for marketing authorisation. The market size that the marketing authorisation (MA) gives access to is the biggest decision driver but there are other factors such as

[7] There was significant prolongation of survival in 24 of the 68 (35%) indications and improvement of quality of life in 7 (10%)

regulatory flexibilities or specific local epidemiological situations. The USA has the largest share of the global market for pharmaceuticals, more than twice the size of the EU market which has the second largest share of the global market (EFPIA, 2021). A 2021 comparison of six regulatory agencies (US, EU, Japan, Canada, Switzerland, Australia) by the Centre for Innovation in Regulatory Science (CIRS) (CIRS, 2021) found that new active substances (NAS) authorised by all 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). Submissions to the other agencies happened 63-150 days later on average compared to the USA. In addition, the proportion of FDA-authorised substances not authorised by EMA decreased (from approx. 40% in 2001-2005 to approx. 20% in 2011-15), with the exception of the latest period (2016-2020, 40%), which may be due to censoring issues of data publication (ACC-1.6, Analytical report, 2022).

The time needed for the assessment of the marketing authorisation application by the agencies is also an important factor for regulatory attractiveness. Figure 6 presents additional results from the CIRS annual analysis of NAS.[8] Data from 2011 to 2020 shows that the FDA had the shortest median approval time overall with the median approval time for the EU 182 days greater in 2020 than for the FDA. The study results suggest that shorter approval times may result from more new active substances going through expedited processes in the USA compared to the EU. Nonetheless, the shorter approval times may also contribute to greater attractiveness of the USA as a jurisdiction to submit application to before the EU.

Figure 6 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

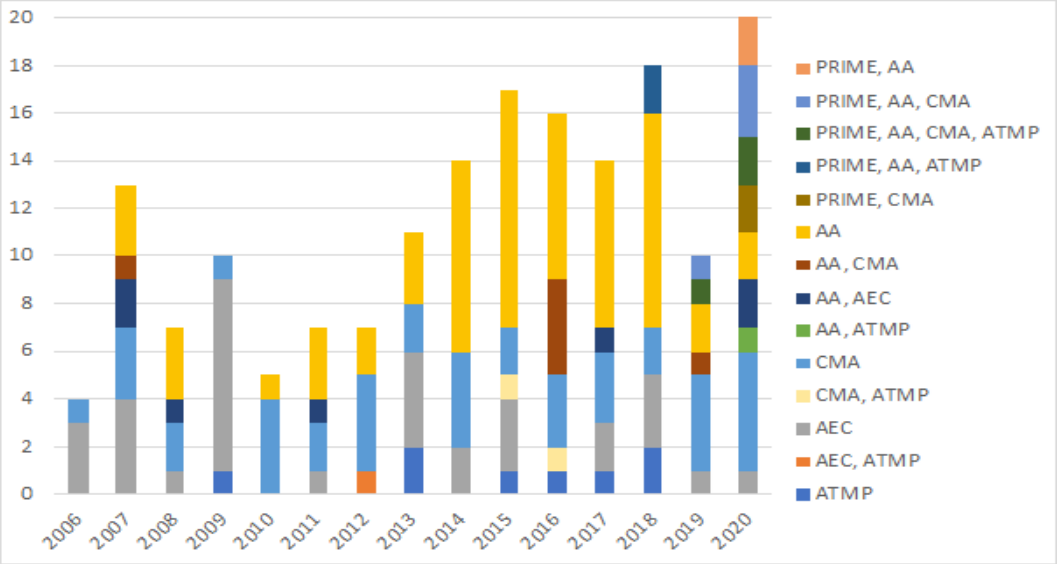
Several industry participants from stakeholder consultations confirmed that the FDA remains the preferred jurisdiction that developers want to file with, including those based in the EU. Reasons for these preferences can be differing data requirements for filing in the USA and EU, greater opportunity for direct interaction on scientific advice (mentioned by an SME) and need to interact with multiple EMA committees for ATMPs (up to five bodies for ATMPs targeting orphan indications, including the Scientific Advice Working Party). One SME mentioned that FDA is their preferred partner as the indication they are developing a product for fits more easily into the FDA's definition of unmet medical need (UMN).

Despite these reasons, the legislation has proven flexible enough to accommodate many developments and innovations in the pharmaceutical sector in the last two decades. There has been

[8] 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.

a growth in the number of innovative medicines (Figure 7) including technologically innovative medicines (e.g. ATMPs) and those addressing UMN (e.g. through PRIME[9] and conditional marketing authorisation [CMA] routes). However, it was the view of several stakeholders that participated in our consultations that the system underpinned by the legislation has not been fully able to accommodate other emerging technological developments as readily, such as combination products/borderlines with medical devices or substances of human origin, digitalisation and new manufacturing methods. It was a common view in the consultations that one of the reasons for this problem is the lack of coherence in certain areas of the regulatory system, which can make it less attractive for developers, in particular for SMEs and companies that are less familiar with the EU system. For example, both public authorities and industry interviewees observed that medical devices, clinical trials and medicines are regulated by different regulations and competent authorities and have divergent requirements, making it difficult to coordinate approaches and navigate the system. As such, there are several areas for improving regulatory efficiency and coherence, in particular the complexities arising from the links between the general pharmaceutical legislation and other EU legislation. For example, the creation of different regulatory 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, it was the view of some industry stakeholders that it also created new layers of complexity, making it more difficult for marketing authorisation applicants to navigate the system and interact with each committee as they have different working timelines.

Figure 7 The number of innovative medicines authorised by EC, 2006-2020



ATMP = Advanced Therapy Medicinal Product; CMA = Conditional Marketing Authorisation; PRIME = Priority Medicine; AA = Accelerated Assessment granted; AEC = Authorisation under exceptional circumstances. Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA

4.1.1.3 Ensure access to medicines

Stakeholders (across different types and consultation methods) agree that there is room for improvement in terms of availability, access, affordability, and unmet medical needs (UMN) in the context of the legislation. Access to medicines is an area where the legislation is seen to have underperformed the most according to all stakeholder groups except for industry responses in the targeted survey. Access was viewed from three distinct angles by stakeholders:

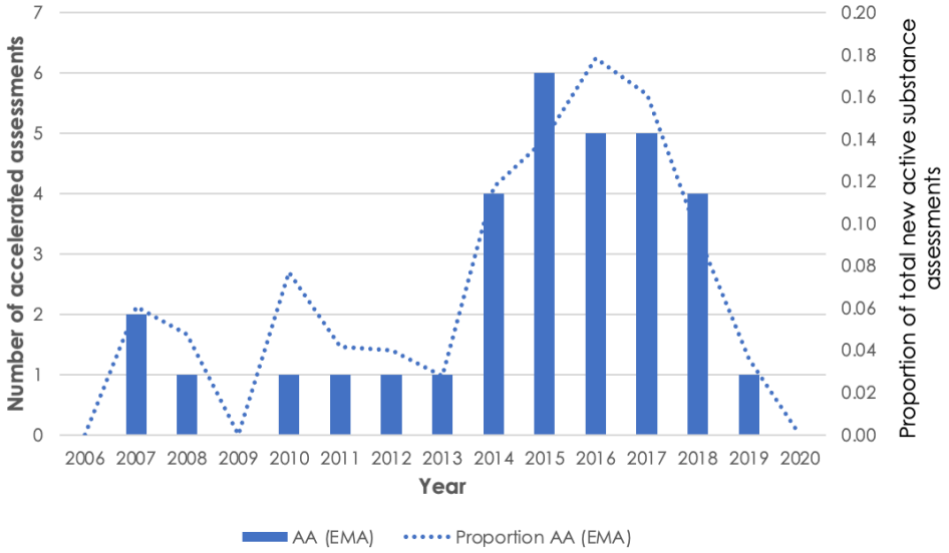
[9] PRIME is a voluntary scheme launched by the EMA to enhance support for the development of medicines that target an unmet medical need. Through PRIME, the Agency offers early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks, to optimise development plans and enable accelerated assessment of medicines applications.

- Evaluation and marketing authorisation of medicines
- Approval and reimbursement by HTA bodies and payers
- Medicine shortages

Of these aspects, the general pharmaceutical legislation is mainly responsible for authorisation, while reimbursement is completely out of its remit.

Medicine authorisation procedures, especially the centralised procedure, have allowed more new medicines to become available for the EU population (see Figure 4) – an outcome that was particularly emphasised by industry and public authorities in interviews. The EMA also gives the option of accelerated assessment to expedite authorisation of products of major interest for public health and therapeutic innovation and thus contribute to improving the speed of access to medicines. The number of accelerated assessments both in absolute terms and as a proportion of all assessments for new active substances have increased since 2013 (Figure 8).

Figure 8 Number and proportion of accelerated assessments by EMA

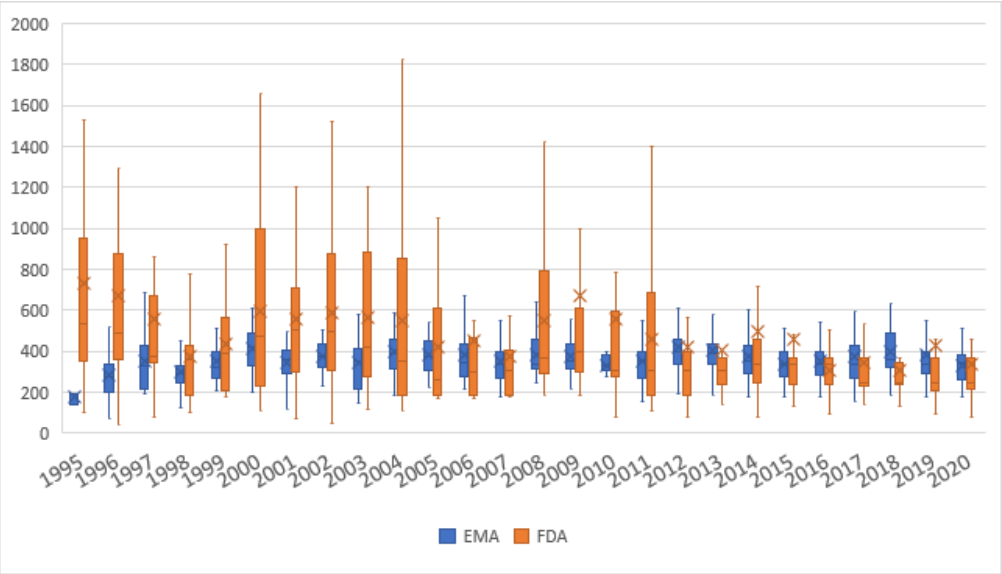


Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA

The 2004 revisions aimed for faster access to innovative products, so we have examined statistics on EMA assessment times. Figure 1 shows the trend in total assessment times by EMA (for centrally authorised medicinal products) and FDA in days (yearly, 1995-2020). The data show a notable improvement in EMA's average assessment times between 2005 (380 days) and 2010 (270 days), which then increased gradually over the next 10 years (340 days in 2020). This suggests the legislative revisions did improve timeliness, for a period before other factors (e.g. resourcing, more complex dossiers) resulted in a reversal. In comparing the EMA and FDA assessment times, EMA average assessment times are shorter than the FDA's for the whole period through to 2015, beyond which the situation has reversed with the FDA reviews 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.[10] The analysis also shows that the average FDA assessment times have been more variable than the average EMA times, over time.

[10] 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.

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

Whilst the legislation has led to improvements in the authorisation of medicines, the system has also become more complex over the years according to the interviewees representing the industry. There are reported inefficiencies related to differing interpretation and implementation of the legislation and other relevant regulations and directives at the MS level (e.g. GMO, ATMP, BTC) which has led to delayed and unequal access across Member States. For example, under current procedures, generic medicines may require repetitive evaluation even where the active substance has been previously approved. Another area of inconsistency across MS as cited in interviews is hospital exemption[11]. A recent study on how hospital exemption has been implemented in seven European countries, showed great variations in how quality, safety and efficacy standards are implemented and controlled across EU MSs for ATMPs which draws concern around potential impact on public health (Hills et al., 2020).

While a marketing authorisation clears the first hurdle of getting safe and efficacious medicines to patients, it does not automatically imply availability for patients. HTA bodies and payers in MSs make reimbursement decisions based on their national assessments of cost-effectiveness of a given medicine. Even though the method of cost-effectiveness assessment can be similar across MSs, the outcomes of assessment may still differ substantially based on the local markets. This means that even if marketing authorisation processes are accelerated, the actual access to medicines is not uniform across MSs.

According to healthcare payers in the public consultations and interviews, HTA result shows that the clinical data available is often insufficient to quantify the benefit for patient care. They consider that such insufficient clinical data, e.g. 'immature' phase II data can sometimes be accepted for authorisation in accelerated/conditional approvals because of a perceived necessity for faster access for patients. However, without data showing verifiable clinical benefit and data transparency on which patient group would benefit the most, many products that enter the market are obliged to fulfil post-marketing conditions. These obligations are often fulfilled with delay, remain incomplete or the data submitted is insufficient to fill the knowledge gaps (Schnog et al., 2021). Therefore, evidence gaps

[11] 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.

on cost-effectiveness may remain which has serious implications for payment and reimbursement decisions and thus ultimately access to medicines for patients.

The 2004 revisions expanded the scope of the centralised procedure and harmonised other procedures and rules to improve availability and access to medicines across the EU. The underlying assumption was that this would facilitate (and accelerate) the market placement of centrally authorised medicines in all EU countries as the central approval negates the need for the MAH to request authorisation in each MS individually. It would thus remove some of the costs and effort associated with these regulatory processes which had contributed to barrier to access. Note however that central authorisation itself does not oblige the MAH to enter all, or even a minimum number, of EU markets.

Crucially, access to medicines is not contingent only on medicine authorisation. Firstly, it requires a willingness by the MAH to place a product on a particular market, typically informed by the MAH's expectations about a positive return on investment in that market. Secondly, payers (health systems or insurers) need to agree to include the medicine in 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 between the MAH and health authorities. Such assessment procedures and outcomes may take months or even years and often strongly influence the actual time to launch a product on national markets.

A 2019 study found that the number of EEA countries in which a new chemical entity is launched has been steadily decreasing (Kyle, 2019). Various other studies have also shown that, even for products that have been approved through the EMA's centralised procedure, access[12] remains uneven across the EU. The evaluation of the EU 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[13] 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 (Zamora et al., 2019). Also, for other centrally authorised medicines, such as oncology medicines, substantial differences have been reported in availability and time to entry (Bergmann et al., 2016; Ferrario, 2018).

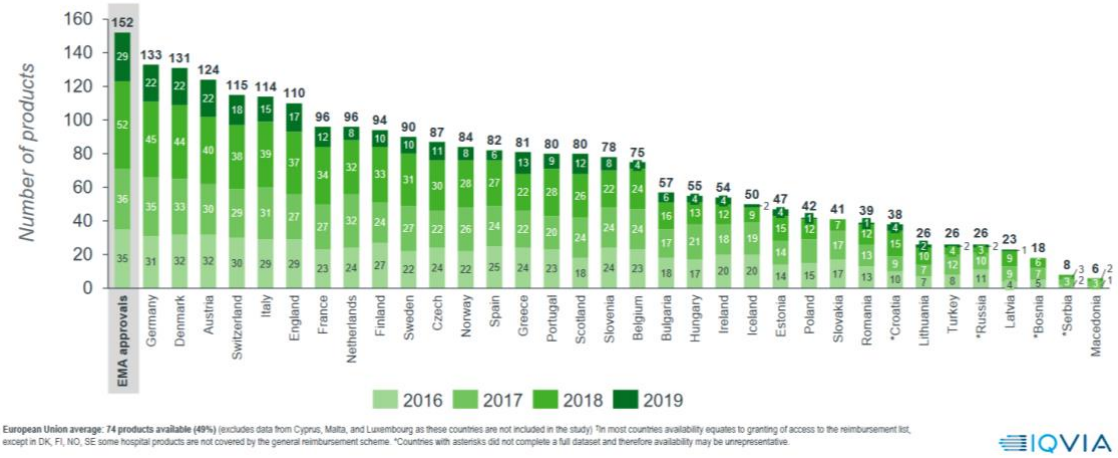
The fact that inequitable access is observed even for centrally authorised products points towards 'downstream' factors beyond the authorisation process that affect whether and when products are placed on specific markets. Such factors relate significantly to the characteristics of national markets. Smaller countries and poorer countries tend to see fewer product entries. To illustrate, data provided by EFPIA member associations and IQVIA showed 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 the Baltic countries or countries with comparatively low price levels, like Romania, had fewer than 50 of these available (Newton et al., 2021). 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.[14]

[12] Access is defined by fulfilment of the following criteria: 1) a medicine has been (conditionally or fully) approved for marketing in the country, 2) has been placed on the market by the MAH, and 3) is made available to patients as part of (partially) reimbursed care.

[13] To allow for the analysis to cover the full evaluation period from 2000 onwards, when the EU Orphan legislation was adopted, the analysis focused only on the 12 countries that were EU Member States in 2000.

[14] 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.

Figure 10 Availability of EU authorised medicines (2016-2019) and their availability in MSs by the end of 2020



European Union average: 74 products available (49%) (excludes data from Cyprus, Malta, and Luxembourg as these countries are not included in the study) In most countries availability equates to granting of access to the reimbursement list, except in DK, FI, NO, SE some hospital products are not covered by the general reimbursement scheme. *Countries with asterisks did not complete a full dataset and therefore availability may be unrepresentative.

Source: EFPIA Patients W.A.I.T. Indicator 2020 Survey, IQVIA (2021)

Collectively, these studies suggest that expanded scope and use of the centralised procedure has not been an effective measure to improve access to innovative medicines in MSs and that more work needs to be done to ensure that a large majority of EU markets have access to authorised medicines.

4.1.1.4 Affordability

Affordability is an essential requirement of medicinal products so that patients can have access to treatment when they need it. In Europe, health systems provide Universal Health Coverage, however, patient co-payment rates for medicines remain high in some countries. The Pharmaceutical Strategy aims to ensure affordability of medicines for patients and health systems' financial and fiscal sustainability. 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 public consultations. The rising costs of medicines and affordability (with their downstream impacts on access, health systems and public health) were key concerns for academics, healthcare professionals, public authorities and civil society stakeholders in the interviews – they were open to any measures that could conceivably address these issues going forward including incentives and new pricing models.

Pharmaceutical spending is the third biggest cost element in healthcare spending, roughly responsible for 1/6 of healthcare spending. According to OECD Health statistics, pharmaceutical spending (expenditure on prescription medicine and self-medication but not on medicines consumed in healthcare settings) remained stable over the last 20 years in EU28, at 17-21% (AFF-3; Analytical report, 2022). This is in line with the findings of a recent report by the IQVIA Institute that highlights that spending on pharmaceuticals has been growing more slowly than overall health spending in most countries, and below GDP growth (IQVIA Institute, 2021). It was noted that this share is lower in the Nordic countries (i.e. Norway, Sweden, Denmark 8-10%) and higher in Eastern European countries (i.e. Hungary, Bulgaria, Czech Republic 18-24%). To compare, IQVIA Institute reported values for Canada (10%), Brazil (13%), USA and Australia (14%), Japan (17%) and Korea (20%)(IQVIA Institute, 2021). Spending levels and trends also depend on therapeutic areas; spending on oncology products increased fastest between 2000-2020, due to increased need from the population and significant health burden, while spending on cardiovascular products decreased over the same period. Understanding spending 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 pharmaceutical spending in hospital settings has been rising faster than expenditure through the retail channel (OECD, 2020).[15]

[15] Annual average growth in retail and hospital pharmaceutical expenditure, in real terms, 2008-2018

The general pharmaceutical legislation does not directly address the affordability of medicines. However, Article 14(11) of Regulation (EC) 726/2004 lays down the principles of data exclusivity and market protection, which effectively prevents generic/biosimilar entry for 10 or 11 years (if additional authorisation granted for a new indication). This regulatory protection, together with patents, SPCs, and protection given to orphan and paediatric medicines delays market entry for follow-on products, generics and biosimilars, which are expected to lower price levels and increase affordability of medicines. Our analysis of top selling medicinal product sales data indicates (AFF-6; Analytical report, 2022) that branded product prices drop on average by one third of the price level prior to generic entry. This is the highest level among comparator countries, and similar to that in Australia and Korea. The discount of the corresponding generic products (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%, which means that the price of available generic products is only about one third of the price of their branded equivalent, before generics were available on the market.

As expected, the share of generics in total medicinal products sales revenue is modestly increasing in the EU (from 13% to 16%) between 2002-2020. It reaches the highest level in Korea (30%) and lowest in Japan and the USA (7%) by 2020 among the comparator countries. When looking at the share of generics volumes sold in the total volumes sold (in standard units), it grows from 25% in 2002 to 40% in 2020 in the EU. However, it grows even more in the USA from 30% to 70% in the same period, while in Japan the growth is more modest from 9% to 22%.

This shows that the EU is on a similar trend as other comparator markets and benefits from generic competition making prices of innovative medicines more affordable once the patent and/or regulatory protection periods expire. A sample of products of EU4 countries (France, Germany, Italy and Spain) with protection expiry between 2016-2024 shows that two thirds of the products are protected by intellectual property rights (patent and SPC) from generic competition, while one third of the products are protected by data exclusivity and market protection.

An example of the innovative biotechnology company Bluebird shows that innovative products command high prices that European markets are not always willing to pay. Bluebird's two gene-therapy candidates, namely Zynteglo and Skysona, were approved first by the EMA in 2019 and 2021, respectively, thanks to a favourable regulatory pathway but subsequent price negotiation did not lead to deals (Dunleavy, 2021; Taylor, 2017). Therefore, Bluebird decided to leave the European market altogether and submitted these products for review by the US FDA[16], in the hope that on the US market the company will be able to generate the expected high revenue to treat rare diseases.

Stakeholders interviewed (across different stakeholder types) agreed that the legislation has been beneficial for increasing competition in the pharmaceutical sector of the EU by facilitating generics and biosimilar entry in the market. This has been enabled by the Bolar exemption[17] 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 (CMS, 2007).

4.1.1.5 Medicine shortages

Medicine shortages present a major problem for the quality and continuity of patient care. A recent study (de Jongh et al., 2021) found that reported medicine shortages in the EU have increased over the last five to ten years and are placing a significant burden on health professionals and, ultimately are putting patients at risk of sub-optimal care and higher healthcare costs. The outcomes of the public consultations confirm the importance all stakeholders (and in particular civil society organisations and healthcare professionals) place on medicines shortages as a key issue impacting on access to medicines and ultimately public health. Health professionals stress that the current legislation has not been effective in addressing the issues of the medicine shortages as evidenced by rising shortage notifications. In the targeted survey, civil society, public authority and health service

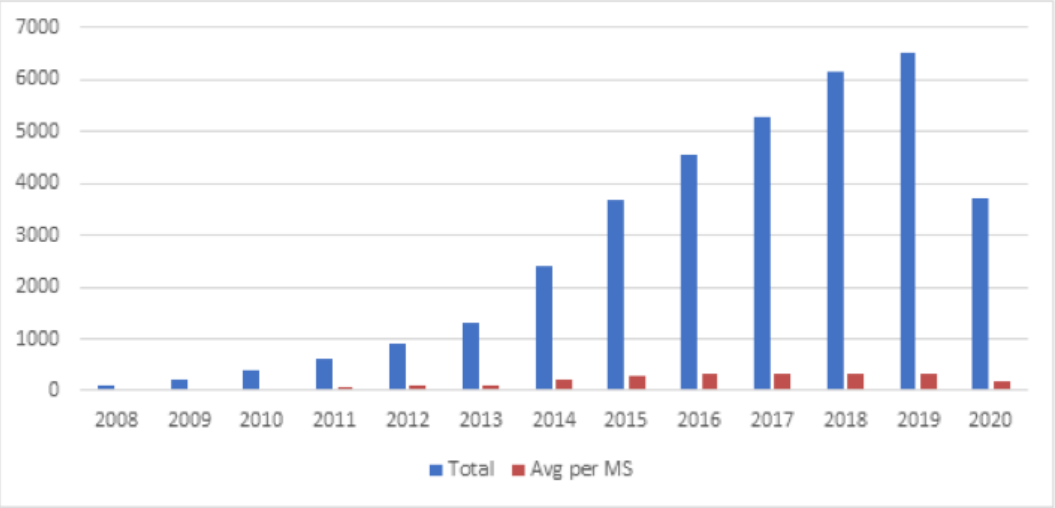
[16] FDA approved Zyntelgo in August 2022, and Skysona (by Accelerated Approval) in September 2022.

[17] 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 e.g. bioequivalence prior to the expiry of a patent.

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

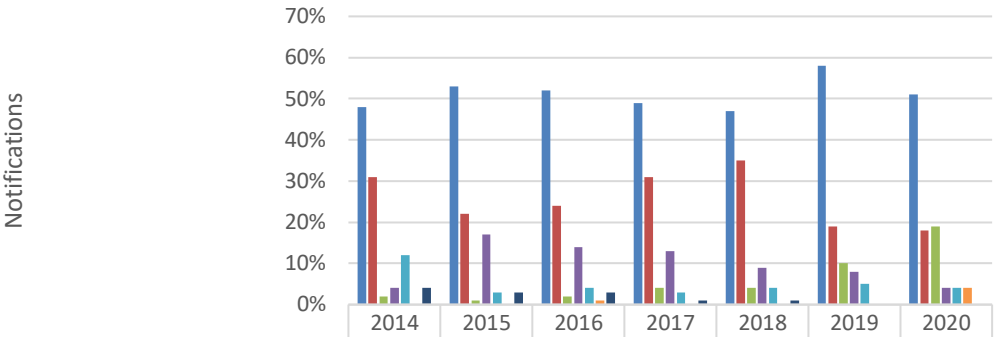
Figure 11 presents an overview of the total number of medicine shortages reported annually. It shows a strong increase in the numbers being notified over the last 10 years, suggesting increasing disruption for patients and health systems. However, there are other factors contributing to the increase, for example, there are more countries tracking and reporting shortages, and or doing so more effectively. Nevertheless, there is a clear increasing trend. Stakeholder feedback, collected both in this evaluation and in the previous study on medicine shortages, also suggests that shortages are indeed becoming more frequent. The implication is that, while the legislation has helped in creating more insight into the scale and the prevalence of medicine shortages (through introduction of shortage notification requirements), it has not sufficiently been able to address the reasons behind the shortages occurring nor has it enabled implementation of effective actions to alleviate their impact.

Figure 11 Total number of shortages reported across the EU



Source: Analysis of data from national shortage registries, Technopolis Group. 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.

Figure 12 Time trends in reported root causes of shortages (2014-2020)



	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%

Source: Analysis of data from national shortage registries, Technopolis Group.

Figure 12 presents an analysis of the root causes of medicine shortages, based on all shortages data from the period 2014-2020. It shows that quality and manufacturing issues dominate the statistics, reflecting unforeseen problems with the quality of ingredients or processes that lead to stoppages, recalls, etc.). The changes to the GMP/GDP guidelines and the more comprehensive scrutiny of manufactured quality / pharmacovigilance, are likely to have reinforced this trend. The dominance of 'quality and manufacturing' issues can also be seen as an example of the legislation having been successful in increasing the observance of manufacturing standards. Stakeholders, particularly industry and NCAs, report that generic medicines are particularly at risk of shortages, given the higher relative fragility of their supply chains. Supply chains for generics have become particularly vulnerable because procurement practices have driven down their prices to such an extent these products cannot be manufactured in the EU profitably and suppliers need to be consolidated, sometimes to one global supplier.

Figure 12 also shows that while manufacturing issues have become more important, commercial issues have decreased in importance, from around 30% of all causes in 2014 to 18% of the causes in 2020. Similarly, distribution issues have declined in importance over time. It is not clear whether this has to do with actual changes or the reporting differences. Taken together, the current pharmaceutical legislation is unlikely to reduce the actual root causes of medicine shortages.

4.1.1.6 Accommodating innovation

Developing new medicines is a capital intensive, high risk and potentially high gain business. Profits from new product sales and a supportive regulatory system with relevant incentives (e.g. intellectual property and regulatory protections) incentivise innovation. The interviews with stakeholders confirmed that the general pharmaceutical legislation has provided a regulatory system which has facilitated innovation across the product lifecycle. 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 for accommodating innovation.

Most stakeholders confirmed that the legislation has proven flexible enough to accommodate innovation. However, some industry stakeholders observed that innovative manufacturing aspects are not adequately considered in accelerated approval pathways, which may cause bottlenecks and impact access. They also observed that overall accelerated approval pathways are not used as much in the EU 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 (CIRS, 2021).

Other 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, generic and biosimilar innovation, and antimicrobial 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 pharmaceutical R&D.

All stakeholder groups concurred that digitalisation and emerging science and technology developments have not been adequately integrated in the current regulatory system. Most stakeholders agreed that the legislation and related guidelines do not provide enough clarity for companies and national regulators when it comes to combination 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, a medical association cited radiopharmaceuticals as a key area where the legislation has not achieved a positive result in terms of facilitating innovation, citing lack of clarity in the regulatory framework for hospital preparations and lack of incentives for R&D in this area. The legislation has not managed to promote innovation in certain areas of unmet medical need such as AMR to the extent desired. Since the launch of the current regulation (2004), no new class of antimicrobials has been discovered globally (Lewis, 2020).

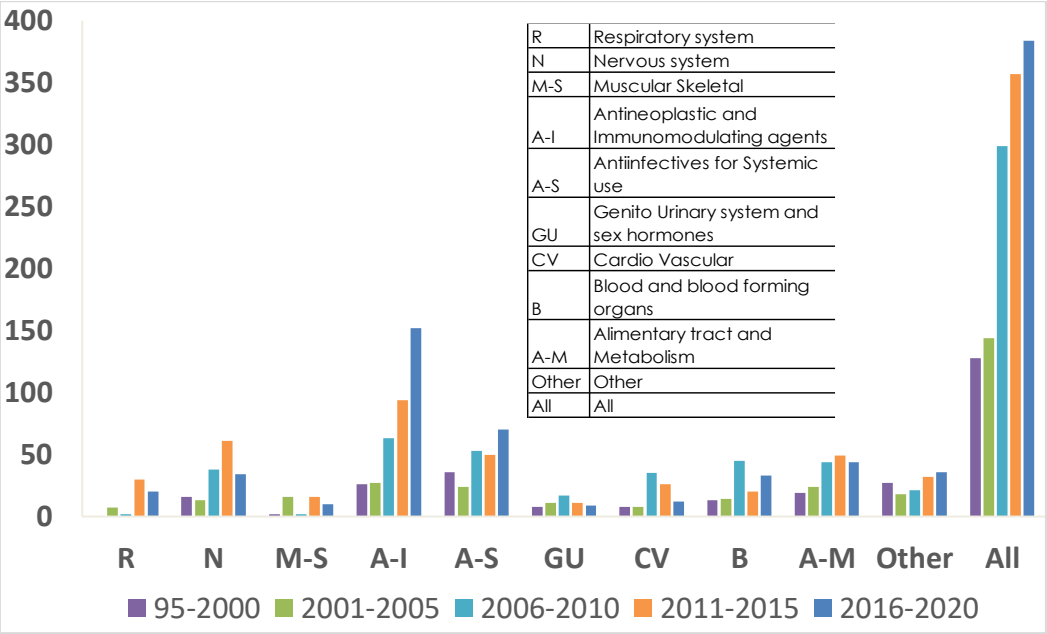
The 2004 revisions introduced several new procedures to encourage pharmaceutical companies to pursue development of innovative products relevant to unmet medical needs with a strong public health benefit, including the conditional marketing authorisation (CMA). The revisions also extended the scope of the standard centralised authorisation procedure and expanded the provision of scientific support / advice and strengthened the relevant EMA committees.

Another objective of the legislation was to attract R&D to the EU, thereby benefiting the EU economy. However, many other contextual factors affect such anchoring within the EU including R&D capacity, market size, availability of funding (public and private), tax system and incentives, etc. often at the national level. Across the EU, on average 1131 people per million population work in the pharmaceutical industry, similar to levels in the US and Japan, but lower than in Switzerland (IEC-7, Analytical report, 2022). As discussed in Chapter 3, 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, albeit no significant change can be attributed to the implementation of the legislation (RI-8, Analytical report, 2022). Nevertheless, R&D investment in the EU has remained significantly lower that than in the US (€74 billion in 2019).

The increase in R&D expenditure and introduction of revised procedures (e.g. PRIME, CMA) has translated to a growth in the numbers of innovative medicines approved with a consistent increase year-on-year from 2012 onwards (Figure 7).

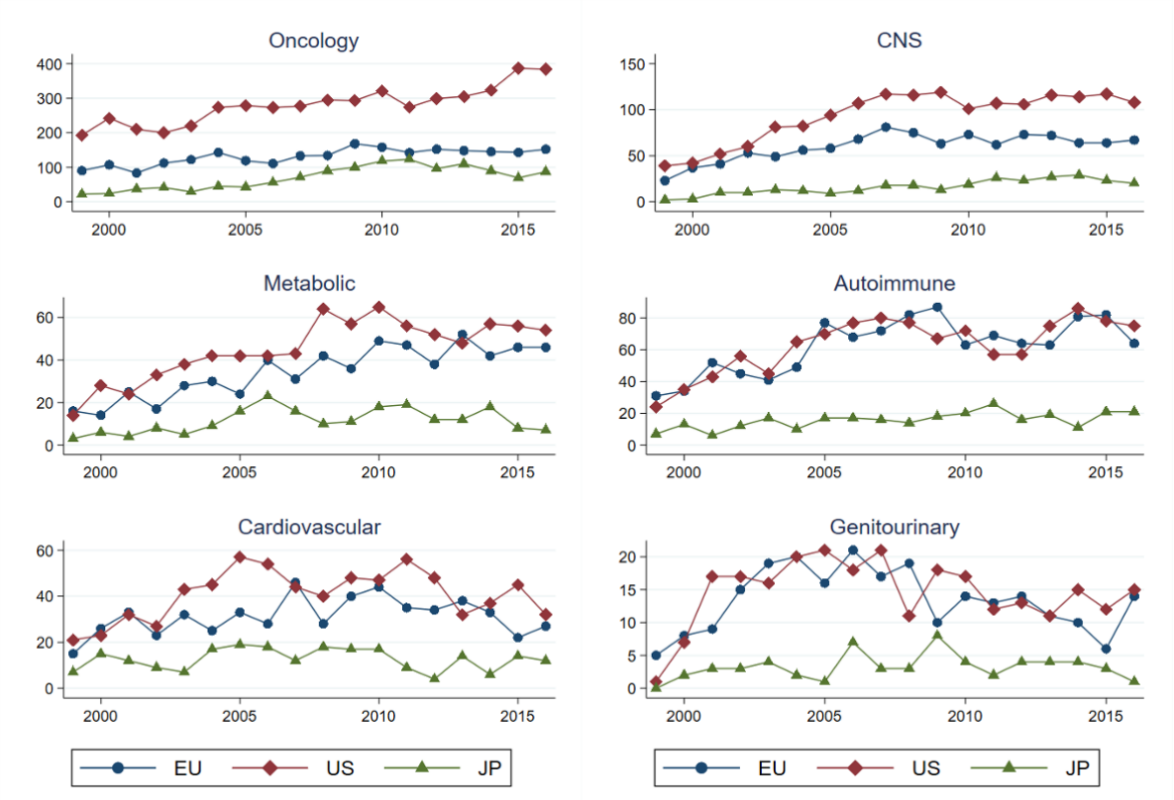
Figure 13 presents an analysis of the evolution in the number of medicinal products recommended for authorisation by the EMA in specific therapeutic classes. There has been an increase in the number of applications overall, likely due to the expansion in the scope of the centralised procedure, and this has been mirrored in large part across various therapeutic areas. The EMA statistics confirm this observation as most therapeutic areas show a sustained increase in the number of authorised medicines after 2005 following the expansion in scope. There has been a proportionately larger expansion (467%) in the number of authorisations of antineoplastics and immunomodulating agents, compared with the increase in the number of authorisations in other therapeutic areas, likely reflecting the expansion in investments in oncology and ATMPs.

Figure 13. Number of centrally authorised medicinal products by Anatomic / Therapeutic classification



R	Respiratory system
N	Nervous system
M-S	Muscular Skeletal
A-I	Antineoplastic and Immunomodulating agents
A-S	Antiinfectives for Systemic use
GU	Genito Urinary system and sex hormones
CV	Cardio Vascular
B	Blood and blood forming organs
A-M	Alimentary tract and Metabolism
Other	Other
All	All

Figure 14 Trends in the number of new candidate medicinal products (pipeline) per year, by therapeutic area in the EU, US and Japan



Source: Informa Pharmaproducts and FDA databases

Figure 14 shows that the number of new candidate medicinal products has increased steadily over time in all therapeutic areas, perhaps with the exception of genito-urinary medicines. The trends look broadly consistent across the three regions analysed (EU, US, Japan), which suggests EU market is functioning broadly in line with other regions internationally 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 revisions, which suggests the legislation and the 2004 revisions have reinforced wider factors and have not boosted incentives substantially in the EU and nor have they hampered industry ambitions and competitiveness.

The 2004 revisions 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 (RI-8 and IEC-6, Analytical report, 2022); however, these effects cannot be attributed solely to the legislation or its revisions.

4.1.1.7 Competitiveness of EU pharmaceutical industry

The increasing complexity of the science and technology that feeds into pharmaceuticals has disrupted the traditional model of pharmaceutical companies that carried out all activities (or most) in the value chain: R&D, clinical development, manufacturing and marketing. 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 stages. In the clinical development phase, the costs sharply increase across the different phases of clinical trials, and usually this is the point when small companies either licence out their product, partner with or get acquired by large pharmaceutical companies. Large and well capitalised global companies are best in conducting and financing late-stage clinical trials, seeking regulatory approval and placing a product on the market. A high concentration of large pharma companies is observed among the market authorisation holders of innovative products (European Medicines Agency, 2021a), but this can hide the original innovator.

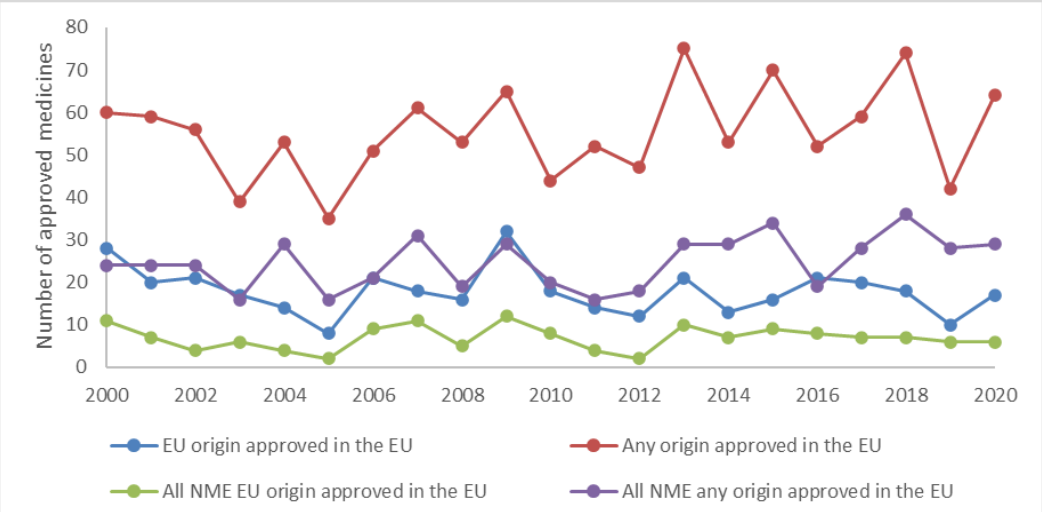
The greatest economic value from the pharmaceutical value chain stems from R&D, and thus this is a key factor to competitiveness. In the previous chapter we have outlined the EU's position in terms of pharmaceutical R&D. The EU has a strong second position globally, especially together with its close neighbours, the UK and Switzerland, that are part of the European biopharmaceutical innovation ecosystem through cross-country collaborations and movement of skilled professionals and capital. The EU biopharma industry's R&D expenditure has continuously grown in the last decades and only the 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), according to EFPIA member associations[18] (EFPIA, 2021).

Figure 15 presents a time-series analysis of medicines approved in the EU that originated with developers based in the EU and those with developers based elsewhere in the world. It suggests the legislation and the 2004 revisions were largely benign in the impact on the relative attractiveness of the EU. We analysed the trends in the number of EU approved medicines ((i) novel, new molecular entities and (ii) all products including biosimilars and other generics) in order to understand whether the changed 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 with their competitors located elsewhere in the world and looking to sell into Europe. The analysis did not support our hypothesis that the 2004 revisions (expansion of the centralised procedure, greater harmonisation of processes and procedures, etc.) might confer a possible environmental advantage and boost to competitiveness for EU industry in comparison with its international competitors. However, the analysis (we ran the same analysis for all competing regions) suggests that any

[18] 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.

additional burden that may have been introduced by the 2004 revisions, such as ERAs and improved pharmacovigilance and manufacturing practices, did not disadvantage EU-based pharmaceutical companies when compared with their international competitors, either within the EU or when exporting to other regions outside the EU (our stakeholder consultations with industry suggest that overall the various revisions resulted in a net increase in total regulatory costs, estimated at 5-10% of total regulatory costs). The analysis found a small increase in the average number of annual approvals pre and post implementation for both the 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 15 EU-origin medicines and any-origin medicines approved in the EU, split by all medicinal products and new active substances only



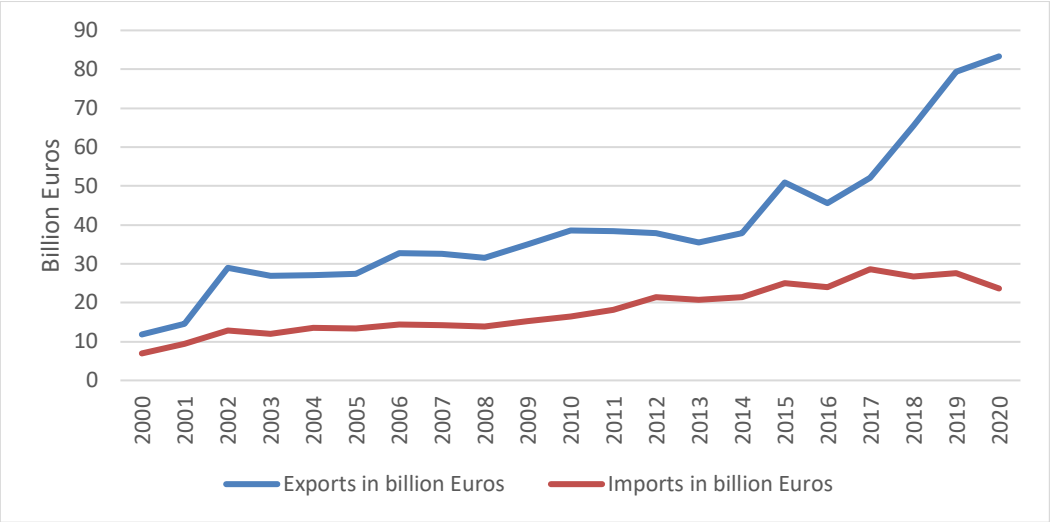
Source: Pharmaprojects, 2000-2020, Informa Pharma Intelligence analysis.

The landscape for pharmaceutical manufacturing has also changed in the 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 (Progenerika, 2020) for off-patent medicinal products. In the EU, small and large companies have shifted production focus to more complex, biological products (e.g. products harvested from living cells), 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, as evidenced by export and import data, 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 (Guinea & Espés, 2021) and while the overall figures are positive for the EU, there is no obvious effect of the 2004 revisions 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.

We see no significant change in growth rates – for exports or imports – in the 3-5 years before or after the implementation of the 2004 revisions for the US (or with other regions). There are no evident discontinuities in the data. There have been no evident points of convergence or divergence. Figure 16 shows an example of one bilateral trading relationship between EU and the USA. We also looked at EU-Japan and EU-Switzerland, and found a similar absence of any obvious impact on EU trade flows or the competitiveness of EU industry.

Figure 16 EU medicines exports to and imports from the USA



Source: Eurostat

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 globally leading role in exporting high-tech vaccines. BioNTech, the German biotechnology company that developed the technology behind Comirnarty, partnered up with Pfizer, a large pharmaceutical company headquartered in the USA with production facilities in the EU, to advance and scale-up human clinical testing and manufacturing capacity. By March 2021, less than three months after receiving conditional marketing authorisation from the EU (European Medicines Agency, 2022c), the BioNTech/Pfizer collaboration had already produced over 70 million vaccine doses in Germany and Belgium, placing the EU in the second place in manufacturing of COVID-19 mRNA vaccines, only behind the USA. In addition, British-Swedish company AstraZeneca, developer of the Vaxzevria vaccine, had produced over 10 million vaccines in the Netherlands and Belgium in the same period.

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.

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	2,276.2	39.7%	64.8%
China	1,869.1	32.6%	32.1%
USA	859.1	15.0%	58.4%
Republic of Korea	235.8	4.1%	91.1%
India	134.7	2.3%	5.7%
Russia	100.2	1.7%	35.8
South Africa	91.2	1.6%	87.0%
Japan	67.0	1.2%	99.8%
Other	105.9	1.8%	

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

[19] Last updated on 28 April 2022, with data for 31 March 2022 on WTO-IMF Covid-19 Vaccine Trade Tracker

4.1.1.8 Competitive functioning of the EU internal market

There are differing views among stakeholders as to what the internal EU market for pharmaceuticals is. In interviews, some stakeholders (e.g. civil society, healthcare professionals and public authorities) disputed the idea that there is a single EU market for medicines. Their view is that there are multiple national/regional markets in practice. It is also worth noting that markets can only be understood for individual therapeutic areas as there is no competition across therapeutic areas – as substitution is not possible. There is strong evidence and agreement across the various stakeholder groups that competition is suboptimal, for example from the targeted survey and interviews.

Nonetheless, many stakeholders agreed that the legislation has been beneficial for increasing competition in the pharmaceutical sector of the EU by facilitating generics and biosimilar entry in the market, particularly through the Bolar exemption. Generics entering the market are hindered by various factors including regulatory and intellectual property protection of the originator products as already discussed. Moreover, while these instruments define a clear date when generics can enter certain EU markets, generic entry in practice is somewhat delayed. This might be because of development and authorisation timelines (2-5 years for generics and 5-8 years for biosimilars; Mohammed, 2019) or lack of return on investment when developing a generic product. The total European biosimilar market has reached €8.8 billion in 2021 (Troein et al., 2021) while the generics market was valued at €67 billion for 2021 (Market Data Forecast, 2022). The market share and uptake of generics and the price reduction on generic entry has already been discussed in previous sections. The same aspects with regard to biosimilars are discussed in the case study below.

The EU has been an early adopter of biosimilars and delineated an authorisation pathway for biosimilars much before any other country. The biosimilar pathways are also a success according to industry and are seen as facilitating access of biosimilars to patients, thus increasing competition with the originator.

The EU's leading role on biosimilars

EMA first developed guidelines for the approval of biosimilars via an abbreviated registration process during 2005/2006, and since then EMA has developed many general and specific guidelines for biosimilars (GaBI, 2016). Based on these guidelines, 84 biosimilars have been authorised for use in the EU between 2006 and 2021 (GaBI, 2022). Biosimilars of biological reference medicinal products within the mandatory scope of the centralised procedure can be authorised only through the centralised procedure, whereas biosimilars of other biological reference medicinal products can be authorised through the other procedures. In practice, however, the vast majority of biosimilars are authorised via the centralised procedure.

IQVIA data show that the EU accounted for around 70% of the world's biosimilar authorisations in the 5-year period 2006-2010, and in 2016-2020 it still accounted for the largest share of authorisations (30%) (Troein et al., 2021). In comparison, the FDA only approved its first biosimilar in 2015, and has since granted 29 approvals for biosimilars with only 18 having been launched on the US market (GaBI, 2021). However, uptake (and access) of biosimilars is not uniform across EU MSs. On a per capita basis, central and eastern European markets lag western European countries (Troein et al., 2021). Uptake is affected by factors such as historic usage of protected brands, lack of clarity on the scientific foundation for interchangeability of biosimilars, national policies on interchangeability and lack of confidence in biosimilars among healthcare professionals and patients (Druedahl et al., 2022). There may be additional costs for biosimilar 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 and originator (Mestre-Ferrandiz et al., 2016). These factors may also influence uptake of biosimilars.

The EC has actively promoted biosimilar uptake within the EU through its Project Group on Market Access and Uptake of Biosimilars. The group involves EU member states, EEA countries' representatives, as well as other stakeholders such as patient organisations, healthcare professionals and experts (Rémuzat et al., 2017). Member states have also provided targets and incentives for biosimilar uptake. For example, France has set a target of 80% biosimilar penetration by 2022 (Haustein et al., 2012). About a dozen countries in Europe including Germany and the UK offer incentives to prescribe biosimilars and countries such as France, Germany and Sweden have made arrangements to share benefits with patients (known as gainsharing).

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 biosimilars (Guntern, 2021). Biosimilars are typically cheaper by 20% compared to originator products (Chen et al., 2021). 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 (Haustein et al., 2012). Savings from biosimilars are smaller compared to generics 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 (Ferrario et al., 2020).

Ordinarily only one market authorisation is granted to an applicant for a specific medicinal product, however the applicant/MAH can obtain a duplicate authorisation at reduced cost for the same medicinal product where "*there are objective verifiable reasons relating to public health regarding the availability of medicinal products to healthcare professionals and/or patients, or co-marketing reasons*" (European Commission, 2019). MAHs have been making use of this exception to obtain a duplicate authorisation for the first generic product on the basis that its inaugural launch into the market can improve availability because it usually increases accessibility. This behaviour has implications for the biosimilar market (including anti-competitive effects) as national pricing, reimbursement and substitution rules are linked to the regulatory status of the medicinal product.

EMA statistics show that there has been a sustained increase in number of authorised medicines after 2005 in several therapeutic areas ranging from oncology and central nervous system medicinal products to those for autoimmune and metabolic disorders (Analytical report, 2022). These developments help to increase choice and competition for medicines within the EU.

4.1.1.9 Key contributing and hindering factors in achieving the intended objectives

The stakeholder consultations provided very little information on how the type of legislative act, i.e. a Directive, has impacted on achieving the intended objectives of the general pharmaceutical legislation. However, variations in the interpretation and implementation of the Directive when transposed by MSs were reported by stakeholders and is discussed in Chapter 3.

There is also a view among individual stakeholder organisations (industry associations, learned societies, SMEs) that the legislation and the incentives applied under it, predominantly incentivise development of traditional product types (e.g. small molecules) and new active substances and the innovation of radiopharmaceuticals, generics and cell-based therapies is not supported to the same degree. These types of medicinal products suffer from lack of coherence with and differing requirements under other regulations such as those for clinical trials and radiation safety (this point is further explained in the coherence section). The European Association of Nuclear Medicine in their statement of December 2021 identified challenges for radiopharmaceuticals within the Directive 2001/83/EC owing to uncertainties among MS authorities, producers and users in interpreting the Directive (EANM, 2021). This had led to increased heterogeneity in interpretation of the Directive and a negative impact on the availability of radiopharmaceuticals.

Moreover, in the public consultations, health professionals highlighted the inconsistencies within the legislation that have impacted on radiopharmaceuticals in particular. They pointed out that Article 6 paragraph 2 of Directive 2001/83/EC imposes the need for a marketing authorisation on "radionuclide precursor radiopharmaceuticals". In Article 1 instead of a definition for "radionuclide precursor radiopharmaceutical" a definition is given for the term radionuclide precursor. This has led to the unintended effect that all radionuclides regardless of the type of preparation they are used in (kit-type procedure or complex preparation) need a marketing authorisation to be distributed from a site that has the technical provisions for radionuclide production (accelerator, nuclear reactor etc.) to another site that is equipped for the radiosynthesis of the final radiopharmaceutical. Strict interpretation of the Directive therefore leads to the non-availability of radionuclides that are prepared by technically demanding infrastructure.

Along with the different routes for authorisation of new medicinal products, the harmonisation of incentives i.e. the 8+2+1 regulatory protection periods enables the legislation to meet its objectives even if EU trend data before and after 2004 indicates that the current system of incentives has not substantially brought more innovation compared to the previous system (Figure 9). The current incentives provide consistency and predictability to developers in terms of the marketing authorisation process and return on investment calculations, allowing easier 'go or no go' decisions with regard to pursuing R&D of a candidate medicinal product.

On the other hand, 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, often the product cannot be brought to market as academics do not have the required regulatory knowledge and capacity, are not very experienced with product development and have limited production capacity (KWF, 2021). Moreover, guidelines and other regulatory standardisation are lacking because of the relative novelty of the field.

The interviews showed a consensus between public authorities, civil society organisations and academics that there is tension between the objectives of facilitating innovation and ensuring access to medicines. Data exclusivity and market protection incentives contribute to high prices according to these public sector stakeholders, which hinder access. While out of the sphere of influence of the legislation, HTA and reimbursement decisions have a major impact on population access to medicines in MSs.

Payers and civil society interviewees commented on the fact that data generated for obtaining authorisation are not useful for decision making by HTA bodies, payers and health professionals (i.e. safety and efficacy are often showed against placebo, and do not include the safety and effectiveness of the product compared to current standard treatment), and hence cannot sufficiently demonstrate the added therapeutic benefit during the reimbursement process for newly authorised medicines especially if they are expensive, leading potentially to delay of access.

Another key tension is between encouraging innovation focussed on addressing unmet medical needs or new antimicrobials and low return on investment (*AMR Review*, n.d.), which results in commercial entities not getting involved in R&D in these areas and impacts on the legislation's ability to safeguard public health in the EU.

4.1.2 Efficiency

4.1.2.1 Cost-benefit analysis

The socio-economic cost-benefit analysis follows the steps as set out in the Better Regulation Toolbox. The first step in assessing costs and benefits is to define the policy intervention to which they relate, and the hypothetical situation that would have occurred in absence of this intervention. We will use the term comparator situation in this analysis to describe the most likely situation in absence of the policy intervention.

The main measures of the policy intervention of the general pharmaceutical legislation have been set out in the terms of reference for the study.

For the comparator situation, it is noted that market trends in terms of medicine development and the pharmaceutical industry (innovation, mergers and acquisitions, etc.) would have taken place in and outside the EU. This means that in the assessment of impacts, such general (market) trends need, in as far as possible, to be separated from the 'pure' impact of the legislation. Thus, if the revision has stimulated innovation, that impact should be separated from the innovation caused by other factors, such as broader technological advances.

There is no unambiguous way to establish this comparator, as the revision touches on many aspects of development, production, distribution and use of medicines, some of which may have occurred (partly) also if the revisions would not have taken place. We therefore take the pre-2004 situation as the comparator situation and the analysis compares the situation before and after 2004 with respect to the legislation. However, as the pharmaceutical market has changed over time, both in terms of size and type of products, market changes may affect a comparison over time. Therefore,

general market trends are taken into account to compare the development in the EU with that in the USA, Japan and other relevant world markets.

Identifying the types of costs and benefits

The 2004 revisions 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. This has been done through our desk research and consultations. In the following table, we list the main types of costs or benefits for each of the main stakeholder groups, specifically:

- Industry relates to pharmaceutical producers based in the EU
- Trade relates to wholesale distributors active in the EU
- Regulatory bodies, separated into: EMA and NCAs
- Health system comprises healthcare providers, patients and their carers, and others in society

Table 2 Potential direct impacts

Actors	Type of cost / benefit	Direct impacts
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	Earlier access
	Market protection	Higher protection level
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 system	Quality of MPs	Measures generally result in higher quality / efficacy of products
	Availability of MPs	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	More and better information available, more informed decision making by reimbursement agencies and precribers
	Environmental impact of MPs	Improved transparency around the environmental risks of specific products / APIs, facilitating improved environmental management

We have collected primary data regarding costs and benefits through desk research, targeted survey and interviews. In addition to this, the results from analyses of secondary data (as presented in the Analytical report) has been used. These data, evidence and examples provided form the basis of our following cost-benefit assessment.

Measuring the costs and benefits

Given the length of time that has elapsed since the implementation of the 2004 revisions, most stakeholders were unable to provide quantitative estimates of the costs and benefits associated with those changes. Most could do no more than list the types of costs and benefits they had experienced, and the main drivers of those additional costs and benefits. Therefore, we have had to rely on quantitative estimates provided by a small number of organisations that had direct experience of the changes and some historical data. This limited number of observations was augmented by several studies and presentations, the number of data are scarce, and we have therefore come forward with large ranges for our estimates of the key impacts.

As described, the approach to identifying and measuring costs and benefits is by comparing the situation post 2004 revisions with the pre 2004 situation, taking into account general market developments when appropriate. The evidence for the size of costs and benefits has been gathered during this study from various sources: interviews, surveys and data analysis.

4.1.2.2 Stakeholder impact

The following sub-sections summarise the evidence on each of the potentially expected impacts of the 2004 revision, as to whether the expected impact (cost, benefit) has occurred and the magnitude of the impact.

Citizens and consumers

The 2004 revisions were intended to improve the quality and safety of medicines overall, through greater harmonisation of definitions and procedures between EU and MSs and among MSs and through a strengthened EU-wide pharmacovigilance system. The revisions also effectively increased the incentives for industry to develop novel medicines through the expansion in the scope of the centralised procedure and the harmonisation of the period of regulatory data protection.

In both cases, our consultations and desk research confirm a positive impact of the revisions on both the quality and safety of medicinal products available in EEA and the number of innovative medicines available to healthcare systems and patients. Our consultations found a generally positive view across all stakeholder groups that the 2004 revisions in general and the more comprehensive inspections and pharmacovigilance systems specifically had delivered a higher level of patient protection as compared with the earlier arrangements.

Table 3 Summary of estimated costs and benefits of the 2004 revisions of the general pharmaceutical legislations

Direct costs	**Citizens / Consumers**	**Citizens / Consumers**	**Businesses**	**Businesses**	**Administrations**	**Administrations**
	Quantitative	**Comment**	**Quantitative**	**Comment**	**Quantitative**	**Comment**
Direct Compliance costs (adjustment costs)	-	-	€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)	-	-	€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)	-	-	-	-	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	**Citizens / Consumers**	**Citizens / Consumers**	**Businesses**	**Businesses**	**Administrations**	**Administrations**
	Quantitative	**Comment**	**Quantitative**	**Comment**	**Quantitative**	**Comment**
Health Impacts	25-30 new innovative medicines, in total; producing 170,000-210,000 QALYs in total; which amounts to €4.8bn-€17.2bn in	The additional number of new products has been estimated based on a comparison between EMA and FDA	-	-	-	-

	monetised benefits, using WHO guidelines on valuing QALYs	authorisations over time; the QALYs are based on estimated average EU income and a median ICER				
Compliance costs: MAH savings	-	-	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: MAH savings	-	-	€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	-	-	-	-	€20m-€40m pa	Cost savings for national competent authorities due to streamlining / harmonisation of national authorisation procedures (switch to DCP away from MRP)

There is no good direct measure of medicine quality that one can link clearly to the legislation, however, statistics do show strong year-on-year growth in the numbers of GMP inspections in the five years following the implementation of the 2004 revisions (EudraGDMP database),[20] clearly reflecting the legislative decision to expand and harmonise the oversight of MA holders' manufacturing and supply chains as a means by which to ensure quality and consistency. These activities have continued – and have been strengthened further – over the ensuing 15 years, ensuring the quality of both manufacturing and distribution (European Medicines Agency, 2021b). The number of GMP inspections and certificates issued by EEA authorities was running at around 2,500 a year pre-COVID,[21] with this extensive programme of quality assurance work resulting in a small but highly variable 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).

There has been a similarly evident expansion in the numbers of safety reports submitted and recorded in the EudraVigilance database, again suggesting the regulatory system is working well. The time-series data published in the EudraVigilance annual report to the Parliament and Council show a clear change in the rate of growth in the numbers of individual case safety reports (ICSRs) being submitted and screened annually, following the 2004 revisions (European Medicines Agency, 2020c). Around 10% of the individual safety reports are judged to warrant an in-depth review by the EMA's signal management team or a Lead Member State (for nationally authorised products) for a possible adverse drug reaction (ADR) and around 20% of these assessments result in a referral to the Pharmacovigilance Risk Assessment Committee (PRAC). Around half of these referrals to PRAC result in an update of the product information for patients and healthcare professionals, thus providing updated guidance on the safe and effective use of the medicines. We have not reproduced the actual statistics here, as these potential safety issues can have many causes, and they do not provide a credible basis for directly measuring quality improvements attributable to the legislation.[22] Notwithstanding this important caveat, the 2004 revisions did however provide the legal basis for the improved monitoring, and the change in the number and trend of reported safety concerns is a good indication that the surveillance system was successfully enhanced. We were similarly unable to quantify the benefits of these quality enhancements to public health in the EU, but studies of more recent enhancements to the overall pharmacovigilance system show the process is identifying more potential risks and enabling these to be acted upon more quickly and decisively (Potts et al., 2020).[23]

The expansion in the scope of the centralised procedure and the extension of the period of regulatory data protection has contributed to an increase in the numbers of innovative medicines being authorised for use in Europe. As such, EU citizens have had access to a larger number of novel medicines than would have been the case without the 2004 revisions. 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 10 years following, from around 35 in 2005 to around 70 in 2015 (European Medicines Agency, 2021a).[24] The same has happened in respect to innovation with the numbers of medicines containing new active substances (NAS) increasing from around 20 a year to around 30. This growth in medicines and NAS is partly a reflection of changes in the scope of the EMA's centralised procedure but it is also a reflection of wider trends, with increasing demand for new medicines globally and an expansion in R&D investment by pharmaceutical companies the world over (OCDE, 2019).[25]

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[20] The data derived 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.

[21] The number of inspections – and physical visits in particular – was reduced substantially during the COVID-19 pandemic, with some potential lessons for streamlining and digitalisation going forward. See the results of an annual survey of inspections and audits.

[22] Better monitoring may mean revealing pre-existing issues to an extent and there can be many reasons for ADR which can include genuine scientific unknowns at the time of the original authorisation or time-limited manufacturing issues and even off-label uses.

[23] In the period 2012-2018, the EU's strengthened pharmacovigilance process resulted in over 26,000 potential signals being reviewed and 453 confirmed signals assessed by the PRAC. More than half of the PRAC recommendations have resulted in changes to medicine product information supporting safe and effective use of medicines, demonstrating that the EU signal management process reliably detects, assesses, and deals with safety issues and enables the risk of ADRs to be minimised.

[24] In 2021, EMA recommended 92 medicines for marketing authorisation. Of these, 54 had a new active substance which had never been authorised in the EU before.

[25] This 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.

Given the widely differing types of novel medicines recommended for authorisation, from cancer to infectious diseases by way of cardiovascular medicines, and the impossibility of inferring which specific products have been brought to market that would otherwise have not been, we have had to make some broad approximations as regards an 'average' innovative medicine in order to estimate an average number of citizens (patients) that may benefit from access to these new treatments, and the likely health gain in terms of Quality Adjusted Life Years (QALYs).[26]

These estimates are set against the backdrop of a reducing EU health burden more generally: research confirms that age-standardised mortality rates have improved in all EU countries in the period since 2007 (Santos et al., 2020), albeit with significant variations in improvements across member states. There are also major differences in the burden / mortality across diseases, with heart conditions, strokes and various cancers dominating the top 25 conditions.[27] These long-term improvements have been attributed to improved education, better socio-economic conditions, stronger public health systems as well as advances in healthcare. The regulatory system will have been an important contributor too, driving innovation in new medicines as well as ensuring the safety and efficacy of the 900,000 medicines[28] recorded in the EMA database (as defined under Article 57).[29]

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 revisions, however, there is a clear discontinuity in the EMA trend data with the 3-year averages declining at around 10% a year across the period 2001-2005 and then growing at around 20% a year from 2006-2009. The US FDA authorisation data exhibit 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, we have assumed the 2004 revisions 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, we have 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. Our 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 simple average figure for sales, we calculated the combined EU sales for these additional products falling in the range €570m-€680m. Based on the number of additional products and EU sales, we estimate the 2004 revisions were associated with an additional 170,000-210,000 QALYs across the period, based on a median ICER of €33k / QALY that 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),[30] as recommended in the Better Regulation toolbox (tool #31), and using an average GDP/capita for the EU of €27,810 (Eurostat Statistics Explained, 2021), we estimated the monetary value of the 2004 revisions would fall in the range €4.8bn-€17.2bn.

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[26] The Better Regulation Tool # 31 lists QALYs as one of the key non-monetary approaches for assessing health impacts. However, there are challenges when working across different patient populations and countries and across different interventions. For example, the same treatment can have markedly different costs across member states and can have markedly different benefits across patient groups (e.g. younger versus older citizens with less good underlying health). See Kocot, E., Kotarba, P. & Dubas-Jakóbczyk, K. The application of the QALY measure in the assessment of the effects of health interventions on an older population: a systematic scoping review. *Arch Public Health* **79,** 201 (2021).

[27] Data from Eurostat on Mortality and life expectancy statistics, as of 25 April 2022.

[28] According to the 2020 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission, at the end of 2020, this database (the so-called "Article 57 database") contained information on more than 900,000 medicinal products (including different formulations and strengths as separate medicines).

[29] All holders of marketing authorisations for medicines in the EU and the EEA must submit information to the EMA on authorised medicines and keep this information up to date. This is a legally binding requirement from the EU pharmaceutical legislation. The Agency uses this information to support the analysis of data, regulatory activities, and communication.

[30] http://www.who.int/choice/cost-effectiveness/en/

Businesses

There are two types of cost impacts for businesses (EU-based pharma industry and wholesalers):

- One-off adjustment costs
- Recurrent adjustment costs

One-off adjustment costs are related to the changes that companies needed to make in order to be able to provide the information for the additional inspections introduced with the 2004 revisions. The interviews and surveys revealed that these costs were mainly related to the need to invest in upgraded IT systems. The survey delivered limited information on this. Based on the data received in the survey, we estimated the one-off costs at €250 million.[31]

Industry also incurred ongoing additional administrative costs associated with several of the new measures, including for example the expansion in the scope of the centralised procedure. Moreover, the revisions included changes to the submission documents (primarily the introduction of the environmental risk assessment [ERA], but also the introduction of the Summary Product Characteristics (SmPC) within the application and the need to improve the readability of the content of the package leaflet and label) and required much greater detail on manufacturing value chains and sites. 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.

For originators, the additional costs amounted to ca. 5-10% increase in companies' regulatory costs. For the generics industry, the greater detail in the regulatory dossier increased the costs associated with notifications of revisions. 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 their storage and distribution systems.

We have estimated these ongoing additional costs at €200m a year or €3bn over 15 years in current prices. Adjusting this for inflation would suggest a total cost of €2bn-€2.3bn.

We identified no significant, quantifiable indirect costs for industry. We had hypothesised that the revisions would have led to more general changes in company operations outside the regulatory department. We had for example anticipated the revisions causing developers to invest more heavily in later-stage clinical trials to secure the evidence necessary to meet the exacting standards of the EMA committees, but this was not confirmed in practice. Feedback from several generics companies does suggest that the Bolar exemption had a positive impact on their product development and earlier launch activities, however, this is a qualitative rather than quantitative observation, with no basis for estimating a quantitative impact.

On the benefits side, 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 being run in different member states. For industry, however, the most significant efficiency gain relates to the withdrawal of the obligation to renew marketing authorisations every five years. We estimate these savings amount overall to around €300m-€375m over the past 15 years.

There are also small cost savings for businesses, due to faster (and thus less costly) approval procedures, through both the expansion of the central procedure and the introduction of the harmonised decentralised procedures (DCP), instead of the more variable national procedures that were in use prior to 2004. Based on the average number of new applications these savings are

[31] Five businesses estimated their one-off costs, which ranged from €25k 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. €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 revisions. 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.

estimated at €40m per year across the period, with 90% of those savings being realised by the generics industry (c. €36m pa).

A second source of costs savings for business relate to the abolition of the 5-year renewal of marketing authorisations. The cost reduction of this is estimated at €23m per annum, covering both the MA holders authorised via the EMA and those authorised by member states. We estimate that this has resulted in a reduction of around 150 EMA renewals annually over the period, and 1,350 NCA renewals. Our stakeholder consultation confirmed that these changes had benefited the generics industry in particular, with its almost total reliance on national authorisation procedures and the abolition of all 5-yearly renewals for off-patent medicines containing well-known molecules. This has resulted in a saving of around €6.8m p.a. in fees and staff costs for the 150 EMA renewals, and around €16.2m for products authorised by member states, where the dossiers were less complex and renewal fees are lower. Taking these two cost items together, the net annual benefit for all companies would be on the order of magnitude of €23m a year.

Our consultations and desk research suggest the legislation has had no significant measurable impact on the EU pharmaceutical industry's overall performance, in terms of its economic output, medicines pipeline or global competitiveness. We had anticipated that several of the revisions might have encouraged and rewarded an increase in R&D, whether that was the extension of the period of regulatory data protection across all EU member states, the expansion in the provision of scientific advice to applicants, the provision of additional data protection for new indications or the introduction of new assessment procedures designed to cope with the evolution in medical science. Feedback from stakeholders suggest that these various positive changes would likely have been lost in a broader set of market pressures affecting the global research-intensive pharm industry. The statistics (e.g. BERD, medicines pipeline) for the EU 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 revisions. The one exception is biosimilars, 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 authorisations in the 5-year period 2006-2010. In 2016-2020, it still accounted for the largest share of authorisations (30%), albeit India and China have registered stronger growth and have bigger pipelines (Troein et al., 2021).

In summary, we estimate 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 (EFPIA & PWC, 2019).

Public authorities

The European Medicines Agency

The 2004 revisions led to a substantial increase in the work of the European Medicines Agency (EMA), related to the expansion in the scope of the central authorisation procedures and an intensification in respect to the provision of scientific advice and greater support for a wide 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 in part the intensification and transfer of authorisation activities from member states.

The EMA annual budget summaries are presented in the annexes to the Agency's annual reports (European Medicines Agency, n.d.-b) and show steady year-on-year growth across the 10 years to 2014 and beyond. The distribution of activities has remained broadly stable over time, split 35% on staff costs (Title 1), 25% on buildings (Title 2) and 40% on operations (Title 3). Operational expenditure (Title 3; mainly consisting of expenditure for meetings [c. 4% of all Title 3 costs] and evaluations [c. 35% of all Title 3 costs]) for EMA increased from €39m in 2004 (European Medicines Agency, 2005) to €168m in 2020 (Samassa, 2021), while staff expenditure (Title 1) increased from €32m to €115m in the same period. Both types of expenditure rose much faster than inflation in these years (while prices in the Eurozone have risen by 29% across the whole of this 15-year period).

The increase in real terms was thus around €190m in the period 2004-2020, for Title 1 and Title 3 combined.

This increase may be partly, though not wholly, attributed to the 2004 revisions. In the absence of these additional EMA-led procedures, businesses would have continued to make use of national procedures. This means that NCA-led authorisations are lower due to expansion of the centralised procedure. We assume these national savings largely mirror the extra costs for EMA. There may be economies of scale, however, the amount to which these MS savings and EU costs differ proved difficult to assess, as our 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, we estimate that around 20-25%, or €40m-€50m, of the real-terms increase in EMA expenditure (Title 1, Title 3) is related to the 2004 revisions. We base this estimate on the fact that about 20-25% of all EPAR/opinion entries on the EMA website are non-paediatric and non-orphan related. Given the substantial increase in EMA costs over time, and the need to make assumptions about attributable impacts, we have worked with an average annual additional cost in the range: €2.5m-€3.1m.

National authorities

Most NCAs provide assistance 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.), whereby the expansion in the scope of the work of the EMA had resulted in a reduction in activities relating to national authorisations and a switch to work in support of the EMA.

Only two NCAs 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 EMA activities in general (the expanded scope of the CP) and in particular the additional enforcement obligations due to the strengthened pharmacovigilance system, however, these stakeholders were not able to quantify those additional costs.

The two estimates provided by the NCAs, for their annual additional costs, fell in the range of €165k-€500k. To estimate the likely total cost for the EU overall, these two smaller EU member states account for around 1.3% of the EU population, and assuming these additional costs are typical, would mean that the additional annual costs for national regulators across the EU would have fallen in the range €12.7m-€38.5m per annum. The EMA reimburses the NCAs for certain activities, whereby the costs associated with these additional national activities are covered in part by the EMA financing. To avoid double counting, we have discounted these estimates by 35%. One of the two NCAs estimated that the EMA reimbursement covered 25-35% of its costs in the period, resulting in an indirect subsidy from national regulators. Applying this discount of 35%, would mean that the additional annual costs for national regulators across the EU fall in the range €8.2m-€25m per annum. Neither of the NCAs that provided an estimate of the additional costs incurred provided a breakdown of costs split between their support for assessments and post-marketing authorisation activities. One of the two did indicate that post-marketing authorisation aspects comprise around 80% of their total EMA-related activities, and if we assume the additional costs are equally distributed, that implies additional annual costs of €1.65m-€5m for NCA support for EMA-related assessment activities and €6.6m-€20m for post-authorisation activities.

Several national regulators commented on the benefits of the switch to the DCP and the use of a more streamlined and harmonised set of authorisation procedures, however, no estimates were offered as to the scale of any cost savings. We reviewed the annual financial accounts of several national competent authorities, which revealed increases in both fee income and staff / operating expenditure in the period 2005-2010, however, those financial accounts offered no view on any efficiency gains relating to changes in authorisation procedures. We have therefore made a conservative estimate of a 1-2% improvement in efficiency for all NCAs resulting from the streamlining measures, which we estimate as resulting in €20m-€40m savings annually.

4.1.2.3 Societal impacts

The 2004 revisions did introduce the environmental risk assessment (ERA) within the application documents, albeit it did not have a bearing on the authorisation opinion. Industry respondents

suggested that this had improved transparency (around the specific risks associated with the molecules / APIs of new medicines) and increased awareness of those environmental risks amongst manufacturers and their supply chains. However, these are small, incremental improvements, and the EU pharmaceutical industry's carbon footprint has not been affected directly, positively, or negatively, albeit indirectly, the high-quality regulatory environment has supported the expansion of the industry and an increase in greenhouse gas emissions. Expansion has also been driven by global consumption of medicines, and the industry has a particularly high carbon footprint that is a growing focus for improvement measures (Ray et al., 2021).

4.1.2.4 Simplification and burden reduction

The preceding paragraphs have detailed three areas of simplification and burden reduction that have been realised following the implementation of the 2004 revisions, which we have captured in the table below, in line with the table presented in the Better Regulation toolbox (Annex III Table 2):

- Cost savings for industry, and 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, and especially the generics industry, due to 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
- Cost savings for NCAs due to streamlining / harmonisation of national authorisation procedures (switch to DCP away from MRP)

In addition to the reduction of burden achieved, there are also evident opportunities for further reductions of administrative burden going forwards.

Our stakeholder 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% (Cardona et al., 2013). We have used this general factor applied to the main regulatory cost components borne by industry and the EU and national administrators to estimate the potential annual savings:

- Industry: we estimate potential annual savings of €9.6m, assuming an EU-wide regulatory budget of around €1.6bn, we estimate the wide-ranging implementation of enhanced ICT solutions, open data and worksharing
- EMA: we estimate potential annual savings of €2.1m, assuming an annual EMA budget of around €350m, we estimate the wide-ranging implementation of enhanced ICT solutions, open data and worksharing
- NCAs: we estimate potential annual savings of €12m, assuming an EU-wide budget for NCAs of around €2bn, we estimate the wide-ranging implementation of enhanced ICT solutions, open data and worksharing

4.1.2.5 A harmonised system of regulatory data protection

The 2004 revisions introduced a harmonised system of regulatory data protection for innovative medicines (8+2+1) that stakeholders viewed positively, with the new arrangements bringing greater clarity, harmonisation and predictability as compared with the previous situation, where there were a variety of different national policies in place.

The baseline situation was defined by Directive 87/21/EEC, which required EU member states to provide a period of six years of data exclusivity for most pharmaceuticals starting at the date of the first market authorisation, and 10 years for biotech and other high-tech medicinal products (Adamini et al., 2009). The Directive allowed member states to define a period of ten years for all pharmaceuticals if they considered this "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 revisions turned the 6-year and or 10-year period into the 8+2 arrangements and made it applicable across all 15 MS and the 13 central and eastern European countries that joined the union in 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 six.

We tried to explore the extent to which this harmonisation of regulatory data protection had produced additional costs or benefits, using the IQVIA sales data, however, we found that the effects of the 2004 revisions did not materialise until much later and with EU expansion, the new countries added individual rules to the system, so it proved impossible to make a quantitative comparison with the 1987 baseline. In practice, we have had to use a difference baseline, comparing trend data on EMA authorisations across the 2000s, with equivalent trend data for the FDA. This does reveal a measurable and positive effect on the EU's relative output of innovative new medicines in the years following the implementation of the revisions.

Industry stakeholders noted that this aspect of the 2004 revisions had contributed to the attractiveness of the EU's regulatory system globally. Our international comparative legal analysis 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).[32] Several stakeholders from patients' groups and academia remarked on what they considered to be the overly generous provisions available within the EU, which they argued have favoured innovation over access. These same groups recommended the EC review the balance between innovation and access in the related Impact Assessment, suggesting there is scope to reduce innovation incentives without damaging Europe's attractiveness globally while also strengthening the rewards / obligations around access and affordability.

4.1.2.6 Proportionality of costs and benefits

The table of costs and benefits shows that the 2004 revision is likely to have resulted in a net increase in regulatory costs to society on the order of €1.1bn-€1.8bn (over 15 years). The higher costs are the result of the higher standards set and the associated additional compliance and regulatory costs.

There have also been benefit gains in terms of reduced costs for MAHs, the EMA and NCAs, which sum to €1.2bn-€1.5bn, largely offsetting the additional costs of increased information requirements and pharmacovigilance activities.

The 2004 revision is also widely believed to have resulted in more innovative medicinal products and a higher quality regulatory system, which is likely to have resulted in a positive health impact for patients treated with such products, which would otherwise not have been available, or would have been available later in time. We have estimated this additional health impact at 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 on valuing QALYs.

The valuation of health impacts is widely accepted to be deeply challenging and was carried out at an aggregate level, however, even working with the lower bound estimate of health impacts and cost savings (€6bn) and the upper bound of the estimated additional costs (€1.8bn), the 2004 revisions have delivered a positive overall social return.

This economic analysis resonates with feedback from stakeholders overall, where the overall balance of opinion is positive: 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 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 revisions

[32] See pages 53 and 54 of the study.

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 needs, and medicines shortages. For this group, the perceived health impact is relatively small as compared with the (indirect) costs of the 2004 revisions and the substantial number of remaining challenges.

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

The 2004 revisions have achieved their objectives in large part, and as such there have been no substantial costs incurred by any stakeholder groups associated with a failed or partially achieved objective. There is arguably an issue around access and affordability in the broadest sense, where the 2004 revisions did little to improve the effectiveness of the general pharmaceutical legislation in ensuring access to medicines for all; and while it was not a specific objective there are widespread concerns that medicines shortages have become a bigger 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. For Public authorities and Civil society organisations, the high price of medicines arising from what they judge to be the misuse/abuse of incentives was cited as a cost to healthcare systems, in particular for small countries.

4.1.2.8 The main costs and drivers of the legislation

The 2004 revisions implemented a series of measures that have contributed to improvements in the effectiveness of the regulatory system, while also having been successful in delivering important efficiency gains for the EU's general regulation of pharmaceuticals.

Several measures stand out as having contributed efficiency gains, including:

The definition of medicinal products, which was adapted to take account of new therapies and their method of administration and provide a new pathway for biosimilar medicines
The expansion in the scope of the centralised authorisation procedure
Introduction of the decentralised authorisation procedure and optimisation of mutual recognition procedure for nationally authorised products together with optimised referral procedures
Reduced administrative burden by withdrawal of obligation to renew marketing authorisation every five years and introduction of sunset clause on validity of marketing authorisation

The 2004 revisions also introduced various new measures, designed to improve the effectiveness of the regulatory system overall, that brought additional costs for some stakeholder groups.

- Changes to documentation requirements, including environmental risk assessment (ERA)
- Increased transparency and harmonisation of key documents, i.e. the EMA began to publish European Public Assessment Reports (EPARs), which are publicly accessible information resource comprising a summary suitable for lay audiences alongside a series of regulatory documents regarding the MA holder, the product (e.g. summary of product information (SmPCs) and package leaflet) and assessment history[33]
- Harmonised application of good manufacturing practice (GMP) for active substances
- Improved pharmacovigilance by more frequent submission of periodic safety update reports (PSURs), which resulted in additional costs for MA holders and regulators
- Reinforcement of inspections with improved coordination by introducing new tools (EudraGMDP database), which brought efficiency gains through improved information exchange among regulators but has created some additional burden for MA holders that must maintain the currency of large numbers of records with frequent changes required with respect to what are inevitably dynamic global supply chains and distribution networks.

[33] Setting up and maintaining the document archive, drafting overviews and upgrading the existing individual components into a publishable suite of consistent and commercially non-disclosive documents involved the EMA in some limited additional costs.

Table 4 Summary of estimated costs savings and potential future savings

PART I **Simplification and burden reduction (savings already achieved)**

Cost savings		**Citizens / Consumers**	**Citizens / Consumers**	**Businesses**	**Businesses**	**Administrations**	**Administrations**
		Quantitative	**Comment**	**Quantitative**	**Comment**	**Quantitative**	**Comment**
Compliance costs: MAH savings	**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: MAH savings	**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 savings (NCAs)	**recurrent**	-	-	-	-	€20m-€40m pa	Cost savings for national competent authorities due to streamlining / harmonisation of national authorisation procedures (switch to DCP away from MRP)

PART II **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.**

Direct benefits		**Citizens / Consumers**	**Citizens / Consumers**	**Businesses**	**Businesses**	**Administrations**	**Administrations**
		Quantitative	**Comment**	**Quantitative**	**Comment**	**Quantitative**	**Comment**
Compliance costs: MAH savings	**recurrent**	-	-	9.6	There are opportunities for substantial further digitalisation across the EU pharma regulatory system to increase efficiency and duplicative activity	-	-

Enforcement savings (EMA)	**recurrent**	-	-	-	-	2.1	There are opportunities for substantial further digitalisation across the EU pharma regulatory system to increase efficiency and duplicative activity
Enforcement savings (NCAs)	**recurrent**	-	-	-	-	12	There are opportunities for substantial further digitalisation across the EU pharma regulatory system to increase efficiency and duplicative activity

Administrative complexity and costs

In carrying out the evaluation, and the analysis of costs and benefits, we have sought to identify the elements of the general pharmaceutical legislation that pose an administrative burden or were overly complex.

For industry, the major administrative burden relates to the additional post-market authorisation procedures that have to be followed in order to support a more robust pharmacovigilance system (partially out of scope of the current evaluation).

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 therapies and more complex products that require relatively greater scientific effort to review and often entail assessments and advice from multiple committees.

For national health technology assessment agencies and health payers, the introduction of the CMA had proved problematic, with substantial additional costs associated with the subsequent assessment of the relative cost-effectiveness of newly authorised medicines. The uncertainty associated with fewer data has led to later challenges on cost-effectiveness and is causing some HTAs to not approve medicines for reimbursement where the evidence is particularly difficult.

4.1.3 Coherence

The criterion of coherence of the legislation refers to both how the various elements of the legislations work internally and how these are complementary (or duplicative) with other EU policies to achieve the legislation's intended objectives.

Coherence has thus been approached and considered in three elements, 1) internal coherence 2) coherence with specialised pharmaceutical legislation 3) coherence with other EU legislations. In the following we respond to the evaluation questions posed in the terms of reference of the study. For a full analysis, see Annex IV.

4.1.3.1 Internal coherence

The legal analysis and literature review on the EU general pharmaceutical legislation has not led to the identification of overlaps, contradictions, or other inconsistencies between the Directive and the Regulation despite the fact that they cover different authorisation procedures as illustrated in the table below. The Directive and Regulation contain multiple cross-references and common requirements (e.g. same definitions, some prohibitions for non-authorised medicinal products).

Table 5 Mapping of cross-references between Directive 2001/83/EC and Regulation (EC) No 726/2004

Directive 2001/83/EC	Cross-reference to Regulation (EC) No 726/2004
Article 6	The prohibition to put in place a medicinal product without a marketing authorisation including the one granted in accordance with Regulation (EC) No 726/2004
Article 11	Medicinal products granted under Regulation (EC) No 726/2004 in accordance to its Article 23 must contain a summary of product requiring a specific statement and symbol
Article 23	The marketing authorisation holder must ensure that the product information is kept up to date with the current scientific knowledge including with information diffused on the EMA web-portal on medicinal products authorised in the Union as set under Article 26 of Regulation (EC) No 726/2004
Article 27	The coordination group must rely on the scientific assessment and the recommendations of the Pharmacovigilance Risk Assessment Committee provided for in Article 56(1) (aa) of Regulation (EC) No 726/2004 as part of EMA and that this coordination group must apply the rules under Article 63 of this Regulation on conflict of interest and transparency
Article 57	Member States when setting labelling requirements on price, reimbursement, legal status for supply to the patient concerning medicinal products authorised under

	Regulation (EC) No 726/2004 must observe the detailed guidance referred to in Article 65 of this Directive
Article 59	Additional statements required for medicinal products included in the list referred to in Article 23 of Regulation (EC) No 726/2004 which are subject to additional monitoring.
Article 76(2)	Medicinal products subject to wholesale distribution and storage must be covered by a marketing authorisation granted pursuant to Regulation (EC) No 726/2004 or by the competent authorities of a Member State in accordance with this Directive.
Article 85(B)	Persons brokering medicinal products shall ensure that the brokered medicinal products are covered by a marketing authorisation granted pursuant to Regulation (EC) No 726/2004 or by the competent authorities of a Member State in accordance with this Directive.
Regulation (EC) No 724/2004	**Cross-reference to Directive 2001/83/EC**
Article 2	The definitions laid down in Article 1 of Directive 2001/83/EC and those laid down in Article 1 of Directive 2001/82/EC shall apply for the purposes of this Regulation.
Article 3(3)	A generic medicinal product of a reference medicinal product authorised by the Community may be authorised by the competent authorities of the Member States in accordance with Directive 2001/83/EC and Directive 2001/82/EC under certain conditions
Article 6	Each application for the authorisation of a medicinal product for human use shall specifically and completely include the particulars and documents as referred to in Articles 8(3), 10, 10a, 10b or 11 of, and Annex I to, Directive 2001/83/EC. […]
Article 12	Authorisation shall likewise be refused if particulars or documents provided by the applicant in accordance with Article 6 are incorrect or if the labelling and package leaflet proposed by the applicant are not in accordance with Title V of Directive 2001/83/EC.
Article 13	Without prejudice to Article 4(4) of Directive 2001/83/EC, a marketing authorisation which has been granted in accordance with this Regulation must be valid throughout the Community. It shall confer the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State in accordance with Article 6 of Directive 2001/83/EC. [...]
Article 19	The supervisory authorities shall be responsible for verifying on behalf of the Community that the holder of the marketing authorisation for the medicinal product for human use or the manufacturer or importer established within the Community satisfies the requirements laid down in Titles IV, IX and XI of Directive 2001/83/EC.

The findings from legal analysis and literature review are supported by the feedback received from the different stakeholder consultations. None of them, including public authorities who are in charge of implementing it and therefore major actors concerned, mentioned coherence issues. On the contrary, several stakeholders consulted explicitly mentioned the good internal coherence of the EU general pharmaceutical legislation (public authorities, industry, healthcare professionals).

More specifically, the targeted surveys indicated that respondents found the legislation moderately coherent internally. Industry rated the internal coherence the highest out of the stakeholder groups while academics the lowest with a lack of consensus within that stakeholder group. When asked about the most and least coherent aspects of the legislation in the targeted surveys or for additional comments in the public consultation, responses focussed on coherence of the legislation with specialised and complementary legislations rather than the internal coherence of the legislation itself. Within the interviews, respondents across all the stakeholder groups were generally positive about the internal coherence of the legislation remarking that there were no major problems and that the components of the legislation were synergistic.

4.1.3.2 Coherence with specialised pharmaceutical frameworks

There are several in-built mechanisms to ensure an adequate articulation between the general pharmaceutical legislation and the specialised pharmaceutical frameworks[34].

Nevertheless, some potential issues of coherence with the specialised pharmaceutical frameworks were identified. For instance, under the **Paediatric Regulation**, the differing national rules on the conduct of trials with children may still delay the completion of a paediatric investigation plan (PIP)[35], hampering the achievement of better compliance checks for PIPs. This may undermine the complementarity of this legislation with the general pharmaceutical legislation. The **Orphan Regulation** does not interact in a coherent fashion with Directive 2001/83/EC as regards generics entry. For orphan medicinal products, generic competitors can only submit an application for marketing authorisation at the end of the 10-year protection period while in general, for all human medicines, at the end of that period generic competitors can directly place generics on the market. Finally, a lack of coordination between the Committee for Medicinal Products for Human Use, on the one hand, and the Paediatric Committee, the Committee for Orphan Medicinal Products and the Committee for Advanced Therapies, on the other hand was identified[36] .

4.1.3.3 Coherence with linked legislation

There are several pieces of legislation not included in the specialised pharmaceutical legislation whose implementation can impact on several objectives of the general pharmaceutical legislation.

Linked legislation on health matters

The **EMA fees Regulation** provides the fees for the various procedures of authorisation and acts in parallel with the general pharmaceutical legislation, i.e. rules underlying the fee system are set by the general pharmaceutical legislation. An efficient fee system helps to ensure quality, safety and efficacy of medical products by creating a robust authorisation system. Nevertheless, according to public authorities and industry respondents, this objective could be hampered by the fact that NCAs are no longer adequately compensated, and this would lead to an authorisation system that is not cost-effective.

The **BTC legislation** raises other concerns. Here the main issue lies in classification, given the difficulties to define a substance/product as a BTC or as a medicinal product. Revision of the BTC legislation foreseen for 2022 aims to address this issue by improving clarity and aligning safety, quality, and efficacy standards to those in the pharmaceutical and medical devices regulation. Similarly, under the **Medical Devices Regulation** difficulties arise when a medical device incorporates substances which if used separately can be considered medicinal products, thus creating a classification issue. The incoherence, raised also unanimously by stakeholders which call for a harmonisation of definitions and processes, is centred around unclear definitions, differing interpretations and regulations between MSs. A reduction of disparities is therefore needed, to create a level playing field between MSs and facilitate free movement of medicinal products through more harmonised processes. The Medical Devices Regulation also raises another concern. EMA remains the only major pharmaceutical regulatory body that is not in charge of medical devices. Thus, a point of contention is whether the pharmaceutical legislation is coherent with the Medical Devices Regulation when the latter has apparently less demanding regulatory standards, affecting the relative safety profiles of drugs and devices (Pane et al., 2017). The tensions are particularly strong for drug-device combination products, and clinical pathways where a device or drug could be recommended. The disparity in regulation could distort medical markets, put pressure on patient safety and access, and generate other inefficiencies from lack of integration.

[34] (e.g., Article 2, 7, 27, 47 of Regulation (EC) 1901/2006; Article 10a (1) of Regulation (EC) 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) 1901/2006; Article 10 to 13 of Regulation 1394/2007).

[35] COMMISSION STAFF WORKING DOCUMENT EVALUATION Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. SWD/2020/0163 final

[36] COMMISSION STAFF WORKING DOCUMENT EVALUATION Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

The **Health Technology Assessment Regulation** contains proper legal coordination mechanisms with the general pharmaceutical legislation. It therefore appears unlikely that the Regulation will limit the realisation of the general pharmaceutical legislation. It may even contribute to ensure the quality, safety and efficacy of medicinal products and reduce duplication of efforts for manufacturers. However, implementation aspects could reveal areas of tension.

The **Cross-border healthcare Directive** has several legal interlinkages with the general pharmaceutical legislation. This Directive is essential to achieve the objective of ensuring an equitable access to medicines. Therefore, two aspects should be clarified: whether the 'restricted' medical prescription foreseen in the Directive 2001/83/EC should be recognised under the Cross-border healthcare Directive and what kind of classification for the dispensing of homeopathic medicinal products is meant in Article 14(1) of Directive 2001/83/EC, to understand how it could affect the recognition of prescriptions under the Cross-border Healthcare Directive.

Significant issues of coherence with the **GMO (Genetically Modified Organisms) legislation** have been identified. These issues may limit the realisation of several objectives of the general pharmaceutical legislation. Medicinal products containing GMOs do not fall under the scope of application of the GMO legislation, but the EMA or national authorities conduct the assessment in accordance with the GMO legislation, which supports the idea of a reduced administrative burden for applicants. Furthermore, the GMO legislation, through its own objectives, supports the general pharmaceutical legislation's objective of ensuring the safety of medicinal products. However, the pursuit of this safety objective is limited by the different national approaches to GMO legislation in medicinal products, in particular regarding the possibility offered in the general pharmaceutical legislation for MSs to authorise the supply of a medicinal product in cases of compassionate use, including medicinal products containing GMOs.

Both the **BSSD (Euratom Basic Safety and Standards Directive)** and the general pharmaceutical legislation apply to radiopharmaceuticals leading to potential issues of coherence (e.g., lack of specialised definitions for radiopharmaceuticals and their associated technologies, inconsistencies with dosage requirements, difficulties linked to the authorisation procedure). This creates a challenging environment for the development and roll-out of radiopharmaceuticals in the EU and thus impacting several objectives of the general pharmaceutical legislation and in particular access to medicines, global attractiveness and innovation.

The **Regulation on food additives** applies to medicinal products and directly impacts the possibility of manufacturers of medicinal products to use certain substances as food additives in medicinal products. Thus, the linkage of food legislation supports the realisation of the pharmaceutical legislation's objectives of ensuring the safety of medicinal products, although it could in theory limit competitiveness and/or innovation.

The **Transparency Directive** is legally coherent with the general pharmaceutical legislation. However, a weak enforcement of the rules of the Directive, as well as the lack of detailed specific requirements on the information to be provided by MAHs in pricing and reimbursement applications can limit the transparency of the process, and ultimately impact the policy objective of access to medicines.

Linked legislation not directly linked to the health sector

The interplay between the IP rights of the **SPC legislation** and the regulatory exclusivity rights of the general pharmaceutical legislation has been described by stakeholders consulted as complex and suboptimal, and fragmented across MSs. This may impede the general pharmaceutical legislation's objectives of achieving attractiveness of the European market in the global context as well as of reducing administrative burden and duplication of efforts. Furthermore, the possibility of evergreening/overcompensation practices may lead to reduced access to medicines, in view of the delayed entry of biosimilars and generics. In general, IP/data protection rules have the potential to limit the possibility of compulsory licensing, thus limiting action in favour of access to medicines. Regulation (EU) 1257/2012 on a **Unitary Patent protection** will create synergies between patent protection and centralised authorisation of medicinal products, thus increasing attractiveness of the European market, reducing administrative burden, disparities and duplication of efforts, while facilitating the free movement of medicinal products.

Data protection laws are coherent with the general pharmaceutical legislation in terms of scope, considering the horizontal aspect of the GDPR/EUDPR covering all activities linked to research on and manufacture of pharmaceuticals. However, the data protection legal framework can create specific limitations to the general pharmaceutical legislation's objectives of accommodating innovation, i.e., for research, due to possible conflicts between their respective objectives (innovation and personal data protection). More specifically, there appears to be a lack of clear and uniform data protection framework and approaches for research, on several matters, hampering the conduct of clinical trials and reuse of data for future research.

The **drug precursor legislation** does not hamper the objectives of the general pharmaceutical legislation, in particular in light of the objective of access to medicines. However, the general pharmaceutical legislation may need to better control medicinal products containing (pseudo)ephedrine, which can be used to produce (meth)amphetamines and can be easily purchased without falling under the control mechanisms applicable to drug precursors.

Substances used in the manufacture of medicinal products are exempted from most part of **REACH Regulation**. This specific exemption regime ensures, inter alia, that REACH does not overlap with the general pharmaceutical legislation. Such exemption regime however raised some concern on the need to align the environmental risk assessment requirements under the general pharmaceutical legislation with the one under REACH. Stakeholders also pointed out limitations brought about by REACH to the production of APIs, potentially impacting the pharmaceutical legislation's objective of wide access to medicines in Europe.

Policy actions to mitigate the impact of medicinal products in water will be in place with the revision of the **Environmental Quality Standard Directive** (2008/108/EC as amended by 2013/39/EU), revision of the **Groundwater Directive** (2006/118/EC) and the revision of **Waste Water Treatment Directive** (91/271/EEC). However, this will imply additional compliance costs for MSs. Only a limited set of pharmaceuticals can be targeted effectively with this legislation (i.e. those monitored in most parts of the EU and posing the biggest risk to nature / human health), leaving the majority of pharmaceuticals unaddressed. As such, updates to guidance are necessary for effective monitoring of pharmaceuticals in water and information/coordination between authorities appears insufficient.

EU Competition law supports the realisation of two of the general pharmaceutical legislation's objectives since it aims at ensuring a competitive functioning of the EU internal market for medicinal products, by limiting the existence of dominant positions of e.g., originators, ensuring a dynamic competitive environment via the control of mergers, while improving access (and affordability) for patients. In fact, the Commission, in the Pharmaceutical Strategy, relies on competition enforcement as one of the instruments to achieve access to affordable and innovative medicines to European patients. The sanction of anticompetitive practices, e.g., abusive patent management, supports the general pharmaceutical legislation's objectives of ensuring a competitive functioning of the internal market, attractiveness in the global context, and accommodate innovation.

4.2 How did the EU intervention make a difference?

The EU added value resulting from the EU legislation is defined as the additional value of EU action compared to what could be achieved at national or regional levels alone. Overall, there was strong consensus among the different stakeholder groups that the general pharmaceutical legislation has large EU added value. Stakeholder consultations pointed to the **legislation providing a robust framework enabling harmonisation of regulations, incentives, standards, administrative requirements, and procedures for pharmaceuticals across the EU.** These centralised and coordinated harmonisation measures across the medicine lifecycle simplified the regulatory system for medicine developers and reduced duplication of efforts across MSs. Moreover, from the perspective of stakeholders, the centralised medicine authorisation procedure and post-authorisation surveillance has improved the availability of high-quality, safe, and effective medicines across MSs.

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 to a moderate to large extent (Table 6). In accordance with the EU added value of the legislation, respondents considered that in the absence of EU level action, member states would have been able to put in place appropriate measures only to a small or moderate extent.

Table 6. 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.

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

Source: Targeted survey data

Interviews with stakeholders and open survey responses highlighted that the **centralised procedure (CP) for authorisation of medicines has been a valuable mechanism to improve the availability of medicines across the EU**. The CP has been particularly valuable for smaller MSs without the necessary resources and expertise to establish their own systems – a view that was shared by public authorities in smaller MSs. Overall, stakeholders wanted greater use of CP across EU. However, some industry stakeholders highlighted the added value of having the decentralised procedure and mutual recognition procedure in addition to the CP, in order to allow flexibility to get approval of medicines at the MS level, in particular for SMEs and generic manufacturers.

Stakeholder groups, including industry and public authorities, highlighted the added value of **EU-level coordination and cooperation to develop best practices**. For example, industry stakeholders 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. Another recognition of EU as a leader in regulatory practices was indicated by an academic stakeholder who pointed out that low- and middle-income countries have benefited from collaboration with EMA to strengthen their regulatory capabilities. For example, EMA has contributed mentorship in the ZaZiBoNa initiative, a collaboration between national medicines regulatory authorities in Africa (Sithole et al., 2020). While it is an unintended impact of the EMA's increasingly recognised international leadership role, it relies on pooling of scientific capabilities across Europe, partly attributable to the 2004 revision of the legislation.

Within interviews, stakeholders commonly cited the creation of the European Medicines Agency (EMA) as one of the biggest achievements of the legislation. Stakeholders regarded **EMA as a key actor in the unification and coordination of the regulatory system across the EU**. Furthermore, several stakeholders confirmed EU regulatory networks coordinated by EMA provide a valuable exchange of experience and access to a wide range of scientific and technical expertise, which would not be available in one country or region alone. Thus, **the pooling and coordination of scientific resources under a common set of rules and practices** has helped foster a common understanding across MSs on how medicinal products are evaluated and approved to a high standard and dealing with safety concerns in a consistent way. Industry stakeholders pointed to increased cooperation between MSs and public authorities and highlighted successful collaboration of EMA with NCAs that has led to the optimisation of their resource use. The pan-EU SPOR (Substance, Product, Organisation and Referential) data management services was cited as an example of a valuable resource for promoting exchange of medicinal product information across MSs.

Furthermore, interviewed 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 were 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). An academic stakeholder highlighted

clinicians have also benefited from access to EPARs when making assessments on whether to prescribe medicines to patients.

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

EU action during COVID-19 crisis was a particularly value added intervention. In the survey, all stakeholders scored the extent of striking the right balance as large to very large (Table 6). In interviews, there was a common theme across stakeholders that EU level action **enabled quicker and concerted action** compared to what MSs would have been able to achieve independently. Stakeholders commonly cited this was made possible because of **regulatory flexibilities and optimisations** enabling resources, capacities, expertise, and IT capabilities 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 environmental risk assessment (Regulation (EU) 2020/1043 of the European Parliament and of the Council, 2020) and allowed remote processes for source data verification, audits and monitoring (European Medicines Agency, 2022b). Thus, accelerating the development and approval of vaccines and coordinating equitable access to vaccines in all MSs.

The pandemic provided an opportunity to display how the legislation enabled MSs 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 added value – especially for less experienced MSs.

The open responses gathered in surveys and interviews highlighted that 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 efforts and timely availability of the right expertise**, which particularly benefited smaller MSs with limited capacity and expertise. 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.

Table 7 provides an overview of the authorisation dates for several COVID-19 vaccines that were approved to tackle the pandemic in the EU, and compares it with the authorisation dates in the USA and Japan.

Table 7 Comparison of authorisation dates for COVID-19 vaccines in the EU, USA and 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

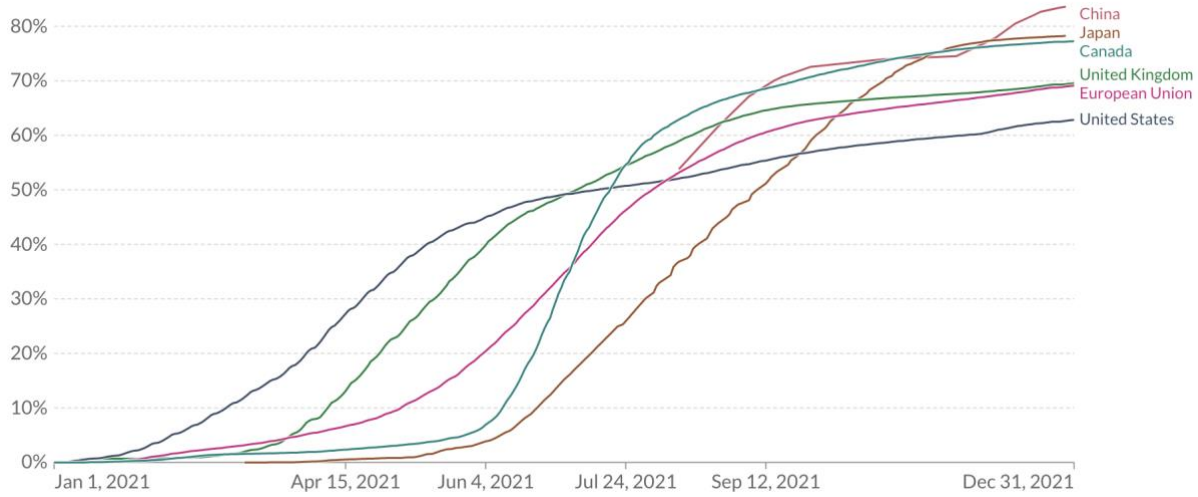
Source: COVID-19 Track Vaccines (COVID19 Vaccine Tracker, n.d.) and EMA (European Medicines Agency, n.d.-c).

While outside the scope of the general pharmaceutical legislation, stakeholders shared the view that the **joint procurement agreement was critical for securing and facilitating equitable access to vaccines** across all MSs. EU-level negotiations with industry helped to establish fair pricing and avoided MSs competing against each other for supplies and driving up prices. It also ensured each MS received vaccines under the same conditions and time. Moreover, the advanced purchase agreement to provide upfront financing for COVID-19 vaccines was a good demonstration of EU added value according to many stakeholders.

A civil society stakeholder mentioned EMA played a central role in **supporting MSs to communicate the risks and benefits of vaccines**. This helped build public confidence in COVID-19 vaccines and

uptake by European citizens (Figure 17). For example, EMA supported regulatory networks to build public trust through various activities such as public stakeholder meetings, media engagement activities and issuing regular pandemic safety updates with accompanying visuals to explain regulatory concepts (Cavaleri et al., 2021).

Figure 17 Total number of people who received all doses prescribed by the initial COVID-19 vaccination protocol, divided by the total population of the country/region, between 1st Jan 2021 and 31st 2021



Source: Our World in Data, 2022

There was consensus across stakeholders that EU-level cooperation was very important for **quick coordinated action to ensure medical supply chains continued to function** during the pandemic. This is important as medical shortages are not limited to one market and cannot be solved at a national level alone. Health services highlighted the EU Executive Steering Group on Shortages of Medicines Caused by Major Events that was an important enabler for the **increased collaboration and data sharing** across MSs to prevent and mitigate supply shortages. Furthermore, EU-level guidelines on the optimal and rational supply of medicines to avoid shortages during the COVID-19 outbreak (2020/C 116 I/01) were cited as being valuable to MSs. These guidelines were important to promote cooperation between MSs, thus preventing stockpiling and encouraging sharing of essential medicines during the pandemic. In particular, green lanes guidelines were seen as instrumental in facilitating cooperation between MSs to prevent shortages across EU according to several stakeholders. Industry stakeholders valued their inclusion in EU-level discussions on serious cross-border health issues which were critical to avoid shortages for patients during the pandemic. Furthermore, EU guidelines for border management measures to protect health and ensure the availability of goods and essential services (2020/C 86 I/01) were cited as valuable in limiting export restrictions and securing free movement of goods across the EU.

4.3 Is the intervention still relevant?

Relevance is the evaluation criterion that explores the relationship between the objectives of an intervention, and thus the provisions of the legislation and actions foreseen within it, and current and anticipated future needs: is the legislation capable of responding to these needs? The main objectives of the legislation are (i) guaranteeing a high level of health protection for the people of Europe, particularly through quick access to innovative and reliable products and increased market surveillance; (ii) ensuring a well-functioning internal EU market in pharmaceutical products in the context of globalisation and encouraging competitiveness of the European pharmaceuticals sector; (iii) respond to challenges presented by the continued enlargement of the European Union; and (iv) improving the overall consistency and visibility of the EU regulatory system through rationalisation and simplification and transparency of procedures and decision-making. Relevance, however does not explore the topic whether the implementation of the legislation in practice has led to positive effects, which was discussed in the section on effectiveness.

Before analysing the links between the current needs and how relevant the legislation is, we need to consider the megatrends that will shape the future of health in Europe. The EU's Joint Research Centre has identified (EC Knowledge for Policy, 2022) the following megatrends relevant to health:

- Acceleration of technological change and hyperconnectivity: this megatrend includes new ways to generate health data at the individual level through personal devices, sensors and tools, often integrated into 'wearables'. These new technologies can support decentralised and virtual clinical trials and generate vast amount of unstructured real-world data. How this translates into evidence through new models and methodologies (including machine learning/artificial intelligence) for regulatory assessment pre- and post-market authorisation has not yet been fully established.

- Emerging infectious diseases require new and innovative approaches as increasing antimicrobial resistance will lead to new epidemics. The COVID-19 pandemic accelerated the arrival of mRNA vaccine technologies, however new classes of antimicrobials will need to be developed against the backdrop of limited commercial incentives.

- Personalised approaches in healthcare will lead to new types of predictive, diagnostic and therapeutic approaches, and solutions will become bespoke and targeted, shifting from the small-molecule blockbuster medicines manufactured large-scale in industrial settings to complex combination products targeting smaller populations sizes.

The objectives of the general pharmaceutical legislation remain valid after 15 years despite the introduction of multiple specialised legislations and several amendments of those. It has responded well to the need to incentivise the development of innovative medicines in Europe and through a globally recognised robust regulatory framework, authorise high quality, safe, and efficacious medicines. It also responded well to the need to continue monitoring the safety of medicines post-authorisation via a centralised pharmacovigilance system and ensuring compliance with rules of marketing, manufacturing and distribution of medicines. This flexible and harmonised system has responded well to the need to make medicines 'available' for EU Member States. In addition, through harmonisation and transparency measures it made the system overall more consistent, an attractive feature in the global context for medicine developers.

However, the legislation has limited provisions, mandate and specific action available to ensure that authorised medicines are launched in all Member States and thus ensure equitable access to those for citizens across the EU. Therefore, the relevance of the legislation to equitable access to medicines is low.

Another but related aspect is affordability of medicines, especially innovative medicines addressing complex diseases often for smaller patient groups, where the legislation has foreseen relevant actions, such as the support for launch of generic medicines without delay after the expiry of regulatory protection period. The legislation is addressing needs with the Bolar provision on the use of research data, however affordability of medicines continues to be a challenge for many EU Member States.

Looking into the future, new objectives would need to be considered for the legislation to remain relevant in the face of the megatrends. This includes the readiness and adaptability of the legislation to respond to technological developments and rapidly increasing presence of digitalisation in new tools generating regulatory evidence and medicinal products preventing, diagnosing and targeting diseases. Continued relevance also involves providing targeted incentives to the development of those medicinal products that respond to high unmet medical needs, for example for therapies against antimicrobial resistant infections.

The recognition of the increasingly complex and advanced therapies as medicinal products within the legislation is also important to ensure continued relevance of the legislation to permit authorisation of those products in a streamlined manner for all manufacturers, small to large, commercial or otherwise.

4.3.1 The extent to which the general pharmaceutical legislation responded to the needs and problems

Changes to the general pharmaceutical legislation in 2004 were rooted in the core principles of enabling 'free movement of goods' and 'protection of public health' (Hartmann & Hartmann-Vareilles, 2005) through a number of specific actions. Data on the extent to which the needs and problems have been addressed are shown in the effectiveness section.

The general pharmaceutical legislation has established a robust and flexible authorisation system for medicines which includes the centralised procedure and national authorisation procedures via the MRP/DCP. This framework ensures availability of high quality, safe and efficacious medicinal products in Europe. However, the EU legislation provides few provisions that would tackle access to medicines and thus it responded overall less well to the need of guaranteeing high-level of public health in Europe.

Stakeholders acknowledged that accelerated assessment and conditional marketing authorisation provide necessary mechanisms for promoting early access to medicines for patients. However, products recommended for authorisation by the EMA are not actually accessible in all EU markets, particularly in smaller Member States. It should be noted that provision of healthcare is the responsibility of individual Member States, including pricing and reimbursement decisions. Therefore, access to medicines remains a complex challenge and depends on many factors, including pharmaceutical companies' market launch decisions, the result of additional relative cost effectiveness assessment, and affordability for patients and national health systems. In summary, the general pharmaceutical legislation has limited relevance regarding ensuring access to medicines in Europe.

The legislation has direct relevance to and responded well to the need of approving innovative medicines in Europe. According to public authority stakeholders, the legislation has a "fairly wide scope that is adaptable and can deal with new products through guidelines". This view was also shared by several industry stakeholders. However, academics and civil society organisations noted that in certain areas, such as nanomedicine and medical devices, the legislation has not responded as well.

Medicine shortage has been recognised as an important problem in Europe and the legislation has direct relevance to identifying and acting on shortages through obligation for MAHs to keep sufficient stocks of medicinal products and report potential future shortages. Nevertheless, civil society and healthcare professionals felt that the problem is not adequately addressed in the current legislation.

Within the survey, stakeholders identified areas where the current legislation has addressed stakeholder needs to the greatest and least extent. Some of these areas are listed in the table below:

Table 8 Extent to which the current legislation has addressed stakeholder needs (survey analysis)

Stakeholder type	Areas addressed to the greatest extent	Areas addressed to the least extent
Industry	Investment in new therapies facilitated by regulatory data protection Development, manufacture and access to biosimilars Development of new medicines and their authorisation (including ATMPs and PDMPs) Access in all member states to high quality medical products GMP requirements for ATMPs Conditional marketing authorisations and additional data protection for a new indication Parallel distribution and parallel import for CAPs and NAPs	Availability of digital information (SmPC, labelling etc) Pharmacovigilance roles and responsibilities – overlapping scope of responsibilities at EU and MS levels Vaccines: development pathways (require accelerated pathway as standard), access (equal across MS) and the supply chain Lack of clear EU regulation on digital information and advertisement Role of EMA in combination products Incentives for manufacturing in EU as opposed to development Harmonisation and usability of IT infrastructure and digital systems – too complex and time-consuming Lack of centralised procedure for clinical trials and their non-interaction with relevant GMO legislation which prevents clinical trials of investigational gene therapies

		Specific recognition of wholesalers in the legislation Hospital exemptions and their differential interpretation in MSs – creates different safety standards Simplification of packaging and licensing to support free movement of medicines Value added medicines – no legal definition and common regulatory pathway
Civil Society organisations representing patients and consumers	Strengthening pharmacovigilance – ability to report side-effects directly Safety and quality of medicinal products Security of supply Antimicrobial resistance ATMPs and their categorisation	Post authorisation safety and efficacy studies Pharmaceutical pollution which leaves too much to the member states Legislation around biosimilars which states they are a priority but does not encourage their use Insufficient measures to ensure availability throughout the EU IP incentives which are too open to abuse without sufficient safeguards Affordability (or measures for) are not sufficiently enforced and current mechanisms allow very high prices. Lack of conditions attached to public funding and transparency
Public Authorities	Quality of medicines - safety and effectiveness ensured via central authorisation Harmonised system for marketing authorisation reducing workload and ensuring smooth processes Transparency around authorisation Bringing new medicines to market Security of supply	Ensuring high quality comparative trial data pre-authorisation suitable for HTA Medicine shortages Access to medicines in smaller member states; affordability Therapeutic radiopharmaceuticals: inconsistent/non-applicable legislations Insufficient EU level support on coordination of data post-marketing authorisation Fee regulations – no longer meeting NCA needs Keeping pace with developments in science and technology - New manufacturing technologies in GMP guidelines, different applicable frameworks/regulations Harmonisation between member states
Academics	Orphan medicine and innovation Quality of medicinal products	Access and affordability Harmonisation of HTA (clinical evidence) Paediatric medicine development Public input for medicine development Research and innovation by academia and not for profit
Health Services	Ensuring high quality and safety of medicinal products Improved pharmacovigilance	Medicine shortages Accelerated approval pathways – opinion that they are overused Lack of support for NCAs in implementing measures that promote financial viability for wholesalers – endangers timely access

4.3.2 Relevance of the general pharmaceutical legislation's objectives and required actions to current needs and problems and expected developments related to medicinal products in the EU

The general pharmaceutical legislation's objectives continue to remain relevant for the present and the future, particularly the objectives responding to the needs of safeguarding public health in Europe, development and authorisation of innovative medicinal products, and ensuring the safety and quality of medicinal products in the EU.

However, stakeholders added that while the legislation's objectives remain relevant, they need to be adapted to fit additional needs and future developments. For example, affordability has become a main problem especially for innovative products which directly impacts on accessibility of these products and further stifling available budgets for procuring other product categories, including generic medicines. The lack of a common definition of unmet medical needs is creating uncertainty regarding incentives available to develop medicines to meet those needs.

Figure 18 Stakeholder views on relevance of the objectives and required actions of the general pharmaceutical legislation (survey analysis)

How relevant is the current legislation, including its objectives and required actions, with regard to the following aspects?	All stakeholders average score	Individual stakeholders average score					Agreement between stakeholders	Ranked Relevance
		Industry	Civil Society	Public Authorities	Academic	Health Services		
Addressing current needs related to the development and authorisation of medicinal products in the EU	3.4	3.5	2.8	3.5	3.5	3.7	High	most relevant
Adapting to new therapies and their method of administration	3.1	3.4	2.6	3.2	2.9	3.3	High	most relevant
Ensuring the safety and quality of medicinal products	4.2	4.5	3.8	4.3	4.4	4.0	Low	most relevant
Ensuring access to affordable medicinal products for those that need them	2.4	3.0	2.2	2.4	2.0	2.4	Low	least relevant
Maintaining security of supply of medicinal products in the EU	2.9	3.3	2.7	2.9	3.3	2.2	Med	least relevant
Maintaining resilience and responsiveness of health systems during health crises	2.9	3.2	2.8	3.1	2.9	2.4	High	least relevant
Minimising the impact of medicines on the environment through appropriate risk assessment	3.0	3.4	3.2	2.6	3.5	2.4	Low	
Supporting successful digital and scientific transformation to meet the needs of medicinal product development and related technological developments	3.0	2.5	3.0	3.0	3.4	3.3	High	
Promoting the attractiveness of the EU system for developers compared to other jurisdictions	2.9	2.7	2.7	3.1	3.3	2.8	High	

Source: Targeted survey data

Stakeholder consultations covered the issue of relevance to identify areas where the legislation may not have suitable objectives and actions foreseen to address needs from stakeholder perspectives. The findings need to be carefully considered as they may not necessarily mean certain areas are highly important (or not important) or whether the legislation delivered on stakeholder expectations. Misunderstandings about the concept of relevance among responding stakeholders cannot be excluded.

All stakeholders considered that the legislation has the highest relevance to ensuring the safety and quality of medicinal products marketed in Europe. This is a positive aspect as the legislation explicitly set out to address this objective. A related aspect recognised by stakeholders as highly relevant is the legislation responding to needs related to the development and authorisation of medicines.

However, the legislation was rated as of low to moderate relevance to other important aspects. The lowest relevance of the legislation was related to ensuring access to affordable medicines, which implies that in stakeholders' views the legislation had limited ability (provisions and actions) to address this need and meet the declared objective of the legislation. This view was confirmed in interviews with

public authorities, civil society and healthcare professionals as an area where the legislation needs to put more emphasis, although there was acknowledgement that access also falls under national competences to a large extent. In addition, it was pointed out that access to medicines is dependent on affordability which in their view needs to be explicitly addressed in the legislation's objectives.

Related to access is the involvement of HTA bodies, pricing & reimbursement (P&R) authorities and payers in providing access to authorised medicines. While the medicines regulatory authorities (national and EMA) promote access through facilitating the authorisation process, ensuring the quality, safety and efficacy of medicines, HTA bodies, P&R authorities and payers ultimately ensure products are available to those that need them. These organisations make decisions based on cost-effectiveness of medicinal products and national contexts and budgets, meaning very expensive medicines may not be reimbursed unless they are seen to be offering a much higher benefit compared to existing treatments. Such comparative effectiveness data or other relevant data are not always readily available as companies do not need these to obtain marketing authorisations, in particular for innovative medicines from the EMA. Data available for products that obtained CMA is even more limited and poses challenges for national authorities in their assessment. Overall, civil society, national regulators and payers highlighted the need to address this problem and improve timely access to new medicines, especially those authorised through the centralised procedure.

Importantly, stakeholders rated the legislation to be of low relevance to maintaining security of supply of medicines. This is an unanticipated finding as the legislation has two specific provisions to address the supply of medical products in the EU: article 23a for MAHs to provide advanced notification to NCAs about supply interruptions and article 81 for MAHs and wholesalers to ensure appropriate and continued supply to cover the needs of patients. It should be noted that since 2016 the EMA/HMA set up a taskforce to improve continuity of supply and publishes a shortage catalogue. Nevertheless, so far medicine shortages are dealt with at national level by NCAs. Nevertheless, healthcare payers and public authorities expressed in open responses and interviews that security of supply is relevant for the legislation and supply chain disruptions continue to be a major issue across the EU.

At a more granular level, public authorities rated the relevance of the current legislation's environmental risk assessment as low to moderate to minimise the environmental impact of medicines. Industry stakeholders rated the current legislation having low relevance to digitalisation and scientific and technological transformation that are needed for medicine development

Overall, stakeholder groups agreed in interviews that the current legislative framework and obligations need to be adapted in light of scientific and technological developments. These new technologies are giving rise to new types of medicinal products that do not fit in with the existing paradigms of what a medicine is and how it should be evaluated. For example, ATMPs and medicine-device combination products find themselves at the borderline between the general pharmaceutical legislation and other legislations e.g. the ATMP and medical device regulations. Therefore, there is demand from stakeholders (civil society, healthcare professionals, industry and public authorities) for clarity with regard to requirements for borderline and combination products. Real-world evidence, big data and digitalisation have not been accommodated to their full potential according to industry and public authorities. Other areas noted include nanomedicines, microbiome-based products, nuclear medicine; the use of artificial intelligence (AI) and digitalisation are not adequately accommodated by the current legislation.

Current needs and problems not sufficiently recognised in the EU general pharmaceutical legislation include actions countering AMR despite a looming public health crisis of resistant infections. A recent study has shown that there are not enough antibiotics under development within the global clinical pipeline to tackle this threat (Theuretzbacher et al., 2020). Environmental impact of medicines is also a relevant concern within the EU, as residues of pharmaceuticals continue to be detected in the environment (Dusi et al., 2019), not yet tackled via the legislation. However, there are a number of other EU regulations that deal with waste and chemicals that target these needs to a small extent (for more information, see the Coherence section).

Further needs and problems identified through the stakeholder consultation where the current legislation has limited or no relevance include: tracking off-label use of medicines (healthcare professionals and civil society), and more deliberative actions (industry and public authority) concerning the objective of ensuring global attractiveness of the EU.

4.3.3 Lessons learned from the COVID-19 pandemic about the relevance of the general pharmaceutical legislation to health crisis resilience and responsiveness

The COVID-19 pandemic brought several challenges for public health, in particular the problem of evaluating the safety and efficacy of urgently needed medicinal products in very short timelines. In this context, the EU general pharmaceutical legislation has allowed the EMA to coordinate appropriate responses to the COVID-19 crisis. Using rolling reviews (an accelerated procedure for assessing data) and collaborating with other regulatory agencies, the EMA was able to grant conditional marketing authorisation (CMA) to the first vaccine for COVID-19 within 9 months since the start of the pandemic (Cavaleri et al., 2021). This success in significantly reducing the timeline for granting conditional marketing authorisation brings lessons for the future on how more flexible and agile approaches can be applied to the EU's regulatory framework for pharmaceuticals. For example, rolling reviews can be adapted to improve interaction between developers and regulators, with the aim of facilitating the development of medicinal products that are needed in preparation for crises and for other areas, such as unmet medical needs. However, these adapted approaches to regulating pharmaceuticals also bring significant costs to regulatory agencies, as more resources are needed, and new ways of working must be developed and implemented. A pandemic (level 4 crisis, according to EMA's plan for health threats) requires the creation of response and strategy teams, additional operational staff and expert groups such as EMA Task Force and Scientific Advisory Groups.

Stakeholders across all groups identified joint procurement and accelerated approval (via rolling review) of vaccines as the chief mechanisms through which resilience and responsiveness was achieved for the EU during the COVID-19 pandemic. Cooperation between MSs through EU bodies and the EMA's flexibility and adaptability were key enablers allowing a coordinated response. These stakeholder views confirm that the EMA has adapted its governance to respond to the scientific, regulatory and operational challenges which can serve as a blueprint for future emergencies (European Medicines Agency, 2022a). Key lessons from this experience include the realisation that approval of new/innovative medicines could be managed at pace and processes could be streamlined without compromising safety and quality to facilitate faster access to innovative medicines and address UMN. However, academics, civil society and some public authorities strongly emphasised that the rolling review and other approaches for accelerating the authorisation process should not be applied routinely as these may compromise safety and quality of medicines when scaled up and EMA's resource requirements (both human and financial) would be prohibitive.

Academic and industry interviewees were positive about increased collaboration among industry and regulators (especially EMA) during the pandemic to share information on stocks and shortages, to provide scientific advice and to generally expedite the medicine development process. Industry actors were hopeful that virtual audits and inspections that were successfully implemented during the pandemic could be continued in the future to reduce the burden on agencies. They were also positive about the exemption of GMO requirements for vaccine development and suggested similar exemptions could be applied for ATMPs in the future that address public health needs. They also suggested that new designs (e.g. adaptive clinical trials) and simplified processes for clinical trials could be accommodated in routine authorisation procedures. Industry also highlighted the temporary flexibilities to the work of qualified personnel, acceptance of digital versions of documents, and remote inspections and audits were helpful adaptions (HMA et al., 2021). Public stakeholders such as academics, civil society organisations and public authorities however felt that higher level of transparency in both regulatory and procurement decision making was warranted in the public interest.

Overall, stakeholders consulted for this study rated as 'low to moderate' the relevance of the legislation in relation to maintaining resilience and responsiveness of health system during health crisis. Health services stakeholders scored this aspect the lowest, while industry stakeholders the highest. It is without doubt that when answering this question, stakeholders were thinking of the ongoing COVID-19 pandemic and both specific elements of the legislations and in broader sense what the EU institutions collectively achieved. Stakeholder interviews specifically pointed to no discernible restrictions stemming from the legislation during the pandemic response, instead they felt that it provided room for flexibility to adapt processes to suit the reality of the situation. In addition to the already mentioned rolling reviews, other flexibilities were achieved through publication of harmonised guidance (e.g. conducting clinical trials during the pandemic) and temporary derogations from certain obligations e.g. environmental risk assessment (Regulation (EU) 2020/1043 of the European Parliament and of the

Council, 2020) and allowed remote processes for source data verification, audits and monitoring (European Medicines Agency, 2022a).

The pandemic also highlighted factors causing shortages such as the reliance on non-EU API producers according to industry and public authorities. The EMA's extended mandate is an important step forward in addressing some of these factors causing shortages. Applicable since 1st March 2022 (Official Journal of the European Union, 2022), the extension of the mandate assigns the EMA the responsibility to set up a monitoring system for events that can lead to public health crises, such as medicine shortages. The extended mandate also seeks to formalise and improve on the regulatory tools used by EMA to respond to the public health crisis brought by the COVID-19 pandemic, such as speeding up regulatory assessments and clinical trial data evaluation. As such, the EMA's extended mandate responds to the early lessons from the COVID-19 pandemic published by the EU Medicines Regulatory Network (EMRN) (Cavaleri et al., 2021), which have parallels in the lessons emerging from our own study. These included:

- Need for rapid and coordinated feedback to medicine developers and the continued dialogue with industry on issues of interest to developers, such as clinical requirements or resolving bottlenecks to scale-up of production
- Need to support and enable rapid advice and approval of large, well-designed trials, including platform trials, that can provide the robust data needed to support decision making and demonstrate that new or repurposed medicines are safe and effective, whilst also refuting as early as possible those which are ineffective and or unsafe
- The emergence of very rare side effects of thrombosis for some vaccines, showed the importance of risk communication and transparency on emerging issues, explaining uncertainty and preliminary nature of interim results
- The side effects also showed how extensive data collection, analysis and visual risk contextualisation can be delivered across Europe in a short time. Early and proactive investment in developing real-world evidence (by EMA) has allowed rapid safety analysis and risk contextualisation. There is room for improving the type and coordination of health data across the EU and enhancing data analytics.

5 CONCLUSIONS & LESSONS LEARNED

5.1 Conclusions

The general pharmaceutical legislation is a successful EU intervention in the sense that it achieved all four high level objectives to some extent. The objective to ensure quality, safety and efficacy of medicinal products was achieved to the largest extent, while that of ensuring access to medicines was achieved to a limited extent. The objectives of ensuring competitive functioning of the EU internal market and attractiveness in a global context were achieved to a moderate extent. With the needs and problems that the 2004 revisions were addressing still remaining relevant, the objectives of the legislation and its revision also continue to remain relevant for the future.

A robust and flexible authorisation system was developed in Europe taking advantage of harmonised processes through the centralised procedure for innovative medicines requiring pooled European scientific expertise; while decentralised procedures at national level available for smaller companies and generic producers 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. These elements contributed strongly to the stated objective of ensuring quality, safety and efficacy of medical products in Europe.

The system includes a predictable incentives framework (8+2 years of regulatory data and market protection period) that has kept Europe an attractive market for medicine developers and allowed innovative medicines to be available to national health systems. However, this does delay market entry of generic products, affecting affordability of medicines and MS health budgets. On the other hand, the Bolar exemption has allowed quicker generic entry, but since the implementation of the exemption varies, the benefits are also variable. The creation of a delineated authorisation pathway for biosimilars in Europe before any other jurisdictions, has made Europe a leader in this space, allowing the launch of biosimilars 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 biosimilars across EU member states.

It is important to note however that the availability of innovative medicines does not lead to equitable access to those across Member States, another stated objective of the legislation. In effect, the relevance of the legislation is rather limited with regard to access, as companies make decisions on market launch while national health systems retain clear responsibility over providing their chosen healthcare provision (including medicinal products) to their population and likewise for the decision to pay for those. Nevertheless, 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 to guarantee a high level of public health.

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 USA or Japan. The US remains the jurisdiction of choice for filing marketing authorisation applications for new active substances but the EU has the second destination for filing and more substances are being authorised by the EMA less than 1 year after the FDA.

The legislation is well-framed, internally coherent and has clear EU added value. However, external coherence has become a challenge in a changing EU regulatory landscape. Emergence of new technologies and borderline cases (that potentially sit between two or more legislations) cause inconsistencies/uncertainties such as the coverage of GMO requirements, environmental challenges and new manufacturing methods along with definition of products e.g. ATMPs, radiopharmaceuticals and medical devices.

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 were scarce and many of the relevant data were also not available in literature. There were cost savings associated with harmonisation and streamlining of procedures (for industry and NCAs) and through switch to a single MA renewal after 5 years. Age-standardised mortality rates have improved in all EU countries in the period since 2007 (Santos et al., 2020), 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, we have estimated that the 2004 revisions were associated with an additional 170,000-210,000 QALYs across the evaluation period, (based on a median ICER of €33k / 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 after 15 years. As discussed above, not all objectives have been fully met through the 2004 revision of the legislation and new approaches are needed to address those challenges. However, these are complex issues that the legislation in itself may not be able to solve effectively.

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 (e.g. GDPR, REACH, IPR) is required to reduce tensions and improve synergies between legislations, increasing the likelihood of impact in terms of public health, environmental sustainability, digitalisation, etc. This will ensure a more systemic fit of the general pharmaceutical legislation in the wider EU policy framework.

Looking into the future, new objectives will need to be considered for the legislation to continue to remain relevant. This includes the readiness and adaptability of the legislation to respond to technological developments, for example, in new manufacturing methods, and rapidly increasing presence of digitalisation in new tools generating (real world) regulatory evidence and medicinal products preventing, diagnosing and targeting diseases. Continued relevance also involves providing targeted incentives to the development of those medicinal products that respond to high unmet medical needs, for example for therapies against antimicrobial resistant infections. The recognition of the increasingly complex and advanced therapies as medicinal products within the legislation is also important to ensure continued relevance of the legislation to permit authorisation of those products in a streamlined manner for all manufacturers, small to large, commercial or otherwise.

Many 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 has demonstrated that there is room for flexibility to adapt regulatory processes and accelerate product development and authorisation processes, including use of remote processes for source data verification, virtual audits and monitoring. This would reduce administrative burden on medicine developers and release capacity for regulatory authorities. EMA has also adapted its governance model 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 as safety and efficacy of increasingly complex and advanced therapies will need to be assessed. It is however noted that EMA has limited resources and its expertise and capacity need to be expanded in order to progress complex dossiers at pace and keep up with the US FDA, where relevant, and do so without compromising safety and quality of authorised medicines.

The pandemic also highlighted factors causing shortages such as over-reliance on one single or very few foreign suppliers for some essential APIs. This might be mitigated through diversification of suppliers. Collaboration between industry and regulators (especially EMA) during the pandemic on stocks and shortages, to provide scientific advice and to generally expedite the medicine development process demonstrated that different interests can be usefully aligned. This however needs to happen under public scrutiny and transparency.

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7 ANNEXES

7.1 Annex I. Methodology and analytical models used

This section summarises the methods used for (i) data identification, collection and analysis and (ii) stakeholder consultations.

7.1.1 Data Identification, collection and analysis

Literature Review

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

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

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

Comparative Legal Analysis

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

Five countries (Japan, Canada, South Korea, Australia, USA) were selected based on the secondary data analysis (Task 2.3) which identified them as relevant markets with developed economies. Two additional countries were included after discussion with the EC; 1) China as the largest market in Asia and a major generic medicine producer and sophisticated regulatory system for the same, 2) Israel where innovative legislative solutions were expected.

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

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

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

The templates were supplemented by targeted interviews (

Table 10) with key stakeholders (competent authorities, pharmaceutical industry association, patient association, payers) which were also conducted by the national experts. Potential interviewees were identified, contacted and followed up at least once in order to get an interview (Table 9). In some cases, interviewee's opted to provide written feedback which was accepted and annexed to the report.

Table 9. Interview Schedule.

Country	Contacted/followed up	Interviewed	Written responses
Australia	7	0	1
Canada	17	2	0
China	6	6	0
Israel	4	0	0
Japan	5	5	0
South Korea	4	0	0
USA	13	0	0

Table 10. Indicative Questions for interviewees

Compared with foreign regulatory frameworks, which features of your country's regulation of pharmaceuticals do you consider distinctive/unorthodox (if any)? When were they introduced? Do you consider these to be advantageous? why?

How does your country evidence the performance of your pharmaceutical regulatory framework? What are the reported indicators (if any)? How do you demonstrate an acceptable trade-off between speed of regulatory approval and clinical performance evaluation?

Which foreign regulatory frameworks have the greatest influence on your country's regulation of pharmaceuticals?

What good practices exist in [X] to:

- Support innovation and address unmet medical needs?
- Ensure the prevention of antimicrobial resistance while promoting the development of new products?
- Regulate new products, new technologies in medicinal products as well as new manufacturing processes?
- Promote wide market coverage by marketing authorisation holders and access to medicines for patients?
- Facilitate the entry onto the market of generics and biosimilar medicinal products?
- Ensure the security of the supply and secure the availability for patients?
- Ensure a high level of quality throughout the supply chain in various production settings, and mitigate the environmental impact of the production of medicinal products?

What formal *international* regulatory collaborations do you have in place?

Is there work on-going regarding regulatory agility?

What are the challenges that remain to be addressed by the legal framework of your country? Have some legislative or policy attempts at addressing these issues remained unsuccessful?

What legislative or policy priority changes were required during the COVID-19 pandemic. What were the related lessons learnt? Are these changes going to be sustained in your country?

What is X's vision, strategy or roadmap for pharmaceutical regulatory framework? What are the related timelines?

+ Country-specific questions to explore the innovative legal options in the country identified via desk research and literature review.

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

Secondary Data Analysis

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

In the first instance indicators were defined. SMART[37] indicators were proposed based on the objectives of the original legislation and the 2020 pharmaceutical strategy. These were verified and matched against data sources during a series of online working sessions and final selection made based on availability of data. There was prioritisation of time series data reaching back to pre 2005 as well as availability across the markets of EU, Switzerland, USA, Canada, Australia, Japan, and Korea.

In total we identified 55 indicators (Table 11 by policy area). The indicators were grouped in seven policy areas to address the policy elements in scope for the study with specific indicators selected to inform the main evaluation criteria of effectiveness, efficiency, coherence, relevance and EU added value of the legislation.

Table 11. Total number of indicators selected by policy area.

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

The indicators were populated using 24 existing proprietary or public databases or sources as listed in Table 12. While each specific indicator must be treated individually depending on completion, coverage, data type and presence of time series element, analysis was conducted to the following plan wherever

[37] Specific Measurable Achievable Relevant Timebound

data allowed and as appropriate. Statistical tests were not applied where the relevant observations were less than 30.

Presentation of longitudinal data covering the period 2000-2020 with stratification where appropriate (e.g. along therapeutic area, indication, product type, company size, legal basis of applications, approval pathway etc).

Comparison of pre and post legislation periods using parametric (Welch's t-test) or non-parametric (Mann Whitney U test) tests for significance between the pre and post periods.

Difference-in-differences estimation by comparing the evolution of the EU 'treated' countries relative to other similar but 'untreated' countries, before and after the 2004 revision of the general pharmaceutical legislation.

Presentation and descriptive analysis of reference groups in other jurisdictions (Japan, US, Switzerland) with statistical comparison wherever possible.

Table 12. List of secondary data sources.

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

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

Case Studies

Case studies were developed focused on specific issues to illustrate linkages and mechanisms behind trends observed in the data. Note, the Case Study Report do not form part of the present Evaluation Report.

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

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

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

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

Summary
Retrospective view

- 1: Nature and extent of the problem
- 2: Objectives of the 2004 regulation
- 3: Evaluation of the achievements of the regulation

Forward looking view

- 1: Evolution of the problem and residual challenges
- 2: Enhanced policy options
- 3: Potential impacts of the revisions
- 4: Synergies and interplay

Key conclusions
Case study references and data sources

In the case of case study 3. SMEs/Regulatory Support there were substantial knowledge gaps and key information interviews were used to address these. We used semi- structured interviews (Table 13) with representatives of 5 leading industry associations to address knowledge gaps that are not covered by the higher levels of evidence. Interviews were performed with relevant stakeholders. Notes were taken and sent back to the interview respondents for validation. The interview notes were analysed and collated in the same way as the documents and referenced in the case study.

Table 13. Interview Protocol for SMEs.

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

7.1.2 Stakeholder Consultation: Primary Data Collection

Feedback for the consultation on the Roadmap/Inception Impact Assessment

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

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

Open Public Consultation

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

The survey had two main topics and several sub-topics (bulleted in Table 14) and served to determine the balance of opinion (overall, and by stakeholder group) on the relative importance of a given issue. The OPC was a mixture of open and closed questions and utilised skip codes to guide participants through the relevant questions depending on their self-categorisation into stakeholder group. There were no character limits imposed on open answers.

Table 14. OPC survey structure.

Backward-looking questions

- Other issues to be addressed in this revision
- Positive and unintended effects of the legislation

Forward-looking questions

- Unmet medical needs
- Incentives for innovation
- Antimicrobial resistance
- Future proofing: adapted, agile and predictable regulatory framework for novel products
- Rewards and obligation related to improved access to medicines
- Enhance the competitive functioning of the market to ensure affordable medicines
- Repurposing of medicines
- Security and supply of medicines
- Quality and manufacturing
- Environmental challenges

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

Table 15. Number of OPC Responses by stakeholder group**.**

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

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

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

Targeted Survey (Survey Report)

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

A survey tool was developed and signed off by the EC. The survey had several modules (bulleted in Table 16 below) and incorporated skip codes such that different stakeholder groups were automatically navigated through the questions appropriate for them. All questions were optional and could be skipped or answered with don't know.

Table 16. Targeted Survey Structure.

- Survey explanation (purpose, privacy, scope, time, instructions)
- About you/your organisation (Organisation name, type, participant name)
- Functioning of the legislation since 2005 (effectiveness, relevance, coherence, value add)
- To what extent has the legislation been effective/relevant/coherent/added value with respect to objectives
- Where has the legislation been most/least effective/relevant/coherent/added value
- Provision of supporting evidence or data
- Efficiency (costs and benefits and explanations of answers)
- Elements of future policy options (incentives UMN, AMR, Futureproofing, Access, Competitive Market Functioning, Manufacturing Quality and Environment, Security of Supply, Streamlining)
- Please rate the impact of the following measures on UMN, AMR, Futureproofing, Access, Competitive Market Functioning, Manufacturing Quality and Environment, Security of Supply, Streamlining
- Further comments on your answers above
- Conclusion (the greatest impacts with supporting data)
  Close (invitation to be contacted with follow up questions)

The questionnaire was delivered electronically using the tool 'Survey Monkey' and 220 participants were directly invited. Invites were sent as individual links were possible to enable tracking of participation and were supported by a letter from the EC endorsing the survey. The EC also shared the survey link within relevant networks of public authorities. Of the total number of invitations, over 90 invitations were send to 'intermediary' organisations who were asked to disseminate the survey link through their networks (e.g civil society or association members) in order to snowball the sample further. The survey targeted five main stakeholder groups (industry, public authorities, health service providers, academic and civil society) and had agreed participant targets that were considered suitably representative. The survey remained open for just under 15 weeks between the dates 16th November 2021 and 14th January 2022, and invited participants were followed up multiple times in this period to try and boost participation. The number of individuals and intermediaries invited is shown in Table 17.

Table 17. Targets and invited participants per stakeholder group.

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

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

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

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

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

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

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

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

Finally, the standard deviation was calculated per question and per stakeholder and utilised as an indicator of within (intra) stakeholder consensus. A higher standard deviation signalled less intra-

stakeholder agreement with those above 1.1 being classified as low agreement and below 0.7 high agreement. Where intra-stakeholder consensus was low and sample size permitted these differences were explored related to geographical area of respondent (public health authorities) and subcategory of the stakeholder group (Industry, public health authority, academic).

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

Interviews

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

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

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

Interviews were conducted remotely via Zoom or Teams by a team of ten consultants over the period 7th December 2021 and 26th January 2022. A shortened version of the topic guide was shared ahead of the interview. Interviews were an hour and half long and were recorded (with permission) and an auto-transcription created and stored. On some occasions interviews were conducted in groups with multiple participants and organisations in attendance (Table 18 shows interviews as groups and individuals). Following completion of the interviews, summary notes were written up and key meta data (participant(s), organisation, stakeholder group) were transcribed onto them.

Table 18. Interviews targeted and conducted by stakeholder group.

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

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

Workshops

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

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

- Introduction from the EC
- Plenary presentation including opening slido (interactive poll) from Technopolis Project Lead

- Breakout groups: Brief presentation followed by participatory discussion.
- Plenary presentation from each breakout group
- Closing presentation on next steps and closing slido from Technopolis Project Lead

In both cases a 'save the date' was followed by an invite and a discussion paper on the workshop topics 2 weeks prior to the event. Breakout group topics were provided in advance after agreement with the EC. Participants were able to state a first and second preference for their breakout groups and first choices were facilitated the vast majority of the time. Each breakout group had a facilitator and a presenter (from either Technopolis or a project partner) and a technical support from Technopolis Group. Breakout groups were large and to facilitate participation muting and unmuting of mics was strictly led by the facilitator while participants were also free to use the chatbox continuously and this was tracked and responded to. Observers from the EC were in attendance in all breakout groups. Key details about the workshops are shown in Table 19.

Table 19. Details of the workshops.

	Workshop 1: Evaluation	Workshop 2: Impact Assessment
Date	19th January 2022	25th April 2022
Invited	246	339
Attended	208	199
Retention at final plenary	80%	90%
Breakout Groups	1. Safeguarding Public Health 2. Europe's regulatory Attractiveness 3. Accommodating advances in science and technology 4. Ensuring access to medicines 5. Functioning of the EU market for medicines	1. Enabling innovation including for UMN 2. Ensuring Access to Affordable Medicines for Patients 3. Enhancing the security of supply of medicines and addressing shortages 4. Reducing the regulatory burden and providing a flexible regulatory framework

7.2 Annex II. Evaluation matrix

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
	Effectiveness								
1. To what extent have the actions envisaged by the general pharmaceutical legislation contributed to achieving the following objectives?	Safeguard public health	For all Effectiveness questions: Degree to which quantitative indicators show positive trend over time and this is corroborated with qualitative information (where available)	RI-9, ACC-1, EFF-2, AMR-1 In addition: adverse reaction data trends (EudraVigilance) Stakeholder view		☐	☐	☐	☐	☐
	An attractive and robust authorisation system for medicines		IEC-2, IEC-4, RI-4, RI-5, ACC-2, EFF-3 Stakeholder view		☐	☐	☐	☐	☐
	Timely patient access to medicines		ACC-3, ACC-4, ACC-8, ACC-9 Stakeholder view		☐	☐		☐	☐
	Minimise inefficiencies and administrative burden of regulatory procedures		ACC-6, EFF-3 Stakeholder view		☐		☐	☐	☐
	Provide harmonised measures for an improved functioning of internal market for medicines		ACC-1 (approval pathway), ACC-6, IEC-7, IEC-8, IEC-10		☐				
	Quality of medicines including through manufacturing rules and manufacturing and supply chain oversight		SM-3, MI-3 Stakeholder view	☐		☐	☐	☐	☐
	An integrated lifecycle model with clear and appropriate responsibilities including post-marketing obligations and oversight		ACC-1 (approval pathways) Expert legal opinion Stakeholder view		☐		☐	☐	☐

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
	A competitive market for medicines in the EU, including taking into account market effects impacting on affordability		IEC-1, IEC-4, IEC-12, IEC-13, AFF-1, AFF-4, AFF-6, SM-5, SM-6, AMR-1		☐	☐			☐
	Make it easier to place generic/biosimilar products on the market		AFF-4, AFF-5 Stakeholder view		☐		☐	☐	
	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		AMR-3, AMR-4, RI-1 to RI-4 Number of clinical trials with digital end points, real world data, complex trial design	☐	☐	☐	☐	☐	☐
	Openness to cutting-edge products and integrated therapies		ACC-1 (product type, approval pathway) Stakeholder view		☐	☐	☐	☐	
	Improve competitiveness of EU pharmaceutical industry on the global market		IEC-3, IEC-5, IEC-12, IEC-13, IEC-10	☐	☐				☐
	Enhance the security of supply of medicines and address shortages		SM-1, SM-2, SM-3, MI-1, MI-2 Stakeholder views		☐	☐	☐	☐	
	Reduce the environmental footprint of medicines		EI indicators	☐	☐				
2. How do the achieved results and impacts compare with the expected ones?	To what extent the results of the legislation meet the need of stakeholders?		Use available indicators and contrast with stakeholder view		☐		☐	☐	☐
3. Which were the key contributing and hindering factors in achieving the intended objectives?	To what extent has the type of legislative act, i.e. a Directive, been a contributing or hindering factor in achieving the intended objectives?		Use available indicators and contrast with stakeholder view		☐		☐	☐	☐

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
	To what extent has Directive 2001/83/EC been transposed by Member States in a way that allows the effective 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?		Expert legal opinion Stakeholder view	☐			☐	☐	
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?	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?		IEC-4, IEC-6, RI-6 (comparative), EFF-1 (comparative)		☐		☐	☐	
	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?	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	☐			☐		☐
	What have been the cost drivers?	Views on relevant drivers and their contribution to overall costs	Top cost elements Stakeholder view	☐			☐	☐	☐

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
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 relevant to estimate?	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 information (where available)	AFF-1, AFF-2, AFF-3, AFF-3 In addition: Change in unmet healthcare needs Stakeholder view		☐	☐		☐	
	What have been the economic benefits of the legislation?	Degree to which quantitative indicators lead to favourable trend over time	IEC-7, IEC-8, IEC10 In addition: Foreign direct investment in the pharmaceutical sector		☐				
	What have been the environmental benefits of the legislation?	Degree to which quantitative indicators lead to favourable trend over time	EI-1, EI-2 Residues of pharmaceuticals in the environment and emissions from manufacturing plants	☐	☐				
7. To what extent were the general pharmaceutical legislation's costs proportionate to its benefits (i.e. positive outcomes)?	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 costs and benefits when including non-monetisable aspects?	The extent to which the model result in positive outcomes	Partial cost benefit analysis will consider monetisable costs and benefits and accompanying multi-criteria analysis will assess the balance 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?	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	The cost and benefit items can be attributed to objectives and these can be aggregated	Cost-Benefit model will integrate share of costs and value of benefits for each objective and jointly	☐	☐		☐	☐	☐

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
	specific objective and attributable to the legislation? What have been the total costs of meeting each of these specific objectives, jointly and severally?								
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?	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	☐			☐		
	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	☐	☐		☐		
	Relevance								
10. To what extent has the general pharmaceutical legislation responded to the needs and problems concerning medicines identified in section 1.3 for the 2004 revision?	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)	ACC-2, SM-5, SM-6 Stakeholder view		☐		☐	☐	
	To what extent the new pathway for biosimilars responded to the needs?	Degree to which quantitative indicators show favourable trend over time and this is corroborated with qualitative information (where available)	AFF-4, AFF-5, AFF-6 Stakeholder view		☐		☐	☐	
11. To what extent are the general pharmaceutical legislation's objectives and required actions relevant today to address the current	How have the needs and problems identified for the 2004 revision evolved since then?	Degree to which quantitative indicators show identifiable trend over time	RI-5, RI-6, RI-7, RI-8, ACC-1, ACC-2, ACC-5, AFF-1, AFF-2, AFF-3		☐				☐

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
needs and problems and expected scientific and technological developments related to medicinal products in the EU?	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 of the supply chain, adaptation of the regulatory framework to scientific and technological developments)?	Views on relevant needs and problems corroborating quantitative trends of indicators	Analysis of the current level of indicator available from T2.3 and contrast those 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?	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 Expert legal opinion Stakeholder view	☐		☐		☐	☐
	What are the lessons learned from the COVID-19 pandemic?	The degree to which stakeholders can articulate learnings	Stakeholder view	☐				☐	☐
	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)***	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.	Expert legal opinion via: analysis of potential overlaps, contradictions, or other inconsistencies between its provisions/requirements analysis of whether its provisions adequately fulfil its objectives (i.e., safeguard public health and ensure the freedom of movement of these products). Stakeholder view on issues and solutions (especially Member State authorities in charge of the implementation and	☐		☐		☐	☐

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
			enforcements of this legislation at national level).						
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)***	Are there overlaps, inconsistencies or ambiguities between the legislation and lex specialis pharmaceutical legislations? Is due to the way the legislation is drafted there is unnecessary complexity in the system? 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	Expert legal opinion via: analysis of potential inconsistencies between the general pharmaceutical legislation and the *lex specialis* pharmaceutical laws of core obligations (e.g., authorisation procedures and in-built mechanisms) using a table of comparison and possible legal solutions	☐		☐		☐	☐
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)***	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 hinder the pharmaceutical legislation to achieve any of its objectives?	The degree to which (positive or negative) interdependencies of the general pharmaceutical legislations and other EU legislations can be identified and their effects assessed	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.	☐				☐	☐

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
	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?	What has been the added value of the EU legislation compared to international actions alone? What has been the added value of the EU legislation compared to EU national actions alone? What has been the added value of the EU legislation 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	Expert legal opinion Stakeholder view	☐				☐	☐
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?	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 centralised procedure (ACC-1) versus MRP or DCP, ACC-6 Expert legal opinion Stakeholder view	☐	☐			☐	☐
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.)?	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	IEC-9 relevant for COVID medicine (therapeutic categorisation) ACC-1 IEC-9 relevant for COVID medicine Stakeholder view	☐	☐	☐		☐	☐
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?	To what extent has the EU intervened in a balanced and proportionate way with respect to national actions during the COVID crisis?	The degree to which EU actions and national actions can be disentangled	Expert legal opinion Stakeholder view	☐		☐		☐	☐

7.3 Annex III. Overview of benefits and costs

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									

		Citizens/Consumers		Businesses		Administrations		Society	
		Quantitative	Comment	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment
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 on valuing QALYs	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 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 /		

		Citizens/Consumers		Businesses		Administrations		Society	
		Quantitative	Comment	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment
							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.

Simplification and burden reduction (savings already achieved)

	Citizens/Consumers/Workers		Businesses		Administrations		Society	
	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment
Title[38]*: (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				

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

				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 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[39].*								
	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%[40]								
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 increase efficiency and		

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

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

						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		

7.4 Annex IV. Coherence analysis

Coherence analysis is based on:

- Desk research and a literature review covering, inter alia, evaluation and impact assessment reports of other EU legislation and policies with relevant interface/links with the EU general pharmaceutical legislation.
- Legal analysis by Milieu legal staff together with the support of a senior legal expert Kathy Liddell.
- Stakeholder feedback from the different consultation streams.
- Feedback from representatives of the European Commission in charge of the other EU legislation and policies covered under this analysis.

Five main aspects of coherence are covered under this analysis:

- Internal coherence of the EU general pharmaceutical legislation
- The coherence of the EU general pharmaceutical legislation with specialised pharmaceutical legislation
- The coherence of the EU general pharmaceutical legislation with other EU health legislation
- The coherence of the EU general pharmaceutical legislation with non-health related EU legislation
- The coherence of the EU general pharmaceutical legislation with other EU policies

The analysis of the coherence of the EU general pharmaceutical legislation with other EU legislation and policies entails assessing, inter alia, whether there is some concern of coherence:

- related to their objectives and scope,
- when implemented (e.g., lack of coordination between competent authorities)
- linked to potential overlaps leading to double regulation,
- related to the need to further develop synergies between the EU pharma legislation and other EU interventions.
- due to limited in-built mechanisms to ensure adequate articulation between the EU pharma legislation and other EU interventions.

Overall, more than 30 other EU interventions (EU legislation and policies) have been assessed for the analysis of external coherence. The findings below focus on the EU interventions where potential issues of coherence were identified.

Table 20 Coherence of the general pharmaceutical legislation (survey analysis)

How coherent is the general pharmaceutical legislation regarding the following aspects?	All stakeholders average score	Individual stakeholders average score					Agreement between stakeholders	Ranked Coherance (Industry and Public Authoriteis only)
		Industry	Civil Society	Public Authorities	Academic	Health Services		
All elements of the legislation operating synergistically to achieve optimal results	3.0	3.43	2.8	3.0	2.57	3.3	Low	
Linking with specialised pharmaceutical legislations (e.g. advanced therapy medicinal products, medicines for children and medicines for rare diseases)	3.1	3.2	2.5	3.2	3.1	3.38	High	
Complementing EU health-related legislations on EMA fees	3.0	3.3		2.7			Low	
Complementing EU health-related legislations on Supplementary protection certificates	3.2	3.5		2.9			Low	most coherent
Complementing EU health-related legislations on Blood, cells and tissues	3.1	3.2		3.0			High	
Complementing EU health-related legislations on Clinical trials	3.4	3.39		3.3			High	most coherent
Complementing EU health-related legislations on Medical devices and in-vitro diagnostics	2.8	2.63		3.0			Low	
Complementing EU health-related legislations on Genetically modified organisms	2.2	1.79		2.7			Low	least coherent
Complementing other EU legislations and policies on Data protection (e.g. GDPR)	2.8	2.9		2.8			High	
Complementing other EU legislations and policies on Digitalisation (e.g. Digital Single Market)	3.0	2.57		2.7	3.7		High	least coherent
Complementing other EU legislations and policies on Intellectual Property	3.5	3.4		3.1	4.0		High	most coherent
Complementing other EU legislations and policies on Environment (e.g. REACH, industrial emissions)	2.59	2.9		2.4	2.5		High	least coherent
Sustainable Development Goals	2.4	2.8	2.0	2.59	1.83	2.7	High	

Source: Targeted survey. Cells with red boundary lines indicate lack of internal consensus within the stakeholder group and the average score should be considered indicative.

Internal coherence

The targeted survey indicated that respondents found the legislation moderately coherent internally. Industry rated the internal coherence the highest out of the stakeholder groups while academics the lowest with a lack of consensus within that stakeholder group.

Within the open-ended questions, when asked about the most and least coherent aspects of the legislation or for additional comments in the public consultation, responses focussed on specialised and complementary legislations rather than internal coherence. Within the interviews, respondents were generally positive about the coherence of the legislation remarking that there were no major problems and that the components of the legislation were synergistic.

The legal analysis and literature review on internal coherence of the EU general pharmaceutical legislation has not led to the identification of issues of coherence. There are strong linkages between Directive 2001/83/EC and Regulation (EC) No 726/2004**.** They contain multiple cross-references to the other legal text and common requirements (e.g. same definitions, some prohibitions for non-authorised medicinal products) ensuring their internal coherence despite they cover two types of authorisation procedures.

Coherence with specialised pharmaceutical legislation

Main findings

Medicines for children (Paediatric Regulation)

- National rules on the conduct of trials with children lead to delays on the completion of paediatric investigation plans and risk to undermine the complementarity between these pieces of legislation
- Better coordination between committees needed
- Suggestions from stakeholders to integrate this regulation within the EU general pharma legislation to address, inter alia, issues related to data exclusivity on old active substances

Medicines for rare diseases (Orphan Regulation)

- Lack of coherence as regards generic entry
- Better coordination between committees needed

Regulation on advanced therapy medicinal products (ATMP)

- Lack of clarity on definition of ATMP and potential misclassification with borderline products
- Better coordination between committees needed

- *Medicines for children (Paediatric Regulation)*[41]

Pursuant to Article 2 of the Paediatric Regulation the definitions of Directive 2001/83/EC are applicable to the Regulation on medicines for children. Article 7 of the Regulation coordinates the legal status of medicines authorised prior to the entry into force of the Regulation. Article 9 limits the scope of application of the Regulation to certain products designated in Directive 2001/83/EC. Most importantly, Article 27 sets out the *lex specialis* nature of the Regulation and recalls the role of the general pharmaceutical legislation for authorisations of medicinal products. Article 47 sets out the principle of differentiated fees for the authorisation of paediatrics in link with Regulation 726/2004. In the Evaluation of 2020, the European Commission states that "the Paediatric Regulation mostly interacts in a coherent manner with related EU and national legislations and measures".[42] The objectives of this legislation are generally aligned with the ones set out by the general pharmaceutical legislation. However, the Evaluation adds that national rules on the conduct of trials with children may still delay the completion of a paediatric investigation plan (PIP). Achieving better compliance checks for PIPs is essential to not undermine the complementarity of this legislation. The Evaluation also underlines that despite five members of the Paediatric committee are appointed by the Committee for Medicinal Products for Human Use a better coordination between these committees may be beneficial to ensure that applicants have sufficient data for the use of their paediatric product to submit a successful market authorisation request, which is one of the aims of the Paediatric Regulation. According to the respondents of the targeted survey, the Paediatric regulation was viewed as not very efficient nor coherent with the general legislation resulting in duplication of very similar processes in the general legislation as concerns unmet need. Multiple respondents suggested it would be better integrated within the framework of the general legislation and that this would also address some issues that arise from data exclusivity on old active substances. Academic stakeholders highlighted that legislation needs to be more favourable to promote development of new paediatric indications where it currently focusses only repurposing medicines authorised for use in adults for children.

- *Medicines for rare diseases (Orphan Regulation)*[43]

According to the 2020 Evaluation (SWD/2020/0163 final) the Orphan Regulation does not interact in a coherent fashion with the Directive on Medicinal Products for Human Use (2001/83/EC) as regards generic entry. This is because, for orphan medicinal products, generic competitors can only submit an application for marketing authorisation at the end of the 10-year protection period; on the contrary, the data and market protection periods applicable to all human medicines allow generic competitors to directly place generics on the market at the end of the 10-year protection period. This difference may delay generic entry for orphan medicinal products. One of the aims of the ongoing revision of the orphan regulation is to improve availability and accessibility. This would also imply that generic entry is happening for products where the market exclusivity expired (something that the European Commission is currently checking in the ongoing Impact Assessment for the revision of the Orphan Regulation). The ongoing supporting study for the

[41] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) 1768/19, Directive 2001/20/EC. Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 378, 27.12.2006, p. 1

[42] COMMISSION STAFF WORKING DOCUMENT EVALUATION Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. SWD/2020/0163 final

[43] 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.

Impact Assessment for revision of the orphan Regulation should bring more clarity about the exact reasons why this entry has been limited so far. This may relate to inconsistencies between the orphan legislative framework and the general pharmaceutical framework, but also to other factors (e.g. other regulatory (IP) protections may still exist after expiry of the market exclusivity or economic factors related to a limited patient population, also in possible other jurisdictions like the US).

The 2020 Evaluation (SWD/2020/0163 final) also underlined that the Committee for Medicinal Products for Human Use and the Committee for Orphan Medicinal Products use different timelines for their assessments and sponsors submit different data to each committee; as a result, the Committee for Orphan Medicinal Products process is not well integrated in the Committee for Medicinal Products for Human Use process, which may lead to delays in some cases. Therefore, it may be beneficial to aim for better coordination between these scientific committees, which should lead to faster assessment of marketing applications.

Finally, it should be added that orphan drug designation is strongly appealing, compared with ordinary routes for drug approval,[44] especially because smaller clinical trials are the norm, and broader disease markets can be accessed after approval.[45] If the drug is genuinely intended for an orphan use, then this is acceptable; but in other instances, it might be a disingenuous short cut around the requirements of the general pharmaceutical legislation. In the same vein, healthcare professionals consulted stressed that the increase in precision and personalised medicine has led to proliferation of orphan indications (taking advantage of orphan policies and incentives) which has limited competitions and does not spur development of the types of medicines for which the policies were intended. Multiple stakeholder groups, including respondents from Industry, raised issues about the misuse of orphan indications where the financially favourable legislation has encouraged 'indication stacking'.

- *Regulation on advanced therapy medicinal products (ATMP)[46]*

Article 3(7) of Directive 2003/81/EC explicitly excludes ATMP as defined in the ATMP from the scope of application of the Directive. Further institutional arrangements aim to ensure the coherence between the general legislation and the Regulation. For instance, the Standing Committee on Medicinal Products for Human Use, assisting the European Commission, is the same for general medicinal products and ATMP. Furthermore, the Committee for Medicinal Products for Human Use must consult the Committee for Advanced Therapies in certain cases. Nevertheless, multiple groups of stakeholders raised a lack of clarity on definition of ATMP and potential misclassification with borderline products (e.g., medical devices containing pharmaceuticals), as well as differing interpretations (and resultant classifications) and regulation in member states. This was indicated to be particularly true for new and emerging medicinal products which lack a regulatory space where definitions do not keep up with technology. The overlap or boundary with BTC was raised a becoming increasingly nebulous with concerns over mission creep that would result in hospital approved ATMPs, which may result in uneven level playing field and potentially compromises safety.

The 2020 Evaluation (SWD/2020/0163 final) also underlined that the Committee for Advanced Therapies and the Committee for Medicinal Products for Human Use use different timelines for their assessments and sponsors submit different data to each committee; as a result, scientific discussion can be difficult as the committees lack common ground, which can adversely affect the outcome or the timing.

Finally, the implementation of Article 28 of Regulation 1394/2007, referred to as the hospital exemption, is problematic in some cases and needs to be flagged. The hospital exemption permits Member States to authorise the development and manufacture of ATMPs in the absence of a marketing authorisation provided that certain conditions are met, including the preparation on a non-routine basis and that quality (including GMP) and pharmacovigilance requirements under pharma framework are complied with. The implementation of the hospital exemption has given

[44] Thomas S, Caplan A. The Orphan Drug Act Revisited. JAMA. 2019 Mar 5;321(9):833-834. doi: 10.1001/jama.2019.0290. Erratum in: JAMA. 2019 Aug 6;322(5):469. PMID: 30768155.
[45] Sarpatwari, A., & Kesselheim, A. S. (2019). Reforming the Orphan Drug Act for the 21st Century. New England Journal of Medicine, 381(2), 106–108. https://doi.org/10.1056/nejmp1902943
[46] Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 324, 10.12.2007, p. 140.

rise to concerns that in some Member States unproven or substandard treatments are given to patients.

Coherence with other EU health legislation

Main findings
EMA fees Regulation • Coherence with sectorial and cross-cutting legislation • According to some public authorities and industry stakeholders, EMA fees do not adequately compensate NCAs' work under the centralised procedure **BTC legislation** • Difficulties concerning the classification of a substance/product as a BTC or as a medicinal product and the establishment of the respective applicable legal framework **Clinical trials Regulation** • One of the higher rated areas of coherence • Issues for borderline products **Medical devices Regulation** • Difficulties regarding combination product, when the medicinal substance if used separately can be considered a medicinal product. • Unclear definition and differing interpretations at national level. • The less stringent requirements of the medical devices' regulation may create safety risks for patients. **Cross-border Healthcare Directive** • Lack of clarity regarding the recognition of restricted medical prescription and the classification for the dispensing of homeopathic medicinal products • Not complete alignment regarding the definition of "prescription" **GMOs Directives** • Doubts raised by Member States regarding the application of some provisions of the general pharma legislation to medicinal products put on the market for emergency or compassionate use • Several issues caused by a lack of common approach for the assessment of GMO aspects of clinical trials with investigational medicinal products for human use **Health Technology Assessment Regulation** • The legal architecture of the HTAR is well articulated with the general pharmaceutical legislation. Potential incoherence in the review processes of EMA and HTA regulators. **Transparency Directive** • No legal incoherence. Improved enforcement by the EC on approvals by Member States and specific requirements on information given by MAH could improve access to medicines for patients. • Pre- and post-approval evaluations could further inform reimbursement/pricing decisions. **Radiopharmaceuticals under the BSSD** • Lack of specialised definitions in the general pharmaceutical legislation. • Discrepancies in the requirement for information on fixed doses (e.g., per weight) in the general authorisation procedure and the tailor-made imperatives of radiopharmaceuticals. • The complex authorisation procedure of the general pharmaceutical legislation limits the development of new treatments. **Food additives** • No legal incoherence. Synergies in the evaluation of additives in medicines and food have been identified (e.g., titanium dioxide). **Patent protection rules** • SPC: Complex overlay and suboptimal interplay of rules between regulatory exclusivity rights (data protection/market exclusivity) and intellectual property rights (patents and IPC). • SPC: Rules for compulsory licensing may require streamlining with the general pharmaceutical legislation. • UPP: The Unitary Patent Protection Regulation and general pharmaceutical legislation could bring synergies for MAHs but potential limitations have been identified.

- *EMA fees Regulation*[47]

The EMA fees Regulation sets out the fee for the various procedures of authorisation defined in the general pharmaceutical legislation as well as annual fees for maintenance activities. As such, it acts in parallel and does not appear to impact coherence. In the 2019 Evaluation of the EMA fees legislation the Commission states that "overall, the fee system is coherent with sectorial and cross-cutting legislation".[48] Nevertheless, there was a lack of consensus from public authorities on the coherence with EMA fees which when investigated geographically suggested Eastern Europe were more satisfied with coherence in this area that other European geographies. Some public authorities are of the view that the EMA fees do no longer adequately compensate NCAs for their increasing role in the centralised procedure and by consequence, high quality scientific evaluation of marketing authorisation applications is becoming increasingly challenging because the NCAs' work for centralized procedures is not cost-effective. Industry respondents also recognised this issue and were in favour that NCAs should be adequately resourced and compensated through this process. According to some academic stakeholders, financing of EMA is too reliant on private funding through pharmaceutical companies and may create some tension considering its role as a public body.

- *BTC legislation (blood,*[49] *tissues and cells*[50]*)*

The 2019 Evaluation of the Union legislation on blood, tissues and cells states that there is a direct link between the BTC directives and the medicinal product legislation.[51] Article 2(1) of both Directives draws the line of the application between the two pieces of legislation (blood or tissues and cells on the one side and Directive 2001/83/EC on the other side). However, classifying a substance/product as a BTC or as a medicinal product or establishing which of the respective legal framework applies can be difficult. According to the 2019 evaluation "while most BTC based substances/products fall clearly into either the medicinal or BTC legal framework (…) in some cases it is challenging to decide on classification and determine which legislation applies".[52] This issue has also been raised unanimously by stakeholders: the incoherence centred around unclear or unagreed definitions, differing interpretations at national level and differing regulation of different product types in different Member States.

With regard to the EU blood directive, the key interface relates to plasma that can be manufactured into plasma derived medicinal products. While the collection of this plasma falls under the blood directive, the manufacturing and following steps fall under the pharma legislation. The incoherence relates to plasma collected outside the EU and then manufactured and/or used within the EU. A lot of this plasma comes from the U.S. (about one fourth) where equivalent, but not identical, criteria apply. Overall, there is a good coordination covering inspection practices.

The tissues and cells framework applies to tissues and cells unless another legal framework applies on manufactured TC products. This framework therefore only applies on the donation, collection and testing. Thus, it is very important to understand when the EU general pharmaceutical framework applies ('industrial process' and 'intention to place on the market' – Article 2 of Directive 2001/83) and consequently when the ATMP framework applies ('substantial manipulation', 'non-homologous use' - Article 2 of regulation 1394/2007). These different definitions are not well described and leave a lot of room for interpretation.

- *Clinical trials Regulation*[53]

The main legal interconnections between this instrument and the general pharmaceutical legislation seem to create a coherent framework. The regulation was considered one of the higher

[47] Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products and Regulation 658/2014

[48] COMMISSION STAFF WORKING DOCUMENT EVALUATION of the European Medicines Agency's fee system. SWD(2019) 336 final.

[49] 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. 30–40.

[50] 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. 48–58.

[51] COMMISSION STAFF WORKING DOCUMENT Evaluation of the Union legislation on blood, tissues and cells. SWD(2019) 376 final.

[52] Ibid.

[53] 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 Text with EEA relevance. OJ L 158, 27.5.2014, p. 1–76.

rated areas of coherence by stakeholders. Only the industry sector pointed out inconsistencies regarding the advice received from different working groups at the EU level. More precisely, clinical trial application phase in national Member States is followed by multiple committees and scientific advisory components that are not joined up despite looking at the same product. In the "old" directive 2001/20 system, there were no mechanisms to harmonise at the European level. Regulation 536/2014 aims to harmonise the scientific elements for multinational trials, although the final decision on a clinical trial remains a Member State prerogative. This leads in some cases to incoherence between the processes for marketing authorisation (and the scientific advice given at European or Member State level) and the clinical trial authorisation process.

It should also be added that the borderline products' definition issues seen for medical devices and BTC arise also for the clinical trials, as the main definitions apply and are decisive on whether research is a clinical trial or not.

- *Medical Devices Regulation*[54]

Article 1(6) of the Medical Devices Regulation excludes medicinal products as defined in Directive 2001/83/EC from its scope and sets the 'principal mode of action of the product' as the primary criterion to distinguish between medicinal products and medical devices. Nevertheless, difficulties arise when a medical device incorporates substances which if used separately can be considered medicinal products and thus being able to receive market authorisation at national level. Stakeholders centred their critics around unclear definitions and differing interpretations at national level – which leaves stakeholders and patients in unequal position in different Member States – calling for a harmonisation of definitions and processes. EMA remains the only major pharmaceutical regulatory body that is not also in charge of medical devices. Thus, a point of contention is whether the pharmaceutical legislation is coherent with the Medical Devices Regulation when the latter has apparently less demanding regulatory standards, affecting the relative safety profiles of drugs and devices.[55] The tensions are particularly strong for drug-device combination products, and clinical pathways where a device or drug could be recommended. The disparity in regulation could distort medical markets, put pressure on patient safety and access, and generate other inefficiencies from lack of integration.

- *Cross-border healthcare Directive*[56]

The Directive has several legal interlinkages with the general EU pharma legislation. This Directive must apply without prejudice to the Medicinal Products Directive (Article 2.h) and Regulation (EC) No 726/2004 (Article 2.l); moreover, a medicinal product is defined by reference to the Medicinal Products Directive (Article 3.i). The cross-border recognition of a prescription is conditional on the authorisation in the territory of the MS of a medicinal product based on Directive 2001/83/EC or Regulation 726/2004 (except for special medical prescriptions pursuant to Article 71 of the Medicinal Products Directive). Nevertheless, this provision does not apply to medicinal products subject to special medical prescription provided for in Article 71(2) of Directive 2001/83/EC (Article 11.6 of Directive 2011/24/EU). However, Directive 2001/83/EC also foresees 'restricted' medical prescription, reserved for use in certain specialised areas. It is not clear whether and how such prescriptions should be recognised under the Cross-border Healthcare Directive.

It should be added that Directive 2001/83/EC and the Cross-border Healthcare Directive's definitions of "prescription" are not completely aligned. Directive 2001/83/EC defines "Medicinal Prescription" as any medicinal prescription issued by a professional person qualified to do so. The Cross-border Healthcare Directive defines "prescription" as prescription for a medicinal product […] issued by a member of a regulated health profession within the meaning of Article 3(1)(a) of Directive 2005/36/EC who is legally entitled to do so in the Member State in which the prescription is issued. Related to this, the CJEU interpreted the definition of "prescription" within the meaning of the Cross-border Healthcare Directive and stated that the term does not comprise order forms issued by a health professional in another Member State that do not contain the name of the patient concerned.[57]

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[54] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. OJ L 117, 5.5.2017, p. 1–175.

[55] Pane J, Coloma PM, Verhamme KM, Sturkenboom MC, Rebollo I. Evaluating the Safety Profile of Non-Active Implantable Medical Devices Compared with Medicines. Drug Saf. 2017 Jan;40(1):37-47.

[56] Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare. OJ L 88, 4.4.2011, p. 45–65

[57] Judgment of the Court (Fifth Chamber) of 18 September 2019. VIPA Kereskedelmi és Szolgáltató Kft. v Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet. EU:C:2019:751.

- Article 14(1) of Directive 2001/83/EC refers to the classification for the dispensing of homeopathic medicinal products. The Cross-border Healthcare Directive concerns dispensing medicinal products on a prescription issued in another Member State. It is not clear however, what kind of classification for the dispensing is meant in Article 14(1) of Directive 2001/83/EC and how it could affect the recognition of prescriptions under the Cross-border Healthcare Directive. *GMOs Directives*[58]

The Union legislation on GMOs encompasses Directive 2009/41/EC on the contained use of genetically modified microorganisms and Directive 2001/18/EC on the deliberate release into the environment of GMOs. Medicinal products that have been granted an EU or national marketing authorisation in accordance with Regulation 726/2004 and Directive 2001/83, respectively, are exempted from Directive 2001/18/EC and Directive 2009/41/EC. The evaluation of the environmental impacts of medicinal products for human use that contain or consist of GMOs is done, in accordance with the principles set out in Directive 2001/18/EC, by the European Medicines Agency or the national competent authority, as applicable, in the context of the assessment of the marketing authorisation application pursuant to the medicinal product legislation. Conversely, the administration of medicinal products that have not been granted a marketing authorisation in accordance with Union legislation is not exempted from the GMO legislation. This is the case, for example, for investigational medicinal products. There is an interlink between the scopes of the pharmaceutical legislation and of the GMO legislation, i.e. medicinal products containing or consisting of GMOs. The objectives are consistent, i.e. protection of human, animal health and the environment.

However, there are many concerns that the GMO Directive impedes the proper functioning of the general EU pharma legislation due to the complexity of national implementing legislation for the GMO requirements. More specifically, Recital 23 of Regulation (EU) 2020/1043[59] indicates that doubts have been raised by some Member States regarding the application of the provisions of Directive 2001/18/EC and Directive 2009/41/EC in the situations contemplated in Article 5(1) and (2) of Directive 2001/83/EC and Article 83 of Regulation (EC) No 726/2004. These provisions allow Member States to authorise the supply and administration of medicinal products for human use (including medicinal products that contain or consist of GMOs) in the absence of a marketing authorisation where there is an urgent need to address the specific needs of a patient, for compassionate use, or in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation that could cause harm. In other words, the Recitals in Regulation 2020/1043 explain the perceived lack of coherence between Member States' implementation of the GMO directives and general pharma legislation. Recital 10 states that it is "particularly difficult to conduct multi-centre clinical trials with investigational medicinal products that contain or consist of GMOs involving several Member States" and Recital 17 adds that the "requirement to satisfy environmental risk assessment and consent under Directives 2001/18/EC and 2009/41/EC can involve high administrative burden due to variation in Member State law". The exceptions inserted in Regulation (EU) 2020/1043 ensures that the conduct of clinical trials in the territory of several Member States with investigational medicinal products containing or consisting of GMOs intended to treat or prevent COVID-19 is not delayed, but for medicinal products other than COVID-19 preventions and treatments, the concerns are on-going; this is because the exceptions pursuant to Part B of Directive 2001/18/EC do not clearly cover medicinal products permitted by the general pharmaceutical legislation to be put on the market for emergency or compassionate use.

This issue has also been raised by stakeholders, that outlined that different national implementations on GMO assessments lead to very complex multinational clinical trials.

Regulation (EC) 536/2014 on clinical trials is without prejudice to the application of the GMO Directives. There is not a common approach for the assessment of GMO aspects of clinical trials with investigational medicinal products for human use in the EU as some Member States apply Directive 2001/18/EC, other Member States apply Directive 2009/41/EC and others decide on a case-by-case basis or apply both. In the Commission's study on new genomic techniques (NGT)[60], Member States and stakeholders noted the challenges of applying the current GMO legislation to

[58] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. OJ L 106, 17.4.2001, p. 1–39 and Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms. OJ L 125, 21.5.2009, p. 75–97.

[59] 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. 12–16.

[60] Study on the status of new genomic techniques under Union law and in light of the Court of Justice ruling in Case C-528/16. SWD(2021) 92 final.

medicinal products for human use. In particular, for clinical trials, some Member States reported that there are doubts as to which techniques and products are subject to the GMO legislation. Stakeholders from the medicinal sector consider that the GMO legislation is not specifically designed for medicinal products. They indicated that the application of the GMO authorisation procedures to investigational medicinal products represents a problem that hinders the development of these products, delays the conduct of clinical trials in the EU and patient access to them as well as affects the EU's competitiveness in the pharmaceutical sector. Specific problems mentioned in relation to the application of the GMO legislation include the lack of harmonisation, the duplication of assessments (under both GMO and pharmaceutical frameworks) and insufficient expertise among GMO authorities on gene therapies, in view of the rising number of applications. The labelling of NGT products raises different considerations in the medicinal sector. The traceability and labelling provisions in Directive 2001/18/EC do not apply to medicinal products, which have to be labelled in accordance with the medicines legislation. Stakeholders active in the medicinal sector believe that no additional labelling rules are needed for NGTs, beyond what is already required under the medicines framework. Several stakeholders consulted in the Commission's study on NGTs ask for reconsideration of the application of the GMO legislation to medicinal products consisting of or containing GMOs. More specifically, they believe that there are no environmental and biosafety risks for non-replicating viral vectors or GM human cells, as these do not duplicate and cannot survive in the environment. They call for a more streamlined and harmonised approach that fully integrates GMO aspects into the clinical trial application process. Also, several Member States competent authorities are in favour of a more harmonised and streamlined regulatory framework.

- *HTA Regulation*[61]

The HTA Regulation (HTAR) establishes a framework to support Member State cooperation and the measures needed for clinical assessment of health technologies. HTAR was adopted on 15 December 2021 with a date of application in January 2025, therefore no practical issues of coherence can be identified yet. The objectives and scope of the HTAR are well aligned to those of the pharmaceutical legislation. The HTAR creates the necessary legal framework for HTA bodies to carry out joint clinical assessments of health technologies, including medicines receiving central marketing authorisation (Article 7(1)(a) and (b)). The provisions of HTAR do not interfere with the legal requirements regarding the authorisation process under the pharmaceutical legislation. The provisions on Joint Scientific Consultations (JSC) to be carried out in parallel with EMA (Article 17.2 of HTAR) create the necessary legal framework for the cooperation between EMA and HTA bodies, facilitating the development of convergent views on the evidence to be generated by the drug developer to satisfy both regulatory and HTA needs. HTAR ensures appropriate articulation with the EU pharmaceutical legislation by making reference to the definitions of medicinal products and marketing authorisation procedure.

- *Transparency Directive*[62]

The aim of this Directive is to ensure that Member States measures on prices and reimbursement of medicinal products are transparent. It details the procedures that Member States must follow so that their decisions and policies do not create obstacles to the EU pharmaceutical trade. No coherence issues have been identified between the two legal regimes. To enhance the synergy between the two legal regimes, it was suggested that regulatory requirements for the evidence generated in pre- and post- approval phase (in particular in case of conditional MA or adaptive pathways) under the EU general pharmaceutical legislation could also cover the needs of the subsequent processes and decision-making at national level (e.g. HTA, pricing and reimbursement). It was stressed during the consultation (industry) that the lack of enforcement by the Commission of the Member States obligation to adopt a decision on the application on price and reimbursement by MAHs impacted the general pharmaceutical legislation in terms of pricing and reimbursement of medicines. In the same vein, another stakeholder (civil society) considers that the lack of detailed requirements on information to be provided by MAHs in pricing and reimbursement applications impacts access to medicines for patients if Member States are unable to make a reimbursement and pricing decision from the information provided.

[61] 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 (Text with EEA relevance) PE/80/2021/INIT OJ L 458, 22.12.2021, p. 1–32

[62] Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems

- *Directive 2013/59/Euratom laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation[63] (BSSD)*

Nuclear medicine is a branch of medicine that focuses on using radioactive substances for the diagnosis and treatment of diseases. Those substances are referred to as radiopharmaceuticals[64]. They are regulated under both the EU pharmaceutical and radiation protection regimes, thus coordination in implementing the different regulatory frameworks is crucial. Currently the general pharmaceutical legislation as well as the BSSD do not include a specific provision to address all the peculiarities of radiopharmaceuticals thus creating a challenging environment for the development and roll-out of radiopharmaceuticals in the EU. The following coherence issues have been identified:

- Lack of specialised definitions for radiopharmaceuticals and their associated technologies: Directive 2001/83/EC does provide several important definitions pertaining to radiopharmaceuticals; however, those are not sufficiently up to date to cover the newly emerged technologies. This refers particularly to the definitions of "radionuclide precursor radiopharmaceuticals" and "radionuclide precursor"[65].
- Inconsistencies with dosage requirements: The BSSD requires individually planned dosimetry of all radiotherapeutic procedures, however, this is not supported by the marketing authorisation requirements of the EU general pharmaceutical legislation. The latter follows traditional dosing schemes and requests prospective MAHs to provide information on fixed doses of medicines, often adjusted based on body weight, but not tailored to the specific patient case. This approach does not fit in the radiopharmaceuticals given their safety profile and safety requirements, which requires tailor-made dosimetry, to deliver the desired therapeutic effect and protect patients. For existing licensed radiopharmaceuticals, fixed-dose values are general, often obtained from phase I or II clinical trials.[66]
- Requirements for marketing authorisation: Overall, the requirement for marketing authorisation is difficult for radiopharmaceuticals and inhibits their commercialisation in the EU. It is important to recognise the market failure factor applicable to radiopharmaceuticals. Mainly, this refers to little involvement of the pharmaceutical industry in this field given that industrial production of radiopharmaceuticals is extremely limited. The low interest from commercial actors leads to overall slower progress in the number of products authorised and a higher burden on other (mostly research and academia) actors, who are not as versed in regulatory subjects as the industry stakeholders. Particularly difficult is the requirement of Directive 2001/83 to apply for a marketing authorisation for all material used in the preparation of radiopharmaceutical products. The Directive considers only one method of production of radiopharmaceuticals, the traditional kit-based preparation, and omits the new production technologies, particularly the complex preparation form (i.e., preparation from starting materials).[67] The latter is already heavily regulated by the European Pharmacopoeia which required extensive quality control before application to the patient. Complex preparation is becoming more and more common in the EU and the Directive does not sufficiently address this development, as it requires marketing authorisation for all material used via this route.

Note that within the context of the SAMIRA action plan[68], the Commission, at the time of writing launched a call for tender to carry out a study addressing these issues and to improve the

[63] Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom

[64] Radiopharmaceuticals are different from other types of pharmaceuticals due to several reasons (e.g. they cannot be industrially produced due to their short half-life, there is very limited interest from commercial players to enter the radiopharmaceutical markets because large-scale industrial production and distribution are impossible; radiopharmaceuticals need to be prepared from radionuclides by specialised personnel in controlled safe environments; the preparation of radiopharmaceuticals involves loading a radionuclide with a vector molecule; radiopharmaceuticals need to be administered to patients shortly after their preparation and based on individually calculated dosimetry; research and development of novel radiopharmaceuticals are performed primarily by academic research institutes, as opposed to the biotech and pharmaceutical industry for other types of medicinal products.

[65] European Commission, Directorate-General for Energy, Developments in nuclear medicine: new radioisotopes in use and associated challenges: EU Scientific Seminar November 2019, Publications Office, 2020, https://data.europa.eu/doi/10.2833/522008.

[66] Statement by the European Association of Nuclear Medicine (EANM) Posology for Radiopharmaceuticals: contradictory legal requirements between BSS Directive 2013/59/Euratom and EMA marketing authorisations schemes. December 2021

[67] Statement of the European Association of Nuclear Medicine (EANM) for a better inclusion of the particularities of Radiopharmaceuticals within the Review of Directive 2001/83EC on Pharmaceutical Legislation. December 2021

[68] COMMISSION STAFF WORKING DOCUMENT on a Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA) Brussels, 5.2.2021 SWD(2021) 14 final available at:
https://ec.europa.eu/energy/sites/default/files/swd_strategic_agenda_for_medical_ionising_radiation_applications_samira.pdf

understanding of the links and the interdependencies between the European pharmaceutical legislations and the Euratom radiation protection requirements[69].

- *Regulation (EC) No 1333/2008 on food additives[70]*

The list of authorised food additives, related restrictions and prohibitions of use under Regulation (EC) No 1333/2008 also applies to food additives in medicinal products[71]. Article 2 of Regulation (EC) No 1333/2008 on the scope does not include any reference to the possibility of exempting medicinal products. There are some coordinated interactions between EU regulators on food additives and on medicinal products as demonstrated in the case of titanium dioxide. On 17 May 2021, the EC requested the EMA to provide an analysis defining the technical purpose of Titanium dioxide in medicinal products; feasibility of alternatives without negative impact on the quality, safety and efficacy of medicines; and if confirmed, considerations to be taken into account to define a transition period for phasing out this excipient. The EC has adopted a Regulation[72] withdrawing the authorisation to use titanium dioxide (TiO2 also known as E171) in food products. This withdrawal however does not apply to uses in medicinal products. Article 3 of this Regulation requires the Commission, following a consultation of the EMA, to review the necessity to maintain or delete titanium dioxide from the Union list of food additives for the exclusive use as a colorant in medicinal products in Part B of Annex II to Regulation (EC) No 1333/2008 within three years after the date of entry into force of this Regulation.

- *Supplementary protection certificate[73] and unitary patent certificate[74]*

Regulation (EC) No 469/2009 establishes a supplementary protection certificate for producers of pharmaceutical products and plant protection products to offset the loss of patent protections due to the compulsory lengthy testing and clinical trials. The IA conducted for Regulation (EU) 2019/933 amending Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products, as well as its recitals, highlight that the SPC legislation applies without prejudice to the authorisation procedure laid down in Directive 2001/83/EC, in particular the regulation of generics and biosimilars, as well as falsified medicines, medical devices' unique identifiers, but also the GMPs.

Consultations however highlight the complex overlay and suboptimal interplay of rules between regulatory exclusivity rights (data protection/market exclusivity) and intellectual property rights (patents and IPC). Specific issues identified by stakeholders from the general public include the limitation of PIP incentives to those products which SPC as the last protection to expire, fragmentation of SPC regulation across Member States, as well as possible evergreening/overcompensation practices, leading to delay in the entry of biosimilars and generics and thus reduction of the affordability of treatments.

Besides, compulsory licensing of pharmaceutical products may be limited by IP/data protection rules, which may prevent the issuance of marketing authorisations[75]. In the same vein, academic stakeholders highlighted the strong focus of the pharmaceutical legislation on the protection of IP rights. Stakeholders from public authorities highlighted the lack of access by MAHs to manufacturers' data to control processes, and a lack of information about patent/SPC's expiration date.

Unitary patent protection

Regulation (EU) 1257/2012 sets out a unitary patent, according to which inventors may submit a single application for intellectual property protection in 25 Member States, without requiring

[69]See tendering documents at: https://etendering.ted.europa.eu/cft/cft-documents.html?cftId=9465

[70] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives (Text with EEA relevance) *OJ L 354, 31.12.2008, p. 16–33*

[71] Regulation (EU) No 231/2012 of 9 March 2012 as amended lays down specifications on colours and sweeteners listed in Annex II (Union list of food additives approved for use in foods and conditions of use) and Annex III (Union list of food additives including carriers approved for use in food additives, food enzymes, food flavourings, nutrients and their conditions of use) to Regulation (EC) No 1333/2008 also applies to medicinal products.

[72]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

[73] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products.

[74] Regulation (EU) No 1257/2012 of the European Parliament and of the Council of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection.

[75]Hoen, Ellen & Boulet, Pascale & Baker, Brook. (2017). Data exclusivity exceptions and compulsory licensing to promote generic medicines in the European Union: A proposal for greater coherence in European pharmaceutical legislation. Journal of Pharmaceutical Policy and Practice. 10. 10.1186/s40545-017-0107-9, available at https://www.researchgate.net/publication/318120659_Data_exclusivity_exceptions_and_compulsory_licensing_to_promote_generic_medicines_in_the_European_Union_A_proposal_for_greater_coherence_in_European_pharmaceutical_legislation, viewed 13 January 2022.

validation in all Member States and with equal protection. It is expected to apply from the second half of 2022. The unitary patent protection could bring synergies with the centralised authorisation procedure of pharmaceutical products by the EMA, boosting regulatory attractiveness.

However, possible limitations include the proportionate character of the duration and scope of market exclusivity granted to pharmaceuticals in view of the risk and investment in innovation and authorisation procedures. Moreover, recital 10 of Regulation (EU) 1257/2012 upholds the concept of compulsory licensing by each Member State within their territory, which requires alignment with pharmaceutical legislation, data protection and market exclusivity.

Coherence with non-health related EU legislation

Main findings
GDPR and EUDPR • Lack of clarity regarding the interpretation and application of GDPR in healthcare and pharmaceuticals • Confusion linked to the definition of consent
Regulation on drug precursors • More coordination could be beneficial, in particular to tackle the production of illegal substances via finished medicinal products, e.g., (pseudo)ephedrine.
Chemicals legislation (REACH) • Coordination is generally achieved. Some gaps have been identified in relation to environmental risk assessment obligations compared to • REACH would limit the production of APIs.
EU Water legislation • Policy actions to mitigate the impact of medicinal products in water will be in place with the revision of the Environmental Quality Standard Directive (2008/108/EC as amended by 2013/39/EU), revision of the Groundwater Directive (2006/118/EC) and the revision of Waste Water Treatment Directive (91/271/EEC). However, this will imply additional compliance costs for the Member States. • Only a limited set of pharmaceuticals can be targeted effectively with this legislation (i.e. those monitored in most parts of the EU and posing the biggest risk to nature / human health), leaving the majority of pharmaceuticals unaddressed. • Currently, updates to guidance are necessary for effective monitoring of pharmaceuticals in water and information/coordination between authorities appears insufficient.
Competition law • Concentration at industry level, with specific concerns on the innovativeness of the European pharmaceutical industry. • Insufficient resources to conduct competition inspections in the pharmaceutical industry.
Chemicals Strategy for Sustainability • No reference to the Strategy actions under the general EU pharmaceutical legislation.
Action plan on antimicrobial resistance • The general pharmaceutical legislation lacks provisions to regulate the use of antimicrobials and to incentivise the authorisation of new antimicrobials.

- *General Data Protection Regulation (GDPR)[76] and EU Data protection Regulation (EUDPR)[77]*

The GDPR and the EUDPR provide a horizontal framework for the processing of personal data, ensuring that it happens "for a good reason, transparently, and securely". Article 9 of the GDPR and 10 EUDPR set out lawful grounds for the processing of special categories of data (including

[76] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). OJ L 119, 4.5.2016, p. 1–88.

[77] Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, and repealing Regulation (EC) No 45/2001 and Decision No 1247/2002/EC. OJ L 295, 21.11.2018, p. 39–98.

heath data) such as scientific research (j) and reasons of public interest in the area of public health (i). The two data laws and the general pharmaceutical legislation complement each other because the GDPR and the EUDPR set out frameworks for processing personal data with well-considered checks and balances; thus, given that they apply horizontally, also the processing of personal data in the context of activities regulated by pharmaceutical legislation needs to comply with it. However, some coherence issues exist. These laws, in some ways, make it difficult to achieve the objectives of the general pharmaceutical legislation. Regarding the GDPR, it is unclear whether and when universities and private companies can rely on Art. 9(j) as a lawful ground for processing data and this makes the provisions in the GDPR for research "complex, dispersed and layered".[78] Moreover, there is a high level of variability from clinical trial ethics committees, data protection advisers and organisations about requirements for anonymisation, for consent for future research uses, and for allowing data subjects to withdraw (while meeting obligations to retain data to verify results);[79] stakeholders' view confirmed that the interpretation and application of GDPR in healthcare and pharmaceuticals is not clear and that guidelines would potentially help to address this issue. Aiming to more clarity by solving these problems would be beneficial giving that gathering data for authorisation of medicinal products is increasingly international and data intensive.

Finally, taking into consideration both data protection laws, there is sometimes confusion between "consent" as a legal basis/condition for processing data in the sense of GDPR and EUDPR and "informed consent" in the sense of informed consent to participate in a clinical trial or more generally, to a medical intervention. The fact that a medical treatment happens with "informed consent" does not mean that the processing of personal data that happens as part of providing the treatment (documentation of intervention in health records, billing for treatment) necessarily use "consent" under GDPR and EUDPR as the lawful basis for processing. The European Data Protection Board has provided guidance clarifying this issue in the context of clinical trials.[80]

- *Regulations on trade in drug precursors*[81]

Drug precursors are chemicals that are primarily used for the legitimate (legal) production of a wide range of products including medicinal products. However, they can also be misused for the illicit (illegal) production of drugs such as amphetamines, heroin or cocaine. For about 5-10 years, illegal drug producers in the EU have increasingly used 'designer-precursors'. Designer-precursors are close chemical relatives of traditional drug precursors, and their purpose is to circumvent the controls. They usually do not have any known legitimate use. Two EU regulations set measures to control these illicit uses. Regulation (EC) No 273/2004 establishes harmonised measures for the intra-Union control and monitoring of certain substances frequently used for the illicit manufacture of narcotic drugs or psychotropic substances with a view to preventing the diversion of such substances. Regulation (EC) No 111/2005 lays down rules for the monitoring of trade between the Community and third countries in certain substances frequently used for the illicit manufacture of narcotic drugs and psychotropic substances. More coordination between the EU general pharmaceutical legislation and these two regulations could be envisaged in particular to tackle the following concerns:

- Ephedrine and pseudoephedrine (to make methamphetamines) are extracted from medicines legally purchased over the counter in pharmacies. In such case these precursors are not 'diverted' in the sense of Regulation (EC) 273/2004 and therefore the diversion monitoring and control under this Regulation is not applied to such situation. These medicines are highly regulated in some Member States, in pharmacies (because they are often misused in certain Member States for making methamphetamine in small-scale kitchen labs). For instance, they can only be sold in very small doses for personal use. However, in pharmacies in neighbouring countries the monitoring may be much less strict. This triggers individuals to shop around in the pharmacies of these neighbouring countries and reintroduce the (pseudo)ephedrine in specific Member States for illegal methamphetamines production.

[78] 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

[79] 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

[80] EDPB, Opinion 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection regulation (GDPR)

[81] Regulation (EC) No 273/2004 of the European Parliament and of the Council of 11 February 2004 on drug precursors and Council Regulation (EC) No 111/2005 of 22 December 2004 laying down rules for the monitoring of trade between the Community and third countries in drug precursors.

- For the export of medicinal products containing (pseudo)ephedrine or its salts, an export authorisation is required under Regulation (EC) 111/2005 but no general licence or registration as for the other drug precursors which may lead to some difficulties for competent authorities in charge of implementing and enforcing the export authorisation requirement since they would not be aware of the economic operators involved in this activity.

- *REACH*[82]

REACH is the cornerstone of the EU legislation on chemicals. Companies must register substances they intend to place on the market. ECHA evaluates the compliance with the registration dossiers, the EU Member States are entitled to evaluate substances registered based on concern for human health or for the environment. Scientific committees assess whether risks linked to substances placed on the market can be managed. As a result, the use of hazardous substances if their risks are unmanageable can be banned or subject to restrictions or a prior authorisation[83].

According to Article 2(5) of REACH, to the extent that a substance is used in medicinal products for human or veterinary use, REACH Title II on Registration, Title V on Downstream users, Title VI on Evaluation, and Title VII on authorisation do not apply. According to Article 2(6) of REACH, medicinal products for human or veterinary use, in the finished state and intended for the final user, are exempted from information requirements through the supply chain (Title IV of REACH). Moreover, the exemption from REACH registration requirements for substances manufactured or imported for PPORD purposes can be extended for an additional five years in the case of substances intended for use in medicinal products. Certain substances used in medicinal products within the scope of the EU general pharmaceutical legislation are also exempted from certain restrictions under Annex XVII of REACH[84]. Some deadline extensions also exist for substances that are subject to the REACH authorisation procedure when they are used in medicinal products[85].

According to the REACH evaluation report[86], an information gap exists in relation to the environmental risks related to the manufacturing or formulation stages of medicinal products for human and veterinary use as a result of their exemption from REACH. Consulted public authorities consider that REACH impedes the provision of some synthesis on APIs. According to a representative of the civil society consulted, the EU general pharmaceutical legislation should give the EMA a mandate to promote alternative methods and ensure animal testing as a last resort in line with REACH requirements.

- *EU Water legislation (i.e., Water Framework Directive[87] and EQS Directive[88])*

The Water Framework Directive sets specific measures for the progressive reduction of discharges, emissions, and losses of priority substances[89] and the cessation or phasing-out of discharges, emissions, and losses of priority hazardous substances[90] into water bodies. The EQS Directive establishes limits on concentrations in surface waters for priority substances listed in its Annex II. This Directive also requires the Commission to establish a watch list of substances for which Union-wide monitoring data are to be gathered for the purpose of supporting the update of the list of priority substances. It specifies that the following medicinal products Diclofenac, 17-beta-estradiol (E2) and 17-alpha-ethinylestradiol (EE2) must be included in the first watch list, to

[82] Regulation (EC) No 1907/2006 of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency

[83] Information retrieved from ECHA webpage 'Understanding REACH' available at: https://echa.europa.eu/regulations/reach/understanding-reach

[84] Substances which are classified as carcinogen category 1A or 1B in Part 3 of Annex VI to Regulation (EC) No 1272/2008, substances which are classified as germ cell mutagen category 1A or 1B in Part 3 of Annex VI to Regulation (EC) No 1272/2008, substances which are classified as reproductive toxicant category 1A or 1B in Part 3 of Annex VI to Regulation (EC) No 1272/2008 (Entry 28 Annex XVII), Chloroform (Entry 32 Annex XVII), 1,1,2-Trichloroethane (Entry 34 Annex XVII), 1,1,2,2-Tetrachloroethane (Entry 35 Annex XVII), 1,1,1,2-Tetrachloroethane (Entry 36 Annex XVII), Pentachloroethane (Entry 37 Annex XVII), 1,1-Dichloroethene (Entry 38 Annex XVII).

[85] Bis(2-ethylhexyl) phthalate, Benzyl butyl phthalate, Dibutyl phthalate, 4-(1,1,3,3-Tetramethylbutyl) phenol, ethoxylated.

[86] COMMISSION STAFF WORKING DOCUMENT Accompanying the document COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL AND THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE Commission General Report on the operation of REACH and review of certain elements Conclusions and Actions SWD/2018/058 final

[87] Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy *OJ L 327, 22.12.2000, p. 1–7*

[88] 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

[89] Priority substances are substances the present a significant risk to or via the aquatic environment, identified on the basis of risk assessment

[90] Within priority substances, priority hazardous substances are substances that are toxic, persistent and liable to bio-accumulate or which give rise to an equivalent level of concern. Annex X of the Water Framework Directive lists the priority substances.

gather monitoring data for the purpose of facilitating the determination of appropriate measures to address the risk posed by those substances. To select substances to be included in the watch list, the Commission must consider all available information including *inter alia* information gathered according to Directive 2001/83/EC.

According to Article 8(c) of the EQS Directive the Commission must develop a strategic approach to pollution of water by pharmaceutical substances. That strategic approach must, where appropriate, include proposals enabling, to the extent necessary, the environmental impacts of medicines to be taken into account more effectively in the procedure for placing medicinal products on the market._In the framework of that strategic approach, the Commission must, where appropriate propose measures to be taken at Union and/or Member State level, as appropriate, to address the possible environmental impacts of pharmaceutical substances and in particular Diclofenac, 17-beta-estradiol and 17-alpha-ethinylestradiol), with a view to reducing discharges, emissions and losses of such substances into the aquatic environment, taking into account public health needs and the cost-effectiveness of the measures proposed.

The European Union Strategic Approach to Pharmaceuticals in the Environment was adopted in March 2019[91]. It contains several actions concerning the general pharmaceutical legislation and its actors. Under Point 5.3 the Commission must in collaboration with the EMA and Member States seek to improve the level of environmental expertise in the Committees and networks involved in the environmental risk assessment of medicinal products; examine how to improve public access to the main environmental risk assessment results and relevant toxicological thresholds for medicinal products while respecting data-protection rules, emphasise to applicants the importance of submitting a completed assessment by the time of the authorisation for marketing human medicinal products, so that adequate risk management measures can be established and published. Under Point 5.4 the Commission must in collaboration with Member States and the EMA explore the possibility of reducing waste by optimising the package size of pharmaceuticals so that medicines can be dispensed in quantities better matching needs, and by safely extending use-by (expiry) dates so that fewer medicines that are still usable have to be thrown away; facilitate the exchange of best practices among healthcare professionals on the environmentally safe disposal of medicinal products and clinical waste, and the collection of pharmaceutical residues as appropriate.

Based on Article 8 of Directive 2001/83/EC on environmental risk assessment, EMA has developed guidelines on the environmental risk assessments of medicinal products for human use published in 2006[2]. These guidelines are being revised and drafts have been published in 2018 but no final version has been adopted yet[3]. Several aspects mentioned above under Points 5.3. and 5.4 of the European Union Strategic Approach to Pharmaceuticals in the Environment are covered in these draft guidelines that details the aspects to be covered by an environmental risk assessment[92] explains how a PBT[93] assessment must be carried out, sets a list of precautionary and safety measures in case environmental risks cannot be excluded[94] and a proposed labelling aimed at minimising discharge of unused medicine into the environment.

Despite the interlinkages described above, the pharmaceutical authorisation process/authorities are not formally informed when a risk for the environment is identified (e.g., when pharmaceuticals are placed on the priority substances list and or from LUCAS survey[95] monitoring presence of pharmaceuticals in soils). Similarly, when an environmental risk is identified within the authorisation process of a medicinal product this is not communicated to competent authorities that deal with environmental matters. As underlined by the evaluation report of the

[91]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 Brussels, 11.3.2019 COM(2019) 128 final

[92] 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, antibiotics, endocrine active substances

[93] Persistent, bioaccumulative and toxic

[94] Such as appropriate product storage and disposal, appropriate measure regarding the use of medicinal products, appropriate disposal of unused pharmaceuticals

[95]More information on Lucas's survey: https://esdac.jrc.ec.europa.eu/projects/lucas

EU water legislation[96], there is no reference to the Water Framework Directive objectives in the legislation on human medicinal products[97].

- *EU Competition law*

In principle, there is good coherence between the EU competition legislation with its primary objective of protecting consumer welfare and the EU pharmaceutical legislation which seeks to safeguard public health. 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 competitors (e.g. generic / biosimilar companies). Merger controls (and to a lesser extent Articles 101 and 102 TFEU) also provide scope for protecting competition based on innovation (dynamic efficiency). Wider issues are also now being investigated by competition authorities following on from the Commission having identified certain "patent filing" and "disparagement" practices as potentially problematic in its sector inquiry report of 2009[98] and its report on competition law enforcement in the pharmaceutical sector of 2019[99]. These include potentially abusive patent management strategies, and campaigns to disparage other products.

However, room for improvement remains. There are concerns that Euro-American merger control has been too permissive due to a focus on market concentration (a measure of competition around a product) without due regard to industry concentration (a measure of competition within the industry).

Coherence with other EU and international policies

- *Chemicals Strategy for Sustainability Towards a Toxic-Free Environment[100]*

The chemical strategy was published in 2020 as part of the EU's zero pollution ambition a key commitment of the European Green Deal. It contains several actions to be implemented by the Commission. Some of these actions will have an impact on how medicinal products will be authorised produced and used to ensure a toxic-free environment such as to promote the development of safe and sustainable-by-design chemical substances, to implement the principle one substance one assessment with strong coordination between EU regulators (e.g., ECHA, EFSA, EMA) to address the impact on the environment of the production and use of pharmaceuticals in the upcoming pharmaceuticals strategy for Europe and following up the 2019 Strategic Approach to Pharmaceuticals in the Environment. Such objectives and action are not yet reflected in the EU general pharmaceutical legislation that only contains an obligation to carry out an environmental risk assessment and related EMA guidelines adopted in 2006 and currently being revised with a draft published in 2018.

- *EU Action Plan on Antimicrobial Resistance[101]*

The general pharmaceutical legislation is not coherent with the EU Strategy on Antimicrobial Resistance. It currently lacks provisions to launch access to new antimicrobials in most/all European countries; to restrict and optimise the use of antimicrobials; to achieve better labelling of antimicrobial product labels; and to promote the authorisation of new *classes* of antimicrobials (as distinct from new types falling within known classes for which resistance will develop relatively quickly).

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[96] COMMISSION STAFF WORKING DOCUMENT FITNESS CHECK of the Water Framework Directive, Groundwater Directive, Environmental Quality Standards Directive and Floods Directive 2000/60/EC of the European Parliament and of the Council establishing a framework for the Community action in the field of water policy Directive 2006/118/EC of the European Parliament and of the Council on the protection of groundwater against pollution and deterioration Directive 2008/105/EC of the European Parliament and of the Council 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 Directive 2007/60/EC on the assessment and management of flood risks {SEC(2019) 438 final} - {SWD(2019) 440 final}

[97] https://ec.europa.eu/info/sites/default/files/swd_2019_0439_en.pdf

[98] Final Report, Pharmaceutical sector inquiry, European Commission, Competition DG available at: https://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf

[99] REPORT FROM THE COMMISSION TO THE COUNCIL AND THE EUROPEAN PARLIAMENT COMPETITION ENFORCEMENT IN THE PHARMACEUTICAL SECTOR (2009-2017) European competition authorities working together for affordable and innovative medicines, Brussels, 28.1.2019 COM(2019) 17 final available at: https://ec.europa.eu/competition/sectors/pharmaceuticals/report2019/report_en.pdf

[100] COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS Chemicals Strategy for Sustainability Towards a Toxic-Free Environment, Brussels, 14.10.2020 COM (2020) 667 final

[101] Available at: https://ec.europa.eu/health/system/files/2020-01/amr_2017_action-plan_0.pdf

7.5 Annex V. Comparative legal analysis

Summary

1. Fostering Innovation

Country	Description
AUSTRALIA	Priority review pathway for medicines for serious or life-threatening conditions. Provisional approval pathway: medicines that provide promising treatment for serious or life-threatening conditions, while clinical trials are still ongoing.
CANADA	Advanced Therapeutic Pathway: tailored assessment for ATPs without technology-specific requirements and exempting the applicants from certain requirements of the regular procedure. Priority review pathway: for medicines treating serious, life-threatening, or severely debilitating disease or condition.
CHINA	Applicants of novel chemical products, biological products: granted with the protection of their product of interest, which should be developed based on self-generated preclinical and clinical data (except safety data, data disclosed before registration application) on Chinese patient. Annual price negotiation mechanism for novel products to be listed by the basic health insurance program immediately after gaining market entry.
ISRAEL	Psifas Initiative for Precision Medicine: designed to collect health data and biological samples from hundreds of thousands of volunteers establishing a community of participants. The information obtained will accelerate the development of medical care specifically tailored to the Israeli population.
JAPAN	A premium for the development of innovative medicine has been implemented in the price calculation. Targeted total examination period: n/a New medicinal product: 12 months. Orphan medicinal products and specific use medicinal product: 9 months. Pioneering medicinal product: 6 months.
SOUTH KOREA	Research and development fund for innovative drugs: the Ministry of Health and Welfare is entitled to designate companies as innovative companies if they fulfil certain conditions (R&D investment in particular). This status gives priority to R&D projects, tax deductions and preferential treatment in drug prices. Support developers of cutting-edge biotechnologies: regulatory guidelines ensure the quality, safety and efficacy for advanced therapy medicinal products including cell therapy products, stem cell therapy products and gene therapy products.
USA	Various accelerated procedures for serious conditions lacking satisfactory treatments providing significant improvements compared to existing treatments. FDA provides personalised assistance to MAHs in developing drugs for unprofitable or unpatentable drugs for less than 200 000 patients. Application fees can be waived to protect public health, for example for small businesses. It is waived for drugs for a rare disease or condition. Wide margin of appreciation regarding the pricing decisions of MAHs, on the basis of market conditions. This is sometimes defended as a way to enhance innovation. Financial grants are granted for innovation under the Orphan Products Grant Program or via post-approval support for drugs treating a rare disease or condition.

	Market exclusivity rules vary depending on product classification, indication to be treated or the intended patient population or the level of innovation provided by a new drug. Transferrable Priority Review Vouchers can be received or purchased, granting a six-month expedite review procedure to the applicant. They are transferrable unlimitedly.

2. Accessibility and affordability of medicines

Country	Description
AUSTRALIA	A large proportion of registered prescription medicines are supplied under the Pharmaceutical Benefits Scheme (PBS) . Necessary drugs selected by an expert panel are supplied to consumers at a reduced cost due to a subsidy by the Commonwealth (federal) Government.
CANADA	The upcoming Regulations Amending the Patented Medicines Regulations will provide new factors for assessing excessive pricing (price regulatory factors of pharmacoeconomic value, market size and the gross domestic product (GDP) and GDP per capita in Canada). Canada intends to renew its Special Access Programme, which allows healthcare professionals to request medicinal products not authorised in Canada, for treating a patient with a serious or life-threatening condition where conventional treatments have failed, are unsuitable or are not available in Canada.
CHINA	Expensive new products have to go through the price negotiation process before being listed.
ISRAEL	The maximum price of a drug is set based on price in a number of European countries. It is possible that in Israel there will be a significant decrease in the price of a drug close to the date of its patent expiration in European countries, and not necessarily close to the expiration of the patent in Israel. Pharmacists have the authority to provide a generic drug even if it is registered under its trade name unless the doctor has expressly stated otherwise.
JAPAN	For generics, application can be submitted in a simplified form, using the original data from the original application and showing only bioequivalence. Detailed fees are specified according to the type and nature of the medicinal product and the content of the application. Pharmaceutical authorisation and insurance reimbursement are simultaneous. Once authorisation is obtained, the product is almost always reimbursed with a significant advantage for patients
SOUTH KOREA	System of exclusivity for the manufacturer of the first generic drug which successfully challenges the patent covering an original drug and proves bioequivalence. This exclusivity prevents the other generic drug manufacturers to market products for nine months. Bundled approval system for generic drugs: generic products from different companies produced in the same manufacturing site can be approved within the same application. Single healthcare insurance system for the reimbursement of medicinal products, covering almost all the population.
USA	Generic drugs are evaluated under the Abbreviated New Drug Application procedure, and do not require animal or human testing. A Centre for Research on Complex Generics has been established to enhance research collaboration and ensure faster marketing of complex generic drugs. Research exemption (Bolar exemption) allowing pre-authorisation research by competitors during the market exclusivity period of a medicinal product.

3. Regulatory Agility

Country	Description
AUSTRALIA	Australia applies the CHMP and EMEA guidelines for fixed combinations of medicinal products. The Generic Medicines Work-Sharing Initiative promotes the coordinated assessment of generic application files with multiple national agencies that are part of the Access Consortium (Australia, Canada, Singapore, Switzerland, United-Kingdom) Clock-stop mechanism: until a full response to the authority's request for information is submitted.
CANADA	The Ministry of Health has powers to impose terms and conditions and require a risk management plan from MAHs. Pause-the-clock mechanism: for up to 30 business days is provided in Canada.
CHINA	Conditional approval: • Life-saving medicines + critical public health needs + no alternative • Vaccines for the critical outbreak of public health events and other vaccines that are accounted for urgent needs. Rapid evaluation: • New chemical product or new traditional medicines applying for extended indication and changing formulation of the protected traditional medicines; • first application associated with an intractable and critical illness to meet the unmet clinical needs, for critical communicable diseases; • a new product for children and paediatric formulation; • urgently needed vaccines, breakthrough product, and product which meet the criteria for conditional approval. Stop the clock: to provide additional information.
JAPAN	A regulatory sandbox scheme was established in June 2018. When authorising a complex product, an application must be submitted and then the MHLW/PMDA will decide which category the product belongs to, the duration is granted according to the decided category, and there are no measures to extend or grant duration on the basis of a complex product.
USA	Personalised medicines using medicinal products and medical devices are assessed via reinforced cooperation between the respective centres responsible for drugs and medical devices within the FDA. The FDA proposed to regulate the use of artificial intelligence in medical devices' software. 3. A simple rule for combination products: they are reviewed on the basis of their primary mode of action. A "Knowledge-aided assessment and Structured Application" has been implemented using algorithms for risk assessments and computer-assisted analysis of drug applications. The FDA also ensures up-to-date knowledge of its inspectors on new technologies through trainings. Emerging Technology Program: enables the resolution of technical and regulatory issues in the assessment of new manufacturing methods.

4. Safety of supply

Country	Description
AUSTRALIA	Notification of market discontinuation and shortages to the national competent authority is required for registered Prescription Medicine, registered Controlled Drug medicines and OTC medicines included in the Therapeutic Goods Reportable Medicines Determination.

CANADA	In 2021, the Regulations Amending Certain Regulations Concerning Drugs and Medical Devices (Shortages) was adopted to prevent and mitigate shortages of key health products (medicines and medical devices).
CHINA	Comprehensive reforms of streamlining new medicines evaluation and creating efficient process of registration in 2015, have been targeting efficiency improvement and responsive review and regulatory process by resolving the backlog of new medicines evaluation and accelerating the time-to-market of novel medicines.
JAPAN	The marketing authorities are required to inform the MHLW as soon as possible (around two months) if they anticipate a supply shortage and to take appropriate measures, such as cooperation with the industry and relevant suppliers. When an authorised medicinal product is listed, the company is obliged to start manufacturing and sale of the product within three months of the date of listing, and continuously supply to medical institutions.
USA	Strategic National Stockpile of medicines and medical devices to be used in case of public health emergency. Notification of temporary or permanent marketing interruptions must occur at least six months in advance in case of a drug that is life-supporting, life-sustaining or intended for use in the prevention or treatment of a debilitating disease or condition.

4. Quality and safety of medicinal products

Country	Description
CANADA	Since 2019, the entire clinical study reports submitted by applicants and negative decisions about applications for new drug approvals are published and publicly available.
JAPAN	Re-examination system: after a certain period since the approval of a new medicinal product, manufacturers collect data from actual use in medical institutions to reconfirm the approved efficacy and safety. Good Distribution Practice (GDP) guidelines have been issued to prevent counterfeit medicines. All medicinal products are required to have a barcode to enable traceability in distribution to the medical institutions.
USA	The FDA adopted Quality Management Maturity Programs aiming at conducting onsite assessment of facility's quality management system. The final aim of the program is to incentivise investments in quality management through the development of a reward system of mature quality management systems of facilities.

6. Environmental assessment

Country	Description
CHINA	Production application of medicines must provide an Environmental Assessment Report issued by the qualified environmental assessment institutions based on the environmental monitoring data generated by the local environmental protection authorities. Environmental risk assessment is not integrated with the risk-benefit appraisal.
USA	Every application for a drug shall contain an environmental assessment and mitigation plan, to be assessed by the FDA.

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