Impact of the EU's General Pharmaceutical Legislation on Europe's Innovation Ecosystem and Biotechnology Companies

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The conclusions presented in this report are the result of comprehensive research, including independent analysis and a synthesis of aggregated findings from interviews with various companies, venture capital funds and national associations. It is important to note that while these entities provided valuable input, we do not directly quote or attribute specific insights to any individual organisation. Instead, the findings are the collective conclusions drawn by the authors, based on the assimilated information from these interviews.

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Glossary

AMR	Antimicrobial resistance	The development by a disease-causing microorganism of the ability to survive exposure to an agent that was previously an effective treatment
ATMP	Advanced therapy medicinal product	A medicine for human use that is based on genes, tissues or cells
BRG	Better Regulatory Toolbox	Principles that the European Commission follows when preparing new initiatives and proposals and when managing and evaluating existing legislation
CDMO	Contract development and manufacturing organisation	A company that provides comprehensive services to the pharmaceutical industry, encompassing both the development and manufacturing of drugs
CRO	Contract research organisation	A company that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis
EMA	European Medicines Agency	An agency of the European Union in charge of the evaluation and supervision of pharmaceutical products
EU27		The 27 countries of the European Union
FDA	United States Food and Drug Administration	A federal government agency that regulates and ensures the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, national food supply, cosmetics, and products that emit radiation
GPL	General Pharmaceutical Legislation	Proposal for a regulation of the European Parliament laying down procedures for the authorisation and supervision of medicinal products for human use
HUMN	High unmet medical need	An orphan medicinal product is considered as addressing a HUMN when no medicinal product has been authorised to treat a disease or the medicine demonstrates exceptional therapeutic advancement, and in addition, use of the medicine results in a meaningful reduction in disease morbidity or mortality
IPO	Initial public offering	The listing of a privately owned company on a stock exchange, making shares available to the public
MA	Market authorisation	The process of reviewing and assigning the evidence to support a medicinal product
OD	Orphan designation	A status assigned to a medicine intended for use in a rare condition
OME	Orphan market exclusivity	A regulatory incentive that encourages development of drugs in rare diseases by providing a period of market exclusivity (currently set at 10 years in the EU) for approval in these diseases
OMP	Orphan medicinal product	A pharmaceutical agent developed to treat a certain rare medical condition
PE	Private equity	A source of investment capital with a focus on investment in private companies
PIP	Paediatric Investigation Plan	A development plan aimed at ensuring that the necessary data are obtained through studies in children, to support the authorisation of a medicine for children
R&D	Research & development	Activities undertaken by companies to innovate and introduce new products
RDP	Regulatory data protection	A period of data exclusivity (currently set at eight years in the EU) in which a generic applicant cannot refer to innovator's data to obtain marketing authorisation, ensuring an investment return
Regulatory sandbox		A regulatory framework within which it is possible to develop, validate and test in a controlled environment innovative or adapted regulatory solutions that facilitate the development and authorisation of innovative products
SME	Micro-, small- and medium-sized enterprises	Companies with fewer than 250 employees or less than €50 million turnover / €43 million annual balance sheet total
SPC	Supplementary protection certificate	An intellectual property (IP) right that extends the duration of certain rights associated with a patent
TEV	Transfer exclusivity voucher	An incentive to provide a voucher for an additional year of RDP to manufacturers of novel antimicrobials
UMN	Unmet medical need	A condition for which there exists no satisfactory method of diagnosis, prevention or treatment, or in relation to a medicinal product that will be of major therapeutic advantage to those affected
VC	Venture capital	A form of private equity and a type of financing that is focused on providing investment to start-up/small companies

Executive summary

EuropaBio asked Charles River Associates to research the potential impact of the proposed changes included within the EU's General Pharmaceutical Legislation (GPL) to Europe's innovation ecosystem, with a particular focus on its impact on the growth of emerging and small biotechnology companies. The proposal is to revise the pharmaceutical legal framework in the European Union (EU). This includes introducing a new Directive and a new Regulation aimed at modernising and streamlining the current system. These proposals are set to replace the existing general pharmaceutical legislation, namely Directive 2001/83/EC and Regulation (EC) No 726/2004. Additionally, they will reform Regulation (EC) No 1901/2006, which focuses on medicines for children (known as the 'Paediatric Regulation'), and Regulation (EC) No 141/2000, which addresses medicines for rare diseases (referred to as the 'Orphan Regulation'). The research involved a three-phase approach including:

- A literature review of recent government and non-government perspectives in the European pharmaceutical landscape and existing analysis of the proposed GPL
- An analysis of the roles that different tiers of companies play in the development of new medicines, the sources of funding and the role of partnerships
- An interview programme with senior executives from biotechnology companies of different sizes from start-ups to mature, national biotechnology trade associations and key investors in the life science venture capital space

Box 1: Summary of key GPL impact

The EU's General Pharmaceutical Legislation (GPL) proposal does not sufficiently consider the impact on the innovation ecosystem and how its impact may vary by company maturity. The legislation will lead to an increase in uncertainty for biotechnology companies, with effective reductions in protections and unguaranteed late-stage offsets.

Changes to the incentive regime have the potential to alter both innovator and investor decisions, impacting Europe's entire healthcare and innovation ecosystem, and ultimately patients. Increased uncertainty affects the ability of investors to accurately gauge the value of their investment, with a disproportionate impact on emerging and smaller companies. The significant contribution of these companies to the origination development of treatments for rare diseases, including novel technologies such as advanced therapy medicinal products (ATMPs), means this is a risk to the foundation of the innovation ecosystem.

There are some positive changes in the GPL. Streamlining regulatory processes will be beneficial, particularly for emerging, small, and mid-cap biotech companies needing help navigating the complex regulatory system. The focus on addressing antimicrobial resistance is a positive step towards tackling a growing challenge. However, these benefits do not offset the negative elements of the rest of the GPL.

Overall, reduced incentives will only exacerbate the impact of the challenges regarding the market access landscape, decreasing Europe's attractiveness for both investment and novel medicines development, leading ultimately to delay in European patients' access to novel treatments with consequences throughout the biopharmaceutical landscape, compared to patients from other parts of the world.

Reduced baselines and certainty for innovation:

A reduced baseline for regulatory data protection (RDP), with extensions based on a restrictive definition of unmet medical need (UMN), undertaking comparative clinical trials, and continuous supply across Member States, are seen by investors and companies as inherently uncertain, and, therefore, investment decisions by venture capital (VC) and mature biotech will be based on the baseline protections offered, reducing the attractiveness of the entire European landscape. This decrease will result in lower commercial valuations, fewer and reduced investments, and limited collaborations, particularly for smaller innovators and medicines at earlier stages.

The requirement to access and supply in all Member States within two years is beyond the control of companies of any size, with even large companies reporting logistical challenges. Offsets proposed by the European Commission such as the proposed time allowance for micro-, small- and medium-sized enterprises (SMEs) are irrelevant. The criteria for qualifying as an SME are not fit for biotech companies, and many companies outgrow this category before they can even enter the market.

Impact on rare diseases: Changes to the orphan medicine incentives in the GPL, such as the cap on orphan designation (OD) duration, disproportionately affect emerging and small companies. OD is an important enabler for attracting early investment, with a seven-year OD limit increasing investment risk and adding additional barriers to attracting capital. Given the role smaller companies play, this could affect a significant number of patients with rare diseases. The overall result is that the reduced security of OD and decreased perceived certainty regarding exclusivity (discussed above), which are currently seen as an important differentiator for Europe to offset the challenging MA landscape, will decrease the attractiveness of Europe as an R&D hub or market target.

Ecosystem-level impact: Decreased investment across companies of different sizes will have knock-on impacts on translational research, clinical trials and industrial partnerships in addition to regional and biotech cluster development, as the European landscape becomes less attractive for innovation. Changes to incentives which make obtaining capital more challenging for emerging and small companies will reduce the overall European attractiveness to mature companies, reducing collaboration and the transfer of expertise, which has been a driver for Europe's biotech delivery over the previous 30 years. This will harm the innovation cycle, reducing Europe's ability to innovate, accelerating the loss of talent and diminishing economic development.

Europe's progress in biotech innovation: Despite strategic recognition of the importance of biotechnology in Europe, the GPL significantly undermines the ability of European innovators to deliver biotechnology from Europe's own research base and sends a clear global message that Europe has deprioritised innovation for healthcare.

In the worst case, global companies and investors will not consider Europe as a primary or even secondary territory to develop or launch innovative therapies, with reduced partnerships, investment, manufacturing and market authorisations. European innovators will struggle to start up and grow, with partners and investors focusing investment and market authorisation into other regions. Patients will not benefit from clinical trials of therapies developing within Europe and will be later recipients of therapies that have entered markets elsewhere, if and when it becomes economically viable to enter the European market.

The current European innovation ecosystem

The GPL risks further weakening Europe's biotechnology innovation, which has already been diminished due to long-standing challenges in the funding model, despite a strong scientific foundation and historical success.

Europe supports a complex biotech innovation ecosystem, with a significant number of graduates with STEM (science, technology, engineering and mathematics) degrees and world-class universities. However, global competition is intensifying, with China increasing its STEM output and the US acting as a magnet for biotech innovation. The long-standing issue of a weaker venture capital (VC) sector continues to affect the European ecosystem, creating a 'Death Valley' for European biotech companies, exacerbated by the initial public offering (IPO) landscape. As a result, Europe is hosting fewer small biotech companies compared to the US, leading to a research and development (R&D) investment imbalance. There is a danger that the changes in GPL will further tilt the balance against Europe. The experience of Japan, where increasing disincentives for investment – such as price controls, an inflexible regulatory system, faltering investment in basic research and disincentives for internationalisation – led to the shrinking of pharmaceutical development, acts as a cautionary tale for Europe, highlighting the potential for pharmaceutical investments to divert elsewhere, such as the US, which offers a more attractive market for initial product launches due to its unified pricing, reward for innovation, reimbursement system and larger market size.

The impact of key elements of the GPL

Benefits from regulatory streamlining are outweighed by increased risks, particularly to emerging and small biotech, from changes on orphan medicines, regulatory data protection and classification of 'high unmet medical need' (HUMN).

Orphan designation (OD) plays an important role within the European innovation ecosystem, as it provides a signal of the potential value of a product to investors. The proposals within the GPL reduce designation duration to seven years. The Commission's Impact Assessment does not consider the impact on different types of companies. This is important as the time from OD to market authorisation (MA) varies by product and company size, notably taking longer for smaller companies and transferred products – longer than the Commission's proposed OD cut-off, at seven years on average and in some cases significantly longer. An artificial seven-year time constraint where none previously existed could impact investment and partnering decisions. Apart from investors and biotech corporations, the suggested duration constraint on OD could potentially impact patients, with up to 1.9 million individuals with rare diseases possibly being affected over a five-year period.

The proposal's conditions of the orphan market exclusivity (OME) extension would also impact smaller companies. The length of orphan medicinal product (OMP) exclusivity – a period when similar medicines for the same indication cannot be placed on the market – is seen as an important differentiator for Europe. This provides a competitive edge over the more-limited exclusivity period offered in the US, mitigating the more challenging market access landscape in Europe. Interviews with VC highlight that the choice to invest in a small company developing orphan medicines typically occurs during late phase I or early phase II. This is, on average, close to seven years prior to launch, based on the length of time it takes for a medicine to reach MA from initial OD. Given this time period, it will be challenging for investors to predict whether certain conditions will be met; for example, whether the products will be launched in most markets, the results of clinical trials, or whether they will be adjudged to address HUMN (as illustrated by the majority of OMPs changing indication from initial OD to MA). The modulation of incentives at launch will therefore be seen as uncertain, resulting in investors focusing on the baseline.

Regulatory data protection (RDP) embodies a critical incentive that underpins the financial viability and attractiveness of biopharmaceutical investments. RDP provides manufacturers with a period of protection for their novel therapeutics during which competitors are prohibited

from using the required preclinical and clinic data submitted to regulatory authorities for approval of competitors. This is particularly important for medicines with long development timelines, which face expiration of their patent protection soon after MA, such as ATMPs. As shown in our research, small companies are responsible for much of the early R&D into ATMPs, meaning they will be the most disadvantaged by this change. Furthermore, this will affect particularly challenging conditions. The importance of RDP is intricately linked with the clinical trials process. Enrolling patients in clinical trials (CTs), especially for challenging conditions like cancer and Alzheimer's disease, can be a prolonged and difficult process. This extended duration is a significant challenge for emerging and small companies, which may rely heavily on RDP to maintain a competitive edge. Therefore, assuming the clinical trials environment in the European Union (EU) does not improve, more small biotech companies will find themselves increasingly dependent on RDP. This situation could lead to a decrease in the development of innovative therapies, particularly affecting areas where there is a high need for new treatments. As in OME, modulation of RDP incentives may be possible for some market participants but not smaller biotech. The Commission envisages that companies will be rewarded with longer exclusivity if a product were to launch in all Member States. SME are given longer to comply with this condition. However, the longer period allowed for SMEs as per the Commissions definition is irrelevant – mainly because these companies grow out of the SME definition by the time they commercialise medicines, and the proposals make no allowance for the true barriers affecting most emerging and small companies. In all, the increased uncertainty will reduce the attractiveness of investing in innovators developing novel medications in the EU, who in turn will continue to look at other regions.

The proposed changes to streamline the governance and committee structure of the European Medicines Agency (EMA), along with changes that put additional caps on approval duration, were welcomed by those in the interview programme. However, it was recognised that the EMA has been falling behind other regulatory agencies, and more needs to be done to make the regulatory process competitive. The quicker approval timeline and more straightforward decision-making process proposed in the GPL could lower barriers to market entry, making the pathway to approval less cumbersome. These adjustments will benefit the pharmaceutical industry at large, but particularly small and mid-cap companies as regulatory delays are common and can cause significant delays and high costs. The regulatory process is integral for emerging and small companies, but EU's regulatory process is longer compared to other regions, particularly in median approval time, which was 285 days longer in the EMA vs the US Food and Drug Administration (FDA). The current EMA expedited review pathways are not sufficient to accelerate access for priority medicines. In the EU, only 9% of new active substances were approved through expedited review in 2021. This is in comparison to 71% of new active substances in the US and 45% in Japan. Additionally, there are fewer medicines eligible for any type of expedited review, 68 (41%) in the EMA vs 127 (60%) in the FDA between 2018 and 2021. The move to consolidate EMA committees will aid this process slightly, but it is important to recognise that specialisation within the committee will be key, to ensure that high standards for new medicines are maintained, but this will still require the EMA to be adequately resourced if it is to achieve a significant reduction in the timeline for expedited reviews.

The Commission's new incentive for antimicrobials is important for emerging and small companies. This was reinforced through interviews: if implemented, the new incentive would bring predictability and reward for investment. However, small or emerging companies highlight that although they play a disproportionately active role in the space of antimicrobial research, antimicrobial research was only an issue for a small proportion of emerging and small companies. This therefore does not offset the worsening of the overall environment that would result from the GPL.

Impact on the European innovation ecosystem

Disrupting the innovation cycle and limiting patient access to novel treatments is perceived as clear signal that EU policymakers are deprioritising innovation in the biopharmaceutical sector. This undermines Europe's strong historical efforts to build and retain critical mass in skills, infrastructure, employment and economic development that underpins resilience of healthcare provision, economic performance and capacity to respond to crises, including pandemics.

The biotech innovation landscape in Europe is falling behind, and the proposed GPL will only worsen the environment for emerging and small biotech companies, which have not been sufficiently considered in the development of the GPL to date. In particular, the GPL will lead to additional uncertainty, diminishing commercial value, and hindering investment prospects, especially in the orphan and ATMP space where small and mid-cap companies are pivotal innovators.

The current European innovation cycle is built on small biotech originators funded through VC investment; these companies subsequently partner with mature biopharma. In turn, mature companies commercialise the medicine and use the resulting profits to fund innovation in emerging and small biotech. The changes proposed in the GPL will damage this innovative cycle.

Reductions in investment and the greater development of innovative companies in other regions can be seen as primarily a commercial or an economic issue. However, ultimately, this affects patients. Fewer medicines will be developed in Europe, and development of those will take considerably longer in an already fragmented European landscape. Reduced innovation will also negatively impact clinical trial participation and the positive spillovers that these trials deliver to healthcare systems by enhancing clinical capacity, capabilities and patient access. Ultimately, these changes, combined with existing trends, could lead to a transition where Europe is not competing globally as a key location to launch new medicines impacting patient access to innovative therapies, but is seen as a follower, with launches after the US and other global markets that are more receptive to innovation. Finally, the proposals are already negatively affecting the perception of European policy as fostering the innovation ecosystem. Although intangible, the degree to which the proposals diminish innovator and investor confidence could be the largest and most immediate repercussion of the proposal for the European innovation ecosystem, with consequences felt even before the implementation of the final legislation.

1. Introduction

Charles River Associates ('CRA') was commissioned by EuropaBio to examine the potential effects of changes to the existing pharmaceutical legislation, as proposed in the General Pharmaceutical Legislation (GPL), on the growth of emerging and small biotech companies in Europe and the implications for policy proposals.

1.1. The proposed changes in the General Pharmaceutical Legislation

The European Commission (the Commission) is proposing the most significant changes to the regulatory framework for pharmaceutical in the last 20 years.

The proposed GPL sets out to revise and consolidate the existing regulatory rules, primarily merging EMA Regulation No. 726/2004, OMP Regulation No. 141/2000, and Paediatric Regulation No. 1901/2006, and amending Pharmaceutical Directive No. 83/2001.[1] The proposal has been in development since June 2016 and was officially published in April 2023. 'Back-to-back' evaluations and impact assessments were carried out by the Commission and external partners, including the Technopolis Group, Copenhagen Economics and Ecorys, to develop these proposals.[2] The main proposals can be summarised as follows:

- Streamlining regulatory processes by cutting some repetitive and redundant processes that therapies need to go through to reach approval.
- Changes to the orphan medicines incentives to decrease the duration of orphan designation (OD) validity to seven years from a previously unlimited time frame, and a baseline decrease in orphan market exclusivity (OME) with additional years that can be added if particular criteria are met, such as but not limited to addressing 'high unmet medical need' (HUMN) and launching in all Member States.
- Changes in regulatory data protection (RDP) to provide greater incentives for generics manufactures while balancing incentives for innovative manufactures by decreasing the baseline RDP from eight to six years, introducing RDP modulation through launch requirements, and an additional incentive for indications addressing 'unmet medical need' (UMN).
- A new incentive for novel antibiotics through a transfer exclusivity voucher (TEV) which can be applied or sold to another company for an additional year of RDP on a selected product.
- Proposed measures to increase transparency of R&D funding, to improve understanding of private and public financing of new medicinal products. The relationship to the national price and reimbursement (P&R) process has not been made fully clear in the proposal; in particular, the requirement to submit "public funding" information, the specification as to source, and how this impacts national P&R decisions across Members States remain unclear.

1 European Commission (2023). Reform of the EU pharmaceutical legislation. Available at https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en

2. External studies included: – Study in support of the evaluation and impact assessment of the general pharmaceutical legislation. Evaluation Report, Technopolis Group (2022). – Study in support of the evaluation and impact assessment of the general pharmaceutical legislation. Impact Assessment Report, Technopolis Group (2022). – Future-proofing pharmaceutical legislation – Study on medicine shortages, Technopolis Group (2021). – Study to support the evaluation of the EU Orphan Regulation, Technopolis Group and Ecorys (2019). – Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe, Copenhagen Economics (2018). – Study on the economic impact of the Paediatric Regulation, including its rewards and incentives, Technopolis Group and Ecorys (2016).

Since the document's initial publication by the Commission, it has undergone a series of reviews by the rapporteurs within the European Parliament. This has included suggested amendments affecting the TEV for novel antibiotics and the regulatory 'sandbox' that are generally considered to be the clearest pro-innovation instruments to the legislation. Changes also include an increase from the Commission's proposed RDP baseline of six years to nine years (currently eight years), removal of the linkage between RDP and access, and a deletion of the Bolar exemption extension beyond marketing approval such as the use of studies and trials to generate data for Health Technology Assessments (HTAs) and the Pricing & Reimbursement (P&R) process. Amendments also include an additional 12-month Supplementary Protection Certificate (SPC) extension for Paediatric Investigation Plans (PIPs) that target a disease different from the intended target in the adult population.[3] These proposed amendments were published alongside other access and regulatory changes. As the Commission has officially published the proposal, it is now up to the co-legislators (Parliament and Council) to reach a consensus, meaning we will likely see additional changes to the GPL before its adoption.

There is a prevailing concern that the current proposal does not adequately recognise the impact it will have on emerging and small biotech companies. In fact, the Parliament Initial Appraisal of the European Commission Impact Assessment highlighted that micro-, small- and medium-sized enterprises (SMEs) were not sufficiently consulted in the writing of the document, and the impact assessment did not follow BRG tool #23 – the 'SME TEST'.[4] In interviews with SMEs, many highlighted that although there were some limited opportunities to participate in consultations, there was a restricted ability to provide input.

The evidence on the impact on the innovation ecosystem is also lacking. For example, when it comes to the RDP modulation, the Commission did not consult Member States' health authorities, nor did any scenario planning (or hypothetical test cases) to assess the ability of (i) small biotech companies to launch and make their product available across EU27 within two years of EMA approval, or (ii) national health authorities to properly administer the expected increase in P&R filing and review activity.

Overall, the impact of the proposed legislative changes on the emerging and small biotech business model has received little attention. Although recent reports have highlighted the impact on financial decisions made by biopharmaceutical companies, regarding both investment and launch decisions,[5] the role that these changes will have on the broader innovation and investment ecosystem across company sizes is still lacking. This report aims to test if aspects of the proposed changes to the pharmaceutical legislation would significantly impact these companies and the overall biotech ecosystem and determine what actions policymakers can take to ensure that the biotech industry thrives and expands in Europe.

In this report, the terms "Europe" or "European" are used to refer to the countries in European Union (EU).

3 European Parliament (2023). Draft Rapporteur report on the Commission's reform of the European pharmaceutical legislation. Available at https://www.europarl.europa.eu/doceo/document/ENVI-PR-753470_EN.pdf

4 European Parliament (2023). Initial appraisal of a European Commission Impact: Revision of the EU pharmaceutical legislation. Available at https://www.europarl.europa.eu/RegData/etudes/BRIE/2023/747464/EPRS_BRI(2023)747464_EN.pdf

5 EFPIA / Dolon (2023). Revision of the General Pharmaceutical Legislation: Impact Assessment of European Commission and EFPIA proposals. Available at https://efpia.eu/media/cm2jbsjx/revision-of-the-general-pharmaceutical-legislation-impact-assessment-of-european-commission-and-efpia-proposals.pdf

1.2. Definition of emerging and small biotech companies

The biotechnology innovation ecosystem is dynamic, encompassing companies of various sizes from start-ups with highly novel modalities or disease focus through to mature companies with global reach and multiple products in the market. They all play a crucial and inter-connected role in developing new therapies. This role is a key segment of the innovation ecosystem as defined by the International Development Innovation Alliance (IDIA).

Box 2: IDIA definition of an innovation ecosystem[6]

"An innovation ecosystem is made up of enabling policies and regulations, accessibility of finance, informed human capital, supportive research, markets, energy, transport and communications infrastructure, a culture supportive of innovation and entrepreneurship, and networking assets, which together support productive relationships between different actors and other parts of the ecosystem."

This report will focus on understanding the GPL in the context of an interconnected system, adopting an ecosystems approach focused on the following tenets:[7]

- An innovative ecosystem is made up of a range of different actors which are all interconnected.
- Effective operation of the ecosystem requires all actors to support one another in executing their function.
- Changes in one segment of the ecosystem will ripple into all other segments and cannot be evaluated in a vacuum.

The interconnectedness of the innovation ecosystem needs to be taken into account. Changes in the investment priorities of venture capital (VC) and mature biotech affect smaller companies looking for investment. Larger companies looking to augment their portfolios will be affected downstream of this change as there will be fewer early-stage projects that are supported. If there are fewer projects being supported by VC, this will in turn impact the number of therapies being commercialised.

To assess the potential impact of proposed changes to the GPL we need to consider if the impact depends on a company's size and maturity. The Commission's definition of SMEs is not specific to the life sciences industry and is not appropriate for understanding development and growth of biotechnology companies. The definition does not allow for differentiation between different types of companies as they evolve.[8] Specifically, long timelines to reach market for novel biotechnology products, significant investment required, and complexity of development mean that most biotechnology companies will exceed the SME definition before they are able

6 IDIA. What is an Innovation Ecosystem? Available at https://www.idiainnovation.org/what-is-an-innovation-ecosystem

7 IDIA. What is an Innovation Ecosystem? Available at https://www.idiainnovation.org/what-is-an-innovation-ecosystem

8 The current SME definition is based on purely quantitative criteria, such as employee count and financial thresholds. Since these financial thresholds have remained unchanged since 2005, companies have been excluded from European SME policy purely due to inflation. Available at https://english.bdi.eu/article/news/future-proofing-the-european-definition-of-smes/

to gain market authorisation for a single product.[9,10] For this reason, a novel company categorisation has been developed specific to the biotech ecosystem based on a range of parameters, including number of employees and balance sheet value, but also the product development phase included in their pipeline or the number of products launched on the market, which determine financial resources (Table 1). This builds upon previous proposals, such as the Commission's definition of SMEs and the European Investment Bank's (EIB) definition of mid-cap companies.[11,12]

Table 1: Definition of companies by tier

Tier	Definition
Tier 1: Emerging biotech companies	Emerging biotech companies align with the Commission's defined SME criteria at levels of SMEs: micro (less than 10 employees and €2m revenues) and small (less than 50 employees and €10m revenues).[11] These companies do not yet have a marketed product but are in the process of developing one or more therapies. This includes small companies like start-ups working on their first drug. Their prospects are uncertain until they grow (potentially the next wave of mature companies), and they heavily depend on external funding to conduct R&D activities.
Tier 2: Small biotech companies	Small biotech companies align with the Commission's defined criteria for medium-sized SMEs (e.g., less than 250 employees); however, they may not meet all the Commission's defined criteria (e.g., annual turnover of less than €50m or a balance sheet total of less than €43m). This tier comprises smaller companies that have successfully advanced a drug to late-stage clinical development (Phase II or Phase III clinical trials) but have not yet launched a product on the market or are at the point of receiving marketing authorisation (MA). These companies typically operate with fewer resources and a smaller development pipeline compared to Tier 3 companies. Their geographic presence is usually limited, and they might be concentrating on a specialised area of medicine. Furthermore, they are likely to be reliant on external funding.
Tier 3: Mid-cap biotech companies	Mid-cap biotech companies do not meet the defined SME criteria but may fall under the European Investment Bank (EIB) definition of mid-cap companies (e.g., 250–3,000 employees).[12] These are companies that have at least one marketed product which generates steady

9 Forbes (2023). To Succeed, Biotech Startups Need More Strategic Support. Available at https://www.forbes.com/sites/forbesfinancecouncil/2023/11/27/to-succeed-biotech-startups-need-more-strategic-support/?sh=7420bc93433e

10 Making the leap from R&D to fully integrated biotech for first launch (2023). Available at https://www.mckinsey.com/industries/life-sciences/our-insights/making-the-leap-from-r-and-d-to-fully-integrated-biotech-for-first-launch

11 European Commission SME definition. Available at https://single-market-economy.ec.europa.eu/smes/sme-definition_en

12 European Investment Bank, SMEs and mid-caps. Available at https://www.eib.org/en/about/priorities/sme/index#:~:text=micro%2Denterprises%20(0%2D9,250%2D3%20000%20employees*)

	revenues. However, they are not yet on the scale of larger multinational biotech/pharmaceutical companies in terms of the size of the pipeline/portfolio and revenues. They might have a few products in various stages of development and a smaller global or regional presence. They primarily fund R&D activities from their own company revenues.
Tier 4: **Mature biotech companies**	Mature biotech companies have a global presence and a robust product portfolio, including multiple marketed products that generate substantial revenues. They do not fall under the SME or mid-cap definitions. They largely fund R&D activities from their company revenues and might also collaborate with other companies or institutions.

1.3. Our approach

To understand the current European pharmaceutical landscape, the current challenges biotech companies are facing, and whether the proposed legislation will remedy or exacerbate these issues, our research involved three key steps:

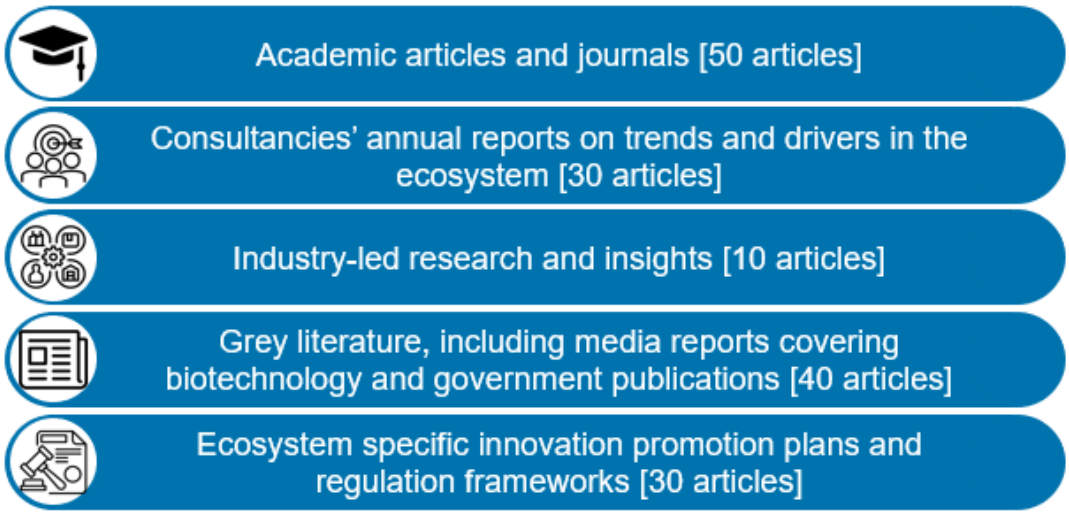
- A literature review of recent government and non-government perspectives in the European biopharmaceutical landscape and existing analysis of the proposed GPL
- An analysis of the role that different tiers of companies play in the development of new medicines, the sources of funding and the role of partnerships
- An interview programme with senior executives from biopharmaceutical companies of diverse sizes, national biotechnology industry associations and key investors in the life science VC space

1.3.1. Literature review

The literature included academic and governmental policy reports, non-governmental organisation (NGO) publications and grey literature. We focused on how the regulatory and investment landscape has changed in the last 10 years, specifically on the recovery of the ecosystem following the COVID-19 pandemic. The search used combinations of the following key terms such as "general pharmaceutical legislation", "biotech innovation ecosystem", and "SMEs".[13] Following this review was a more targeted approach to how companies of specific tiers are impacted by the current pharmaceutical regulations and how the wider environment will react to the proposed changes.

13 Other key search terms include but are not limited to "Foreign direct investment in European pharmaceuticals", "Regional variation in pharmaceutical R&D spending", "Europe's position in the global pharma landscape", "Comparative study of pharmaceutical innovation policies", "SMEs in the global pharmaceutical industry", "Regulatory impact on global pharmaceutical investments", "Comparative analysis of pharmaceutical regulations in Europe and other regions", "Pharmaceutical partnerships in Europe", "Impact of pharmaceutical regulations on SMEs", "Pharmaceutical industry regulations Europe", amongst others.

Figure 1: Review of literature considered



1.3.2. Data analysis

Alongside the literature review, quantitative data was analysed to understand historical investment and regulatory patterns for key medicines in Europe and in other regions such as the US and China. The data was sourced from open-access and subscription-based databases from regulatory agencies, including the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), government and expert reports and industry-published statistics. The data was validated and quality checked with relevant experts where possible prior to incorporation into the analysis. The data included a range of indicators on the performance of the current European pharmaceutical landscape, including:

- Investment from VC and factors affecting investment.
- The use and corresponding timing of regulatory instruments, for example:
    - Time to market authorisation (MA), from OD approval to assessment, investigating if there is a notable difference between company tiers and impact of changes in the length of designation period.
    - Stage of development prior to OD (no clinical trial, clinical trial in process, clinical trial finalised). The aim was to investigate the number of products that remain in the development phase and ascertain the significance of securing OD in obtaining additional funding to advance through development stages.
- The nature of partnerships – in terms of changes in drug licensing, partnerships, and OD transfers prior to Market Authorisation.

1.3.3. Interview programme

To gain an understanding of the GPL's impact on emerging and small biotech companies and on the innovation ecosystem, we interviewed representatives across different company tiers and geographies, key associations at the national level, and individuals working in VC.

The purpose of these interviews was to

- Understand the main concerns around R&D funding and the innovation ecosystem in Europe today
- Clarify the extent to which interviewees were aware of the GPL, and record their views
- Explore the potential impact of the GPL across a set of elements and company tiers

The range of stakeholders allowed for a comprehensive review across the innovation ecosystem and of how different stakeholders work together. National-level SME platforms and biotech associations were also interviewed to understand the impact of the proposals in the context of country-specific characteristics. Finally, we spoke with individuals working in VC who are key investors in early-stage companies and therefore have a fundamental role in funding emerging and small biotech companies and the path by with they grow, and consequently have a unique perspective on the impact on smaller companies.

The interviews included a review of the current landscape, and an examination of how specific changes in the GPL will impact operations in the future. In total, 38 one-hour interviews were conducted between June and October 2023.

Table 2 provides a summary of the stakeholders interviewed. Insights from the interviews were used to inform the report, but views and comments are not attributed to individual companies.

Table 2: Stakeholder Interviewed

Stakeholder Group	Stakeholder
Industry: Emerging	Priovant Therapeutics, Matisse Pharmaceuticals, SwiftPharma, TheraCell
Industry: Small	BioArctic, Calliditas Therapeutics, EryDel, Flamingo Therapeutics, Neogene Therapeutics, UNION Therapeutics
Industry: Mid-cap	Galapagos, PTC Therapeutics
Industry: Mature	BioMarin, CSL Behring, Cytiva, J&J, Novartis, Pfizer, Vertex
National association	AseBio (Spain), Assobiotec (Italy), Bio Deutschland (Germany), BioForum (Poland), Deutsche Industrievereinigung Biotechnologie (DIB, Germany), BioPharmaChem (Ireland), Finnish Bioindustries, France Biotech, Health & Life Sciences Cluster (Bulgaria), HollandBio, SwedenBIO, Swiss Biotech Association
Venture capital	Forbion, Indaco Sgr, Panakes, Novatis Venture Fund, Novo Holdings, Sofinnova Partners, TVM Capital

The interviews provided nuance and insight into the factors affecting the development and launch of new pharmaceuticals as well as the considerations that influence investment decisions. Particular attention was paid to how stakeholders view the European pharmaceutical market versus other regions, and how that perspective is evolving with the potential introduction of new regulations within the GPL.

The insights from these discussions are drawn upon throughout the report. Information from the public domain is combined with aggregate findings from the literature review, data analysis and interview program, to inform and validate our perspectives.

1.4. Structure of the report

The structure of the rest of the report is as follows:

- Chapter 2 examines the current state of the biotech innovation ecosystem in Europe and considers what we know about different factors that influence a company's opportunity to grow.
- Chapter 3 assesses the impact of proposed changes in the GPL on emerging and small biotech companies.
- Chapter 4 discusses the implications of this analysis on the innovation ecosystem in Europe.

2. The European innovation ecosystem

In evaluating the potential impact of proposed changes on the biotech sector, it is important to start with how the innovation ecosystem operates today. This ecosystem is a complex network of different stakeholders, each crucial in driving innovation, from initial scientific discoveries to marketed products.

There are worrying signs that Europe's performance as a hub for the biotech sector is declining, as evidenced by the geographical distribution of biotech companies. Available data suggest that just under a quarter (24%) of new biotech enterprises established between 2018 and 2020 originated in Europe. This proportion is substantially lower compared to the prevalence of new biotech companies in the US, which accounted for a dominant 65% share during the same time frame.[14]

In this chapter, we briefly review the scientific, financial and collaborative frameworks that are the foundations of the biotech sector (and which could be affected by the introduction of the GPL).

Summary

To assess the impact of the General Pharmaceutical Legislation (GPL), we need to recognise that Europe's innovation ecosystem is already at risk of losing out to other global regions. Biotechnology investment is expensive, long term and high risk. Investors constantly weigh up opportunities based on relative attractiveness and commercial potential.

The European science base is a key strength of the European innovation ecosystem due to its substantial number of STEM graduates and the strength of university research capabilities. However, this is not the sole indicator for innovation success. In other regions, notably the US, there are closer academic/industry interactions; more universities are drivers of commercial R&D, with more spin-offs. There is a perception that Europe's historical advantage in R&D is a declining driver of investment partnerships, and this reflects a weaker innovation ecosystem.

Funding for emerging and early-stage biotechnology companies is divided across multiple stakeholders, including public and charitable grants. A key investment source is private equity (PE) specifically VC. The global VC investment ecosystem has seen a decrease in recent years, but while other regions have seen recovery, Europe, specifically the EU27, has not seen the same trend. The challenges are mirrored in terms of data on partnerships between emerging/small biotech and mature biotech, where R&D investment is flowing out of the EU in comparison to the historic inflow. This is exemplified in the data on the number of IPOs being undertaken in Europe.

2.1. The European science base

The European science base is broadly recognised as a key strength in the European innovation ecosystem. According to the most recent UNESCO data from 2022, the percentage of students with STEM (Science, Technology, Engineering and Mathematics) degrees is 36% in Germany, 25% in France and 23% in Spain.[15] This leads the US, which was at less than 20% in 2022. Although comparable data is not available for China as the nation uses a relatively broad

14 McKinsey and Company (2023) Europe's Bio Revolution: Biological innovations for complex problems. Available at https://www.mckinsey.com/industries/life-sciences/our-insights/europes-bio-revolution-biological-innovations-for-complex-problems

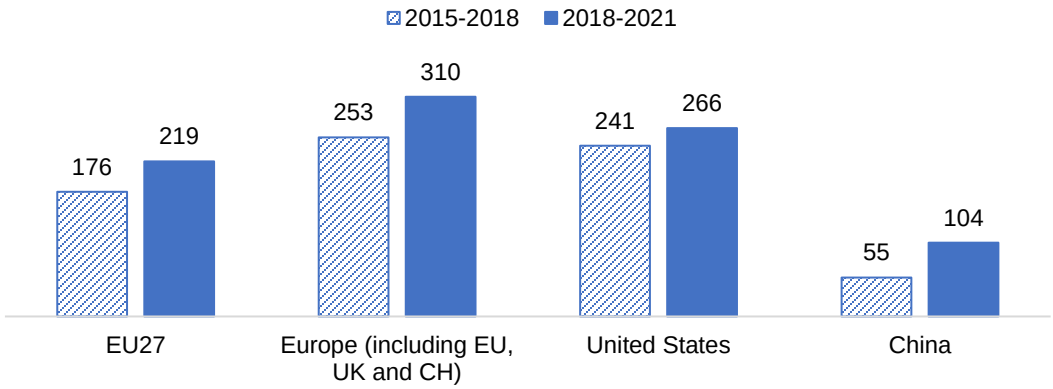
15 UNESCO Institute for Statistics

definition of STEM,[16] the Centre for Security and Emerging Technology (CSET) found that China has consistently produced more STEM doctorates than the US since the mid-2000s, with a projected 77,000 STEM PhD graduates in China per year by 2025 vs 40,000 in the US.[17] The expertise and innovation of these graduates are critical as they constitute the core of the biotech innovation landscape.

Additionally, the presence of leading life sciences universities is crucial for nurturing academic excellence and promoting a culture of R&D. The volume of scientific publications from these institutions is a measure of scientific activity, and often a precursor to innovative breakthroughs in the biotech sector. European universities stand out as global leaders, particularly in the life sciences. Europe is home to 39 of the top 100 life science universities in the world.[18] In the most recent available CWTS Leiden ranking, Europe leads the US and China regarding both volume and quality of research in biological science.[19] However, narrowing this down to the EU alone, the US begins to pull ahead, suggesting that a significant proportion of the academic excellence in Europe is concentrated outside of the EU (

Figure 2).

Figure 2: Total number of biomedical publications in the top 10% cited by region (thousands)



Source: CRA analysis (2023), CWTS Leiden Ranking (2023)

2.2. Funding for innovation

For companies to grow and continue the development of their innovative assets, they need to be able to attract funding. Emerging biotech companies often are required to progress through several stages of funding, tied to specific operations such as product development, clinical trials funding and launch planning.

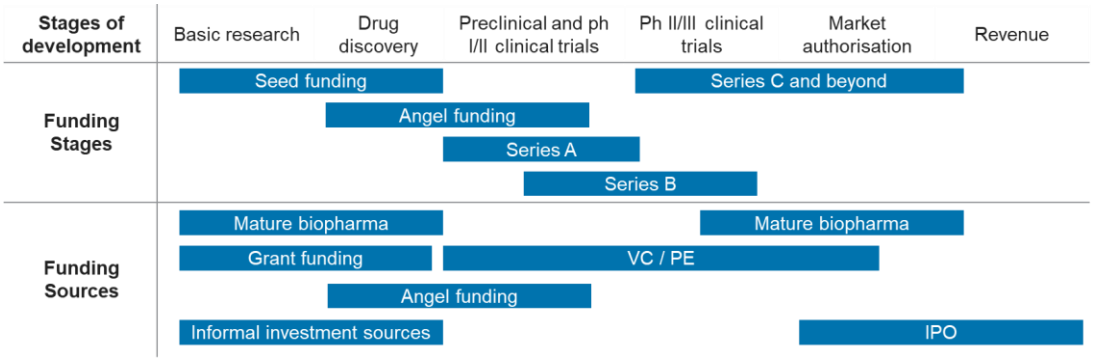
16 Buchholz, K. "Which countries' students are getting most involved in STEM?" World Economic Forum. Available at www.weforum.org/agenda/2023/03/which-countries-students-are-getting-most-involved-in-stem/

17 Zwetsloot, R., Corrigan, J., Weinstein, E., Peterson, D., Gehlhaus, D. and Fedasiuk, R. "China is Fast Outpacing U.S. STEM PhD Growth" (2023). Center for Security and Emerging Technology. Available at https://cset.georgetown.edu/publication/china-is-fast-outpacing-u-s-stem-phd-growth/

18 Times World University Ranking (2023). Available at https://www.timeshighereducation.com/world-university-rankings/2023/subject-ranking/life-sciences#!/length/-1/sort_by/rank/sort_order/asc/cols/stats

19 Leiden Ranking (2023). CWTS. Available at https://www.leidenranking.com/ranking/2023/list

Figure 3: Funding stage and source by emerging biotech development stage



Source: CRA assessment of the funding landscape based on stakeholder interviews

Funding stages are segmented to allow investors from VC and Private Equity (PE) to mature pharmaceutical companies and even the public via initial public offerings (IPOs) (

Figure 3):[20,21]

- *Seed stage:* This is the first stage emerging companies go through and relies on a small initial investment to complete proof of concept/early research.
- *Pre-clinical/angel funding:* Funds are raised in this stage for preclinical R&D and this is often supported by government grants or individual "angel" investors.
- *Early-stage financing (series A):* This is the stage where most VCs begin to be involved. This stage centres around the initiation of clinical trials, building laboratory infrastructure and further development.
- *Late-stage financing (series B):* Biotech companies require substantial funding to progress through clinical trials; this funding is often tied to progression through phase II trials and building infrastructure for potential commercialisation. The funding is often provided by VC, although some mature pharmaceutical companies will also begin to partner with emerging and small biotech companies in this stage.
- *Late-stage financing (series C and beyond):* Each stage in the series denotes a new round of funding. Late-stage financing is connected to late-stage clinical development including large-scale phase III trials and commercialisation/investment into R&D for a new asset. Venture capital, private equity and mature pharmaceutical companies are common participants in this stage.
- *Strategic partnerships, licensing deals and IPO*: During late-stage financing, many biotech companies may choose to pay out their initial investors (exit), allow another organisation to take over the asset they have been developing, or open up public investment.

20 Kang, H. (2018). "A Start-Up's R&D Stages and the Evolution of Financing Sources: Evidence from the Biotechnology Industry". *Entrepreneurship Research Journal.* Available at https://www.degruyter.com/document/doi/10.1515/erj-2017-0159/html

21 Interviews with biotech stakeholders

2.2.1. Venture capital funding

Europe has historically competed globally with the US and China regarding angel investment, early funding, and early-stage partnerships as a share of their investment ecosystem.[22,23] However, there is growing concern regarding the availability of funding in Europe for late-stage clinical development where VC and PE play an important role. VC investments in biopharmaceuticals have shown a recent global decline, with European funding decreasing to a greater extent than funding in the US and China. The inability of European companies to access VC funding to the same extent as similar companies in the US is not new, and many have identified this weakness in the European innovative ecosystem, but the concern is that this problem is getting worse.[24,25,26,27,28,29]

When comparing the first quarter of 2023 to the same period in 2021 of global VC deals in life sciences, there is a striking 70% decline in global VC investments.[30] The decline in VC investment is particularly pronounced in Europe, especially for series B and C funding, where the VC sector is smaller, less mature, and more fragmented. Adjusting for differences in the size of the economy, there is an approximate eightfold difference between the availability of VC funding in Europe and the US.[31] Comparing deal value in 2022, the sum of deals originating from UK- and Switzerland-based VC are equivalent to ~82% of the EU27's total value.[32] While declining, the amount of VC investment drawn by the US is still notably higher overall compared to Europe, both in absolute terms – with the US figure over three times that of the EU27 – and as a relative change from pre-pandemic investment.[33] As evident in Figure 4, in addition to lagging the US in the value of VC funding, the EU also lags behind the US in regard to the number of deals completed, with a threefold difference between the two regions.

22 CRA analysis of Global Data Investment Tracker (2023)

23 McKinsey and Company (2021). Can European biotechs achieve greater scale in a fragmented landscape? Available at https://www.mckinsey.com/industries/life-sciences/our-insights/can-european-biotechs-achieve-greater-scale-in-a-fragmented-landscape

24 EY (2023). Beyond Borders: EY Biotechnology Report. Available at https://www.ey.com/en_us/life-sciences/beyond-borders

25 McKinsey and Company (2022). How the European biotech sector can navigate turbulent times. Available at https://www.mckinsey.com/industries/life-sciences/our-insights/how-the-european-biotech-sector-can-navigate-turbulent-times

26 McKinsey and Company (2021). Capital landscape for European biotechs is maturing, but it continues to trail the United States. Available at https://www.mckinsey.com/industries/life-sciences/our-insights/infographic-capital-landscape-for-european-biotechs-is-maturing-but-it-continues-to-trail-the-united-states

27 EFPIA and Charles River Associates. Access to finance and barriers to growth in the innovative biopharmaceuticals sector. Available at https://www.efpia.eu/media/24995/access-to-finance-and-barriers-to-growth-in-the-innovative-biopharmaceuticals-sector-may-2015.pdf

28 Politico (2023). The real reason Europe's medicines industry is dying. Available at https://www.politico.eu/article/europe-medicines-industry-dying-pharma/

29 Life Science Acceleration Alliance (2023). The importance of venture capital in Europe's life science ecosystem. Available at https://static1.squarespace.com/static/60f1b323d27a3027d5f158e5/t/63e134645f4c597312c8b024/1675703396550/LSAA_VC+REPORT_FINAL.pdf

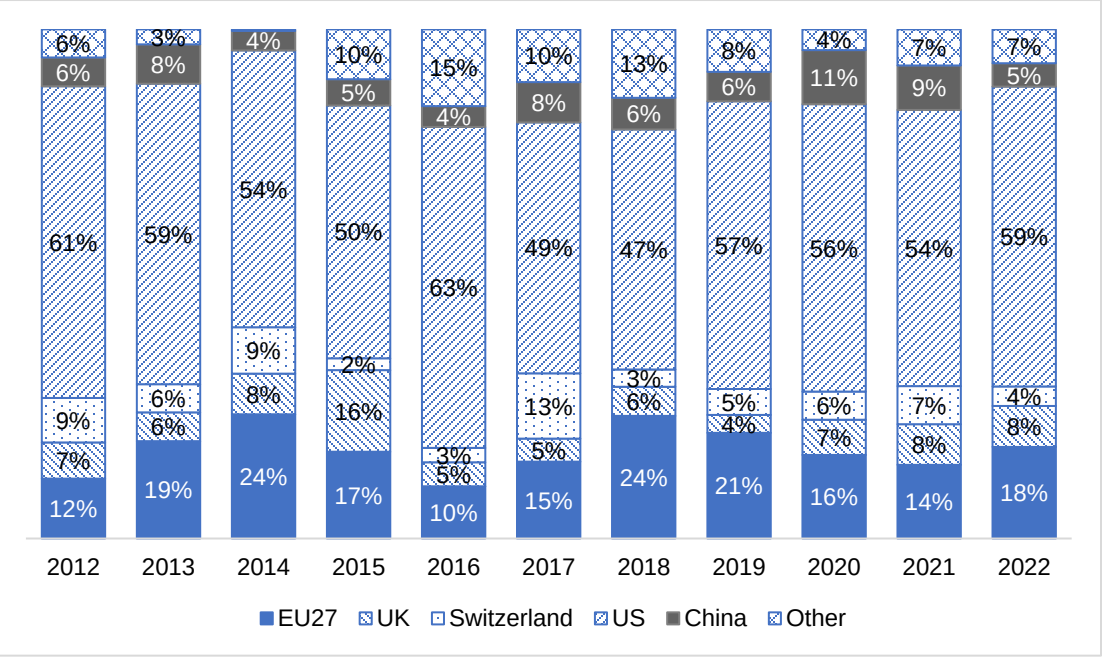
30 CRA analysis of Global Data Investment Tracker (2023)

31 Politico (2023). The real reason Europe's medicines industry is dying. Available at https://www.politico.eu/article/europe-medicines-industry-dying-pharma/

32 CRA analysis of Global Data Investment Tracker (2023)

33 CRA analysis of Global Data Investment Tracker (2023)

Figure 4: Venture capital deal activity by geography (2012–2022)

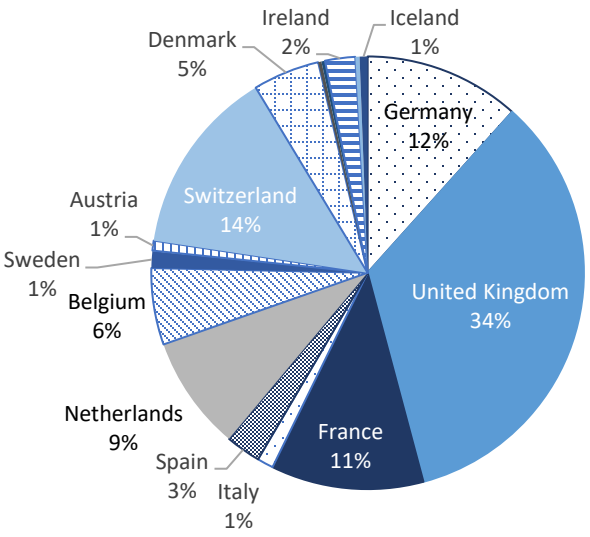


Source: CRA analysis (2023), Global Data

The disparities between Europe, particularly the EU, and other key regions are partly explained by concentration and the geography of investment. Unlike the more consolidated VC hubs in the US – particularly in Silicon Valley or the Boston area – funding, exit opportunities, and the options to go public are significantly more fragmented in Europe. Additionally, it is important to separate out investment in the EU from that in ex-EU European countries, as a substantial proportion of European investment lies outside the EU (Figure 5). The result of this is a 'Death Valley' in Europe for emerging and small biotech companies. There is a risk that they will move out of Europe in order to be closer to their investors and ensure they receive sufficient funding. Between 2017 and 2021, the number of new companies established in the US was double that of Europe.[34]

34 Life Science Acceleration Alliance (2023). The importance of venture capital in Europe's life science ecosystem. Available at https://static1.squarespace.com/static/60f1b323d27a3027d5f158e5/t/63e134645f4c597312c8b024/1675703396550/LSAA_VC+REPORT_FINAL.pdf

Figure 5: Venture capital deal activity by geography in Europe (2019–2022)



Source: CRA analysis (2023*), GlobalData*

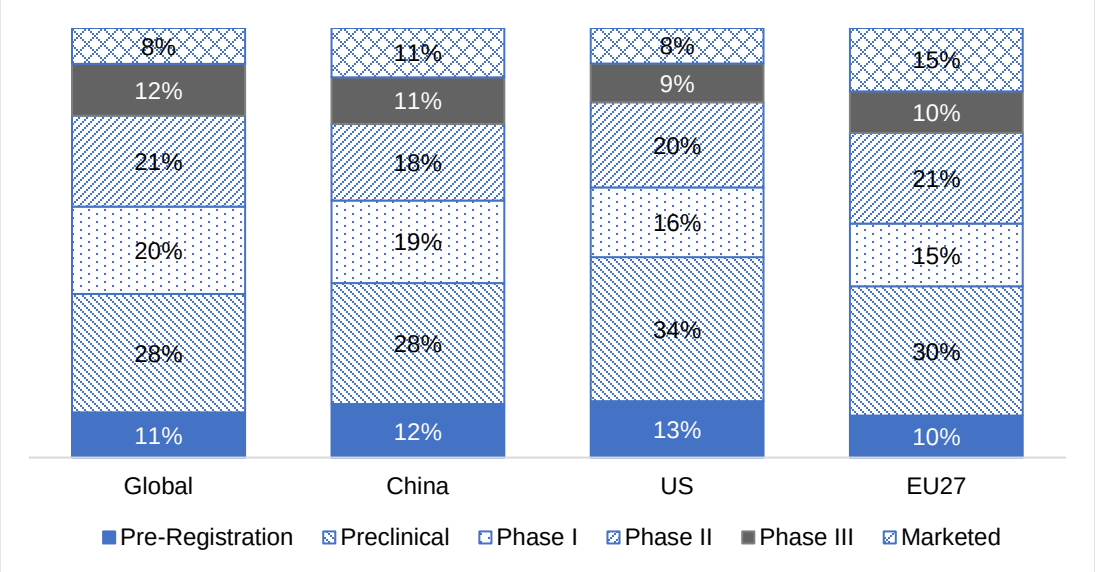
The GPL clearly directly affects countries within the EU, so it is important to note that most of the VC deal activity in Europe occurs outside of the EU. This is consistent in interviews with emerging and small biotech companies and national trade associations, who highlight that VC funds prefer to support innovation "in their backyard", which tends to be outside of the EU. In turn, the available funding must be pieced together from multiple geographies, which carries a significant burden where individual EU countries take small slivers of the deal activity rather than consolidation into innovation hubs (Figure 5).

2.2.2. Importance of partnership

Few emerging and small biotech companies commercialise medicines. It is much more common for them to enter partnerships with larger biopharma. Partnerships enable companies to distribute both responsibility and risk, fostering collaboration and shared investment. Furthermore, when smaller companies partner with mature companies, they gain access to resources that support the costly clinical development phase and subsequent commercialisation. In addition to partnering with mature pharmaceutical companies, small biotech tends to partner with other small companies to increase efficiencies by sharing the know-how on research and development.

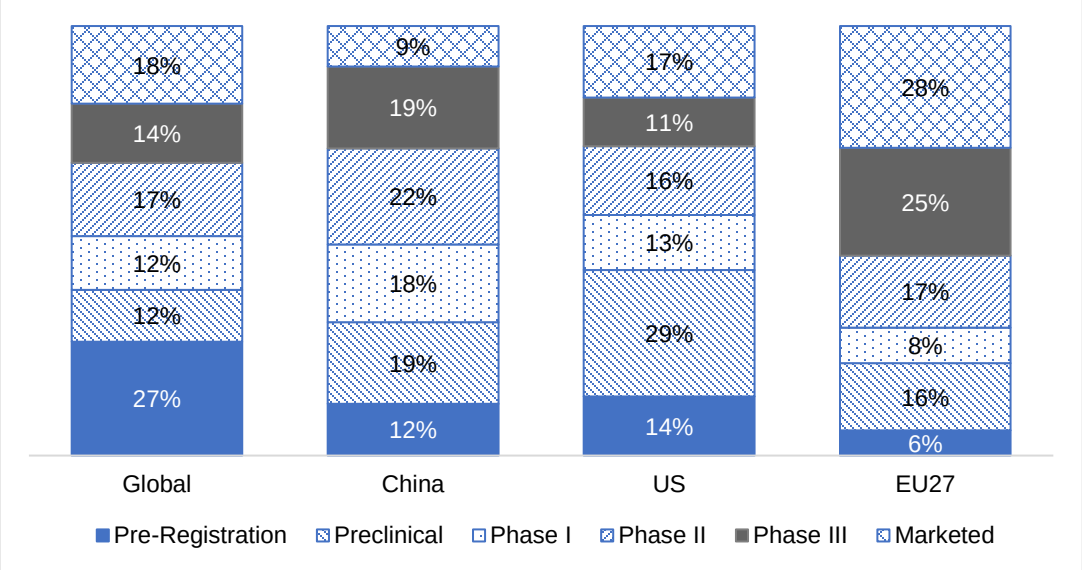
Looking at the trends of early- versus late-stage investment confirms that life sciences VCs (and particularly biotechnology VCs) invest more often in early- than in late-stage assets, but tend to invest larger sums of resources in late-stage deals (Figure 6, Figure 7). Following VC investment, partnerships or acquisitions of small companies also enable a VC exit, the promise of which is a strong incentive for greater investment.

Figure 6: Venture capital deals volume share by development stage EU27 vs key regions (2018–2022)



Source: GlobalData (2023)

Figure 7:Venture capital funding share by development stage EU27 vs key regions (2018–2022)



Source: GlobalData (2023)

The nature of European partnerships between emerging/small biotech and mature pharmaceutical companies is changing. Even if capital is available for partnerships between originator companies, mature pharmaceutical companies, and investors, in interviews, companies of all tiers and VCs highlighted that there is a growing sense of caution and hesitancy in Europe to invest in early-stage biotech due to the current geopolitical context, inflation and cost of capital.

US biotechnology companies invested 11 times more in R&D than their European counterparts in 2020.[35] Furthermore, only six out of the top 25 R&D investors in the health industry are companies headquartered in the EU.[36] As other key regions, in particular the US, have begun to stabilise investment back to pre-pandemic levels, Europe has been left behind. In 2018 and 2019, European companies received an average of $15.2 billion total R&D funding, while in 2022 the amount was down to $7.8 billion.[37]

The EU is losing compared to other regions, as evidenced by a shift in corporate R&D investments from the EU to other parts of the globe, surpassing the R&D investments that the EU receives in return. This imbalance is primarily attributable to the EU's significant negative balance concerning the US (Table 3). The numbers can be interpreted as a cautionary signal, particularly when contrasted with the analysis of R&D flows in the 2016 edition of the EU Industrial R&D Investment Scoreboard.[38] Indeed, at that time, the EU's negative R&D balance was minimal, but it has since increased considerably. This growth is largely attributed to a substantial rise in R&D investments flowing from the EU to the US.

Table 3:R&D flows from and to the EU in the health industry (EUR million)

	China	Japan	Other Europe	RoW	US
Outflows (From EU companies to other areas)	130	241	2,445	1,362	12,190
Inflows (From other areas to EU)	227	686	6,805	627	5,556
EU net balance (Inflows-outflows)	97	445	4,360	-735	-6,634

Source: JRC/OECD COR&DIP© database, v.3. 2021[39]

Both VC funds and pharmaceutical companies interviewed signalled that they are beginning to prefer partnerships with late-stage, de-risked assets, leaving early-stage biotech with an increasingly uphill battle to find investors. This is due to a general atmosphere of funding shifting from portfolios that promise value creation to those that already exhibit commercial

35 Life Science Acceleration Alliance (2023). The importance of venture capital in Europe's life science ecosystem. Available at https://static1.squarespace.com/static/60f1b323d27a3027d5f158e5/t/63e134645f4c597312c8b024/1675703396550/LSAA_VC+REPORT_FINAL.pdf

36 European Commission (2022). Vezzani, A. Top EU R&D investors in the global economy: Benchmarking technological capabilities in the health industry. Available at https://iri.jrc.ec.europa.eu/sites/default/files/2022-10/Vezzani_Pubsy130769.pdf

37 IQVIA Institute (2023). Global Trends in R&D. Available at https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-trends-in-r-and-d-2023/iqvia-institute-global-trends-in-rd-2023-forweb.pdf

38 Guevara, H. H., Soriano, F. H., Tuebke, A., Vezzani, A., Amoroso, S., Coad, A., Gkotsis, P. and Grassano, N. (2017). The 2016 EU Industrial R&D Investment Scoreboard (No. JRC103716). Joint Research Centre (Seville site). Available at https://ideas.repec.org/p/ipt/iptwpa/jrc103716.html

39 European Commission (2022). Vezzani, A. Top EU R&D investors in the global economy: Benchmarking technological capabilities in the health industry. Available at https://iri.jrc.ec.europa.eu/sites/default/files/2022-10/Vezzani_Pubsy130769.pdf

value.[40] Both small biotech and mature pharmaceutical companies reported (in interviews) that discussions regarding partnerships took longer to crystallise in 2023 than they did pre-pandemic due to hesitancy to invest in uncertain, un-scientifically proven assets.[41] In all, partnerships happen across all stages of asset development, but interviews suggest that there will be a growing trend to focus on late-stage assets, not only in terms of the volume of funding, as has traditionally taken place, but also in the volume of deals.

2.2.3. Initial public offerings

Beyond investment from VC, growing biotech companies look to raise capital on international markets. Funding by initial public offerings (IPOs) is highly cyclical. The year 2020 was record-setting for IPOs, with biotech companies globally attracting $29 billion. However, this was followed by a sharp slowdown in IPO activity in 2021, and an almost complete stoppage in the first half of 2022. The capital collected through biotech IPOs between the last quarter of 2021 and the first quarter of 2022 plummeted by 63% in comparison to the same time frame the previous year.[42,43] Similar to VC investment, Europe continues to lag competitor regions following the pandemic slump.[44]

There is a diminishing number of IPOs in Europe; in interviews, emerging and small biotech companies stressed how the EU is no longer as an attractive place for their growth, a perception driven by a lack of financial infrastructure, investment opportunities and IPO pathways. The diminishing number of IPOs in Europe also impacts the funding landscape, especially for companies that reach phase II clinical trials, which traditionally mark the transition for companies to start looking towards the public market for funding.[45] This insight is based on interviews with VC and small companies, who expressed concerns regarding the knock-on effects of this trend on the availability and accessibility of capital required to propel them into their next stages of growth and development. In addition, this trend also influences private investors' willingness to fund early-stage projects (who see IPOs as a means to crystallise their investments), further straining the early-stage biotech ecosystem in Europe.

Challenges in going public due to the fragmented stock exchanges further contribute to barriers for biotech companies on top of fragmented regional regulatory guidelines and pricing / market access dynamics. In contrast to the US, where exchanges such as NASDAQ and NYSE support investment across the regional funding ecosystem, there is no dominant European exchange. Rather, companies must list on multiple national stock exchanges and thus may be spread across up to 15 different exchanges, each with its own regulatory and reporting

40 McKinsey and Company (2022). How the European biotech sector can navigate turbulent times. Available at https://www.mckinsey.com/industries/life-sciences/our-insights/how-the-european-biotech-sector-can-navigate-turbulent-times

41 Interviews with biotech stakeholders

42 Nasdaq (2023) NBI index. Available at https://indexes.nasdaqomx.com/index/overview/NBI

43 McKinsey and Company (2022). How the European biotech sector can navigate turbulent times. Available at https://www.mckinsey.com/industries/life-sciences/our-insights/how-the-european-biotech-sector-can-navigate-turbulent-times

44 McKinsey and Company (2022). How the European biotech sector can navigate turbulent times. Available at https://www.mckinsey.com/industries/life-sciences/our-insights/how-the-european-biotech-sector-can-navigate-turbulent-times

45 Kang, H. (2018). "A Start-Up's R&D Stages and the Evolution of Financing Sources: Evidence from the Biotechnology Industry". *Entrepreneurship Research Journal*. Available at https://www.degruyter.com/document/doi/10.1515/erj-2017-0159/html

requirements.[46] Ninety percent of biotech companies are listed only in their home countries.[47] This has contributed to institutional investors being unable to sufficiently invest in European biotechnology; institutional investors held 60% of available share in the top 10 European biotech companies vs 85% of share in the US by US-based investors in 2021.[48]

The weakness of European funding is a constraining factor for the growth of innovative companies, especially in high-risk sectors like biotechnology. Compared to the well-established US model, the European landscape, both in VC / mature biopharma investment and public funding, creates challenges for emerging and small biotech in securing the necessary funding.

2.3. The role of the European biotech innovation ecosystem in the development of innovative medicine

Advanced therapy medicinal products (ATMPs) represent the next wave of innovation in biopharma. These products are novel therapeutics based on genes, tissues or cells, including gene therapy, somatic-cell therapy, and tissue engineering.[49] These products have historically been focused on the orphan / rare disease space, although interviews with VC companies indicated that there are many companies looking to expand these therapies to reach a broader audience. ATMPs are particularly important as a signal for where innovation hubs will be concentrated in the future. However, Europe is falling behind the US regarding the development, funding and approval of these therapies. As of 2023, the EMA has approved 17 ATMPs, which are still active, while there are 21 marketed ATMPs available in the US.[50] Additionally, ATMP manufacturers face increased challenges post approval regarding market access and commercial take-up.

Although Europe has historically been a leader in scientific discovery, this has not translated to this latest wave of innovation. Figure 8 shows that the US clearly outperforms other regions, with over twice as many ATMP clinical trials taking place versus the EU between January 2020 and October 2023. In fact, the EU is also lagging China on this front, further placing emphasis on the need to accelerate the clinical trial process.

46 McKinsey and Company (2021). Can European biotechs achieve greater scale in a fragmented landscape? Available at https://www.mckinsey.com/industries/life-sciences/our-insights/can-european-biotechs-achieve-greater-scale-in-a-fragmented-landscape

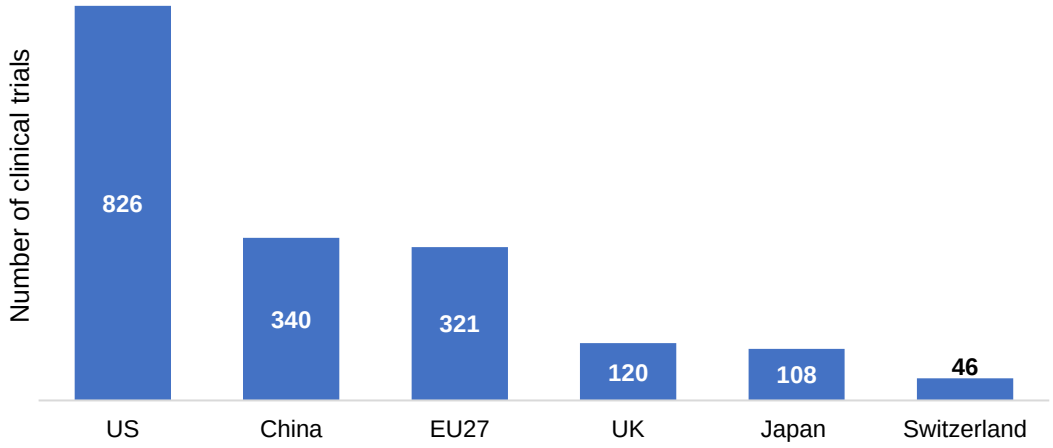
47 McKinsey and Company (2021). Capital landscape for European biotechs is maturing, but it continues to trail the United States. Available at https://www.mckinsey.com/industries/life-sciences/our-insights/infographic-capital-landscape-for-european-biotechs-is-maturing-but-it-continues-to-trail-the-united-states

48 McKinsey and Company (2022). How the European biotech sector can navigate turbulent times. Available at https://www.mckinsey.com/industries/life-sciences/our-insights/how-the-european-biotech-sector-can-navigate-turbulent-times

49 European Medical Agency. Advanced therapy medicinal products: Overview. Available at https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview#:~:text=Advanced%20therapy%20medicinal%20products%20(ATMPs,treatment%20of%20disease%20and%20injury

50 CRA analysis of GlobalData Drug Database (2023)

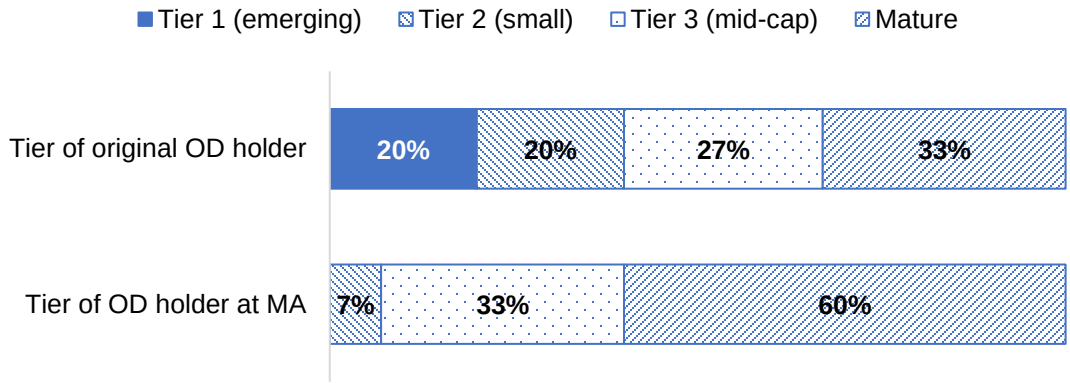
Figure 8: ATMP clinical trials activity across geographies (January 2020–October 2023)



CRA analysis of Global Data Clinical Trials Database[51]

ATMPs are a key measure of innovation from emerging and small biotech. Although the majority of ATMPs are owned by mature companies at launch, this does not reflect the originators of ATMPs, of which emerging and small biotech companies make up a significant portion (Figure 9).

Figure 9: Tier of orphan designation holder for companies with an ATMP at OD and at market authorisation (2018–2022)



Source: CRA analysis of EMA (2018–2022)

It is useful to look at ATMPs to diagnose the health of the investment environment, as external capital plays a key role in early-stage emerging and small companies.[52] In Q2 2023, there was

51 CRA assessed the number of ATMP trials across different geographies, which was determined using the GlobalData Trials Database, focusing on cell and gene therapies. The search included EU27, US, China, Japan, UK, and Switzerland, encompassing all clinical trial phases. All trials, whether completed, ongoing, planned or suspended, from January 2020 to October 2023, were included in this analysis.

52 Kang, H. (2018). "A Start-Up's R&D Stages and the Evolution of Financing Sources: Evidence from the Biotechnology Industry". *Entrepreneurship Research Journal*. Available at https://www.degruyter.com/document/doi/10.1515/erj-2017-0159/html

close to nine times as much funding for ATMPs in North America vs Europe, and six times as much VC funding specifically.[53] This lack of innovative therapy investment is also an indicator of how the EU is falling behind other regions in regard to R&D, as well as an indicator of a larger impact on the ecosystem. It has led to Europe no longer being a key location for clinical trials in innovative therapies. This affects patients, as they will no longer have early access to novel therapies, and the clinical trials for novel products will no longer reflect European patients as accurately as in the past.[54,55]

It may be tempting to assume, regarding the investment process, that changes in regulation will only have an impact over the longer term and be mitigated by other factors in the commercial environment. However, the regulatory landscape does affect investment decision-making. This is clear when analysing the Japanese case study where policy changes reduced the incentives to invest, while limiting drug company revenues, undermining the industry's capacity to invest. Evidence shows that from 1995 to 2018, due in large part to policy changes, Japan's global share of the annual value added to the pharmaceutical industry plummeted by 70%, from 18.5% to 5.5%.[56] Policy changes that triggered this fall include moving to a more inflexible regulatory system, increased price controls, faltering investment in basic research, weakened industry–university relations, and increasing barriers to internationalisation. Japan's history should function as a warning to European legislators, that decreases in incentives for pharmaceutical manufacturers could prompt them to invest elsewhere in the world. The US, on the other hand, serves as the more attractive market for the development of novel therapies and for initial product launches due to its unified pricing and reimbursement system, along with a large market size. Favouring the US over Europe as a key investment location can already be seen in the geographical concentration of innovative development. Although Europe has historical strengths in developing novel and breakthrough therapies, the EU is falling behind other regions regarding the development, funding and approval of ATMPs. Companies are likely to grow and invest more in regions where there is a flexible regulatory environment, where policy is seen to support innovation, and where they can secure favourable pricing, reimbursement and market access conditions.

53 Alliance for Regenerative Medicine (Q2 2023). Cell and Gene Therapy Sector Data. Available at https://alliancerm.org/data/

54 Interviews with biotechnology companies

55 EFPIA (2022). Europe's share of global medicines R&D shrinks by a quarter in 20 years – as sector's declining trends continue. Available at https://www.efpia.eu/news-events/the-efpia-view/efpia-news/europe-s-share-of-global-medicines-rd-shrinks-by-a-quarter-in-20-years-as-sector-s-declining-trends-continue/

56 ITIF (2022). Stephen Ezell. How Japan Squandered Its Biopharmaceutical Competitiveness: A Cautionary Tale. Available at https://itif.org/publications/2022/07/25/how-japan-squandered-its-biopharmaceutical-competitiveness-a-cautionary-tale/

3. Impact across key elements of the GPL

In this chapter we consider the impact of the proposed changes in the GPL on the innovation ecosystem, with a particular focus on companies of different levels of maturity.

Summary

The Commission has not comprehensively assessed the impact that the changes in the GPL will have on the innovation ecosystem. Specifically, little attention has been given to emerging and small biotech companies which will be most significantly impacted by reduced protections, increased uncertainty, and limiting the attractiveness for European investment by both VC and mature biopharmaceutical companies.

The Commission aims to encourage manufacturers to accelerate their development timelines but does not consider how capping of the previously unlimited time limit on the orphan designation period will disproportionately disadvantage smaller companies, which already take longer to reach MA. Furthermore, the Commission's concessions do not balance these offsets. Instead of accelerating development, this could increase uncertainty and disrupt funding and partnerships. Given the important role of smaller companies in establishing novel biotechnologies and disease targets, there is a danger that this will limit the flow of advances within Europe, with a knock-on effect on clinical trials and patient access.

Modulation based on 'high unmet medical need' (HUMN), launch requirements in all Member States, and potential extensions based on successful additional indications will be seen as highly uncertain. The result is that biotechnology companies will have a reduced capacity to attract investment, as investors will not consider modulated protection periods. Decreased baseline exclusivity will result in lower commercial valuations. The overall result is that the reduced length of OMP exclusivity, seen as an important differentiator in Europe to offset the challenging market access landscape, will decrease the attractiveness of investing in Europe.

Similarly, RDP extensions based on 'unmet medical need' (UMN), comparative clinical trials and continuous supply across Member States are seen by investors as uncertain. As such, investment decisions by VC and mature biotech will be based on the baseline protections, reducing the attractiveness of the entire European landscape. These incentives are vital for attracting investment to fund clinical development, and any reduction in incentives will make costly investments, such as comparative trials, more difficult for emerging and small biotech companies.

The requirement to supply across all Member States does not take into account the considerable barriers facing smaller companies wishing to commercialise. The proposed allowance for SMEs is irrelevant, given that the definition of SMEs is not suitable for biotechnology. SMEs as defined by the Commission are very unlikely to be responsible for MA, as companies will have grown beyond 'SME' at this point. Given this, the baseline will be used in valuation, reducing the opportunity to attract investment. Decreased investment will have knock-on impacts on biotech clusters and national associations as the European landscape becomes less attractive for innovation, and departure of talent from the European biotech ecosystem could accelerate further.

There are some positive changes included in the GPL. Streamlining the regulatory process will be beneficial to the entire ecosystem, particularly small and mid-cap biotech companies struggling to navigate the complex regulatory system – although companies are sceptical whether these proposed changes will actually translate to faster approvals. Additionally, there are many challenges that are not addressed by these guidelines, such as the clinical trials system and the lack of sufficient expedited review pathways.

3.1. The extent to which company maturity is taken into account in the proposed changes to the GPL

The Commission aims to strike a balance between providing attractive incentives for innovation and supporting timely patient access to innovative treatments. They propose to accomplish this by introducing measures such as the tiering of unmet need and measures to accelerate entry of generic and biosimilar medicines to prioritise affordability. Although the Commission highlights some of the impacts that these proposed regulations will have on SMEs and other members of the innovation ecosystem, they do not do so thoroughly. Additionally, as noted in the parliament's initial assessment of the GPL, the impact assessments do not follow the standardised framework for assessment as outlined by BRG tool #23.[57] Therefore, it is first useful to assess the degree to which the maturity of companies has been considered in the existing impact assessment. However, it is important to note that even if the Commission had conducted a thorough SME impact assessment, its relevance would be questionable. This is because the Commission's definition of an SME is not adequately suited for the biotech sector, a point elaborated in Chapter 1. This mismatch in definitions underlines the need for a more tailored approach when assessing the impacts on biotech sector. The Commission's reported impact of the GPL on SMEs is as follows:

Box 3: Commission's reported impact of the proposed regulations on SMEs[58]

- SMEs will find it more difficult to adapt to the proposed modulation of protections and lack the capacity to effectively serve all Member States in a timely manner.
- SMEs will benefit from the provisions for unmet need and antimicrobial benefits (transferable exclusivity vouchers) more than other companies as they are engaged in riskier R&D in underserved areas.
- Additional administrative obligations (environmental and supply) will harm SMEs in the short term but will be balanced by the systemic changes to simplify regulatory processes.

The recent Dolon report highlights that SMEs hold a unique and vital position in the innovation ecosystem and deliver a significant number of breakthrough innovations. However, SMEs are particularly vulnerable to any change in the policy environment that reduces their valuation for investors or strategic partnerships. Such changes directly impair their capacity to attract essential capital and prevent the development, manufacturing, and distribution of their products.[59]

To completely understand the impact of the GPL on the biotech sector, 15 companies across our described four tiers, plus national associations and investors were interviewed. This company sample was achieved through working with European and national trade

57 European Parliament (2023). Initial appraisal of a European Commission Impact: Revision of the EU pharmaceutical legislation. Available at https://www.europarl.europa.eu/RegData/etudes/BRIE/2023/747464/EPRS_BRI(2023)747464_EN.pdf

58 European Commission (2023). Executive summary of the impact assessment report: Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC. Available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52023SC0193

59 Dolon (2023) Revision of the General Pharmaceutical Legislation: Impact Assessment of European Commission and EFPIA proposals. Available at https://dolon.com/wp-content/uploads/2023/11/Revision-of-the-General-Pharmaceutical-Legislation-GPL-Impact-Assessment_vFinal.pdf?x23572

associations, to select those who are likely to be more aware of the changes in policy environment than average companies of this size.

The majority of companies interviewed in summer 2023 were familiar with the GPL. Larger companies demonstrated significant awareness and had considered the potential impact on operations through the whole legislative package. However, smaller companies had had less exposure to the proposals and had less awareness of potential long-term impact.

3.2. The impact of changes to orphan medicines incentives on emerging and small biotech companies

While the impact assessments, the central GPL text and the impact assessment on orphan medicines consider the role of SMEs in the ecosystem and attempt to assess the impact of proposed changes based on each recommended regulation change, the revision of the GPL by Parliament finds that no full and formal SME test was carried out and SMEs were not specifically consulted in the process of drafting the proposal or assessing its impact.[60]

It is well recognised that orphan medicines regulation has supported the establishment and growth of biotech companies. In the last two decades, more than 150 SMEs focusing on rare disease have emerged following the introduction of the regulation.[61] Considering over half of orphan medicinal products (OMPs) are developed by emerging and small biotech companies, changes to these incentives could greatly impede innovation in these companies and, overall, impact access to innovative medicines within the EU.[62] Between 2015 and 2020, 55% of the products developed by emerging biotech (defined as companies with a market capitalisation of less than US$10 billion at the time of EMA approval, and aligning with the definition of Tier 1–3 companies) were orphan drugs, compared to 29% of those developed by mature pharmaceutical companies (Figure 10).[63]

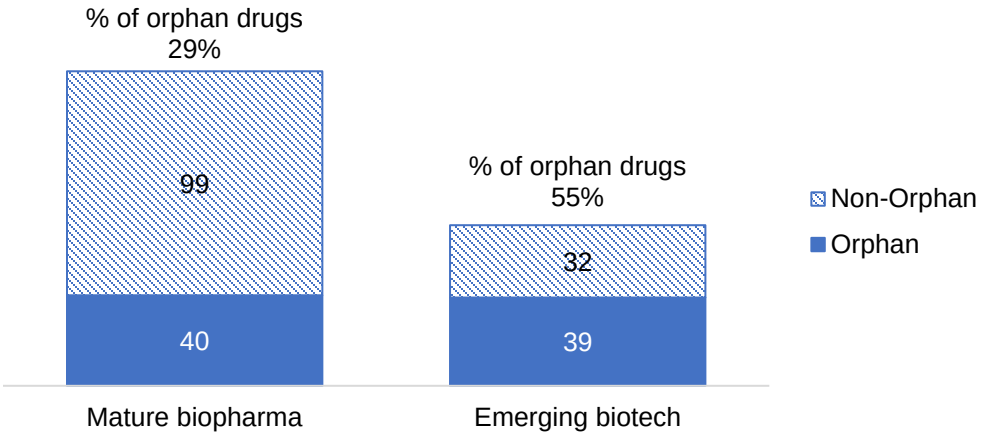
60 European Parliamentary Research Service. (2023, September). Initial Appraisal of a European Commission Impact Assessment: Revision of the EU pharmaceutical legislation. Available at https://www.europarl.europa.eu/RegData/etudes/BRIE/2023/747464/EPRS_BRI(2023)747464_EN.pdf

61 Horgan, D., Moss, B., Boccia, S., Genuardi, M., Gajewski, M., Capurso, G., Fenaux, P., Gulbis, B., Pellegrini, M., Mañú Pereira, M. D. M., Gutiérrez Valle, V., Gutiérrez Ibarluzea, I., Kent, A., Cattaneo, I., Jagielska, B., Belina, I., Tumiene, B., Ward, A., and Papaluca, M. (2020). "Time for Change? The Why, What and How of Promoting Innovation to Tackle Rare Diseases – Is It Time to Update the EU's Orphan Regulation? And if so, What Should be Changed?" *Biomedicine hub,* 5(2), 1–11. https://doi.org/10.1159/000509272

62 Deloitte (2022). Deciding on the right path. How biotechs should expand in(to) Europe. Available at https://www.deloitte.com/global/en/our-thinking/insights/industry/life-sciences/expanding-into-european-biotech-industry.html

63 Deloitte (2022). Deciding on the right path. How biotechs should expand in(to) Europe. Available at https://www.deloitte.com/global/en/our-thinking/insights/industry/life-sciences/expanding-into-european-biotech-industry.html

Figure 10: Proportion of orphan medical products gaining European Medicines Agency approval (2015–2020)



Source: Deloitte (2022) [64]

3.2.1. Orphan designation

The European Commission proposes to restrict the validity of OD to a seven-year term, with opportunities for extension if a clinical trial is ongoing, aiming to accelerate the authorisation process of designated products.

The introduction of an OD cap would be a significant change to the current framework, which, under normal circumstances of meeting all requirements, allows for an unlimited validity period. This enables companies to obtain OD early in the development journey and secure investment to progress through clinical trials and ensure success as they commercialise. The designation is important as it signals that a product might achieve orphan market exclusivity when authorised, and therefore, is useful for potential investors. While capping the OD period may lead to expiry for some designations, the Commission postulates it would also encourage companies to advance towards the authorisation process more quickly.[65] To support this assertion, they considered evidence that the transformation from concept to authorised medicine remains slow for OMPs.

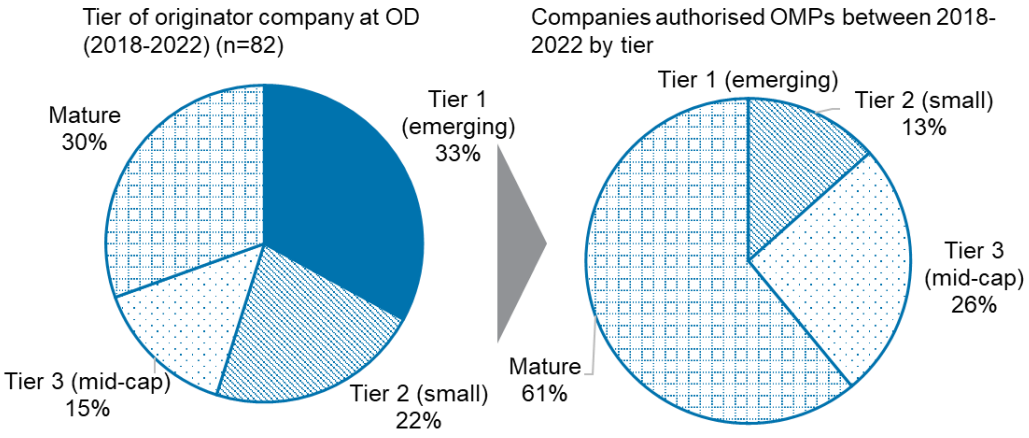
Drawing from interviews with small biotech companies and our data analysis, there are several reasons to question the Commission's assumption.

The length of time between OD and MA varies by product and by company tier: The time between OD and regulatory approval tends to be longer for smaller companies due to resource constraints which limit their ability to rapidly progress through clinical trials. Based on tiering of biotech companies, CRA analysis of the 2018–2022 EU regulatory approvals (Figure 11) shows that at initial filing for OD, 30% of the drugs originate from mature companies, 15% by mid-cap companies (Tier 3), 22% by small companies (Tier 2) and 33% by emerging companies (Tier 1). This changes dramatically by the time these drugs reach authorisation, with 61% now being held by mature companies.

64 Deloitte (2022). Deciding on the right path. How biotechs should expand in(to) Europe. Available at https://www.deloitte.com/global/en/our-thinking/insights/industry/life-sciences/expanding-into-european-biotech-industry.html

65 European Commission (2023, April 26). Impact assessment report and executive summary accompanying the revision of the medicines for rare diseases and children legislation. Available at https://health.ec.europa.eu/system/files/2023-04/swd_2023_192_1-2_ia_en.pdf

Figure 11: The role of companies in designation between 2018 and 2022 by tier

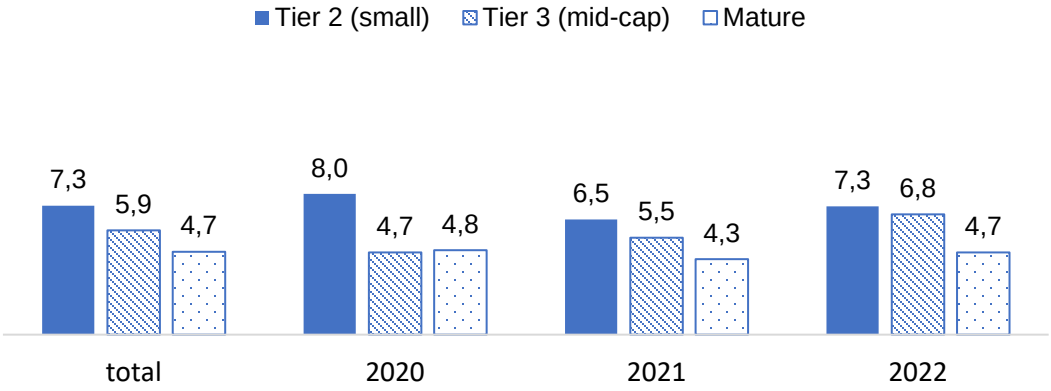


Source: CRA analysis of EPARs published by the EMA 2020–2022[66]

We need to consider the cyclical landscape when crafting incentives for emerging (Tier 1) biotechs, as these companies are vital for innovation but do not commercialise their products. Emerging companies with an OD are typically characterised as single-asset entities focused predominantly on one main product. Through the interviews, it was highlighted that the emerging biotech companies are missing from the commercialised landscape not because of lack of innovation but because they partner with, or their assets are acquired by, mature companies.

Based on CRA analysis, for OMPs that reached market approval between 2020 and 2022, the average time from OD to MA was 4.7 years for mature companies and 7.3 years for small biotech companies, with 15 out of 56 approved products taking longer than 7 years to reach MA (Figure 12). This initial review falls in line with the Commission's assessment, with most companies falling under 7 years; however, segmentation by tier suggests a significantly bigger impact on small companies into the future if OD is capped at 7 years where half of their products could pass the cap before MA.

Figure 12: Average number of years from OD to MA (2020–2022)



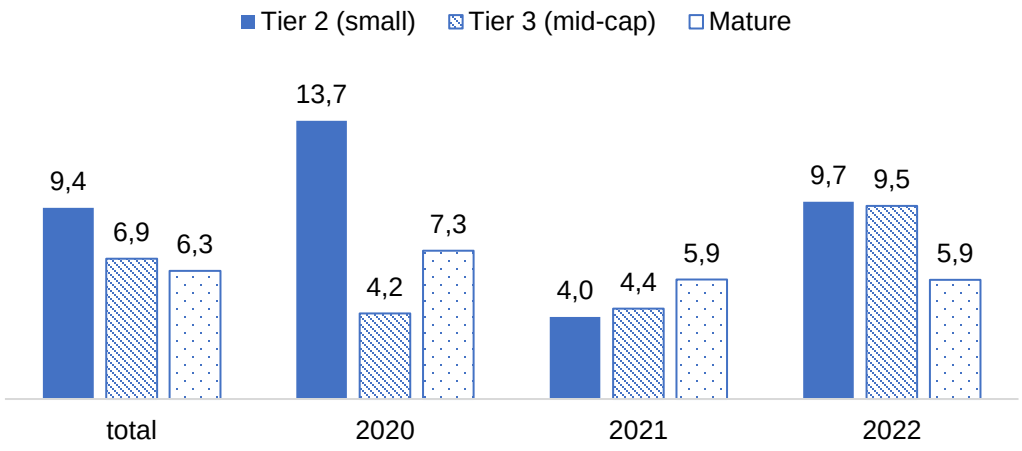
Source: CRA analysis of EPARs published by the EMA 2020–2022[67]

66 EMA (2018–2023). EPARs. Available at https://www.ema.europa.eu/en/medicines

67 EMA (2020–2023). EPARs. Available at https://www.ema.europa.eu/en/medicines

Additionally, the average time extends further when focusing solely on OD transfers (from emerging/small biotech to mid-cap/mature companies) (Figure 13). Of 32 products with an OD transfer and an MA between 2020 and 2022, 12 of them took longer than seven years to reach MA (~38%). This highlights a potential impact on partnerships, as many assets will lose their OD if they are transferred from one organisation to another.

Figure 13: Average number of years from OD to MA of those with OD transfer (2020–2022)



Source: CRA analysis of EPARs published by the EMA 2020–2022[68]

Given the unlimited length of the current OD period, there is a risk that artificial capping will disadvantage smaller companies, which already take longer to reach MA. This could impact investment decisions and the opportunity to collaborate with mature companies, which contradicts the Commission's goal to foster the growth of small biotech companies in Europe.[69] Based on interviews, the limited number of emerging and small biotech companies that are able to reach commercialisation would have yet another roadblock put in their path, further inhibiting their ability to complete asset development. Their ability to partner with mature biotech will be further restricted as the majority of products will have their OD expire before they are able to reach commercialisation, if they are transferred. This disincentivises investment into these products, limiting exit options available for emerging and small companies, and in turn also making them less attractive for VC.

Emerging and small biotech companies rely on external investment via OD signals: Companies confirmed in interviews that early OD plays a key role in supporting their ability to secure R&D funding, particularly for clinical development.[70] This is also reflected in evidence from the literature, particularly in ecosystem changes following the introduction of the Orphan Drug Act in the US. Investors value the FDA's orphan drug designation, and receipt of OD had positive and statistically significant signalling power for IPO investors. Stock prices of pharmaceutical companies in the US have historically increased by an average of 3.36% after the OD receipt

68 EMA (2020–2023). EPARs. Available at https://www.ema.europa.eu/en/medicines

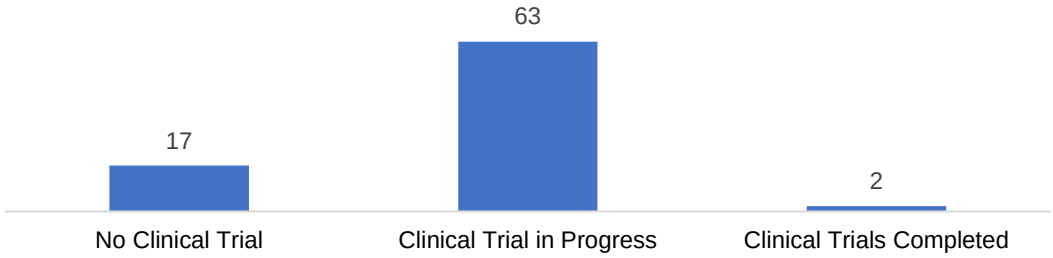
69 CRA interview discussion with VC expert

70 RAND Corporation (2022). The Financial Ecosystem of Pharmaceutical R&D. Available at https://www.rand.org/pubs/external_publications/EP68954.html

is announced.[71] Regression results also suggest that ODs are stronger than patent applications in attracting IPO investors.[72]

A reduction in OD duration could impact investment in the clinical development of orphan medicines. OD is a critical catalyst in attracting investment, especially during the clinical development phase, which necessitates a substantial financial commitment. Historically, most companies submit proposals for OD while their asset is still in clinical trials to attract greater R&D funding (Figure 14). If companies delay applying for OD, this could delay investment by VCs and mature companies, and increase their growing preference or partnering with late-stage, de-risked assets that already demonstrate significant scientific value. To illustrate the costs, R&D investment begins with tens of millions of Euros in early-stage preclinical products and can reach hundreds of millions by phase III trials.[73] Additionally, there's a notable trend concerning the escalation in the duration and cost of clinical trials attributed to the growing complexity of treatments and challenges in patient recruitment, which will only increase the need for early investment into the future.[74]

Figure 14: Number of products by stage of development at the time of OD (2018–2022)



Source: CRA analysis of EPARs published by the EMA 2018–2022 [75]

In interviews, investors clearly signalled that they would be less likely to invest in orphan medicines developed by smaller companies, should a time restriction be implemented. The concern arises from the potential inability of many small biotech companies to adhere to these timeline requirements, which jeopardises their eligibility for vital incentives like market exclusivity periods, essential for recovering investments.

The Commission acknowledges the importance that receipt of OD holds for SMEs, particularly its ability to help SMEs attract capital and dedicated support from the EMA. However, rather than aligning incentives to shorten the time these companies need to reach MA, the Commission claims that the lengthy development timelines are due to companies losing

71 Miller, K. L. (2017). "Do investors value the FDA orphan drug designation?" *Orphanet journal of rare diseases*, 12(1): 114. https://doi.org/10.1186/s13023-017-0665-6

72 Orphan Drug Designations as Valuable Intangible Assets for IPO Investors in Pharma-Biotech Companies. Available at https://www.nber.org/papers/w24021

73 European Commission (2020). Impact assessment report and evaluation of the orphan medicinal products and medicinal products for paediatric use. Available at https://health.ec.europa.eu/system/files/2020-08/orphan-regulation_eval_swd_2020-163_part-1_0.pdf

74 ABCAM (2021). Improving efficiency in drug discovery and preclinical development. Available at https://docs.abcam.com/pdf/general/drug-discovery-efficiency.pdf

75 EMA (2018–2023). EPARs. Available at https://www.ema.europa.eu/en/medicines

commercial interest in marketing an orphan product.[76] This contradicts the real-world situation, according to companies interviewed, who say the limiting factor in reaching MA in a timely manner is a lack of capabilities and resources. Changes in the reward structure that reduce potential investment will negatively impact these companies who cannot further accelerate product development and face increasing challenges with a shrinking potential return.

The argument that the OD period cap will accelerate development is flawed: The Commission argues that reducing the designation period will not have negative ramifications. They argue that instead, this limit on OD could accelerate product development. There is no evidence presented to support this assertion. It assumes that companies intentionally delay product launches. This is not the business model for small companies. In interviews, emerging and small companies reported that they depend on investment from outside partners who are looking to crystallise their investment as soon as possible. VC funds look to invest in small companies and support them through the development stages of an asset, and once alternative sources of support are available, the VC investor will recover their investment.[77] Smaller companies aspire to reach their development goals as promptly as possible – particularly as investors are keen to recoup investments and often offer rounds of funding contingent on meeting development milestones.[78] Further, small companies often engage with contract development manufacturing organisations (CDMOs) and contract research organisations (CROs), who support efficient clinical development, contributing to the region's scientific knowledge base through research activities, high-skilled employment, manufacturing sites and technological innovation. These companies will also begin to disappear as innovation is hampered in Europe.[79] Interviews also highlighted that development of orphan medicines faces longer timelines than non-orphan medicines, resulting from characteristics specific to rare disease, such as the challenge of identifying and recruiting patients for clinical trials. [80] In addition to the cap on the OD period, the Commission has proposed another arbitrary cap in the form of a five-year time limit for deferred Paediatric Investigation Plan (PIP) measures. This proposal, as outlined in Article 81 of the suggested Regulation, raises concerns due to its lack of scientific grounding. It fails to consider the practicalities and challenges associated with conducting clinical trials, especially in terms of feasibility and patient recruitment. This approach may hinder rather than foster R&D of new and innovative treatments for children in Europe, potentially leading to a decrease in the advancement of paediatric healthcare.

The proposed seven-year limit on OD could also have a notable impact on patients: To illustrate the magnitude of this impact, we considered the patients affected by these products. CRA analysis examined products that span more than seven years between OD and marketing approval. An estimation of the potential number of targeted patients was derived using the prevalence data of rare diseases from the OD approval report (Figure 15).

76 European Commission. (2023, April 26). Impact assessment report and executive summary accompanying the revision of the medicines for rare diseases and children legislation. Available at https://health.ec.europa.eu/system/files/2023-04/swd_2023_192_1-2_ia_en.pdf

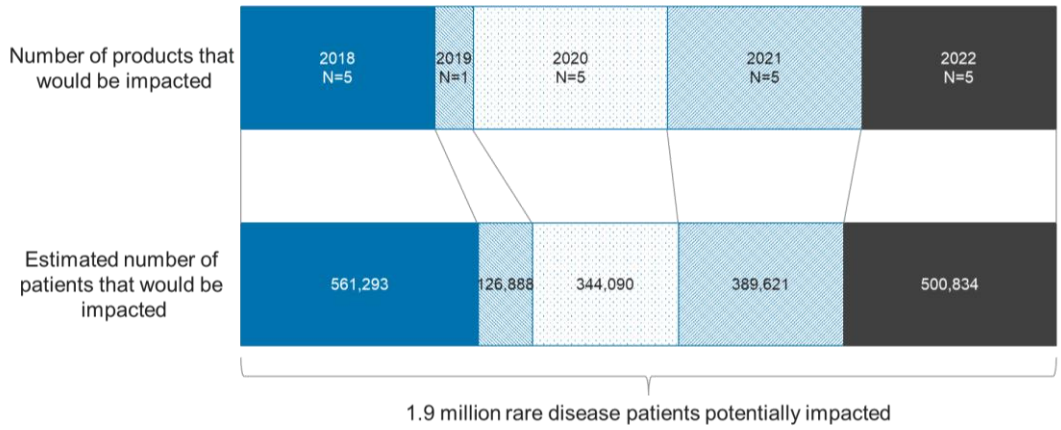
77 RAND Corporation (2022). The Financial Ecosystem of Pharmaceutical R&D. Available at https://www.rand.org/pubs/external_publications/EP68954.html

78 CRA interview discussion with VC experts

79 ACRO Health (2023). The Value of Clinical Research and Technology Organizations. Available at https://www.acrohealth.org/value-of-clinical-research-organizations/

80 CRA interview discussion with VC experts

Figure 15: Number of patients potentially impacted if the proposed seven years OD cut-off was retroactively used (products with MA between 2018–2022)



Source: CRA analysis leveraging EPARs published by the EMA[81],[82]

This analysis sheds light on the possible patient impact in scenarios where companies, constrained by a seven-year OD limit without other benefits such as external funding or market exclusivity, opt to discontinue trials or delay European launches. Without the necessary incentives and available time frame to take a drug from OD to market approval, the likelihood of companies halting or postponing critical drug development projects increases. Consequently, this might lead to a scenario where patients with rare diseases could face prolonged wait times for potentially life-saving treatments or, in the worst case, have no access to these treatments at all. This proposed limit could, therefore, stand in the way of meeting the healthcare needs of patients.

3.2.2. Orphan market exclusivity

The European Commission's proposal aims to amend the baseline orphan market exclusivity (OME) from 10 to nine years, with a possibility of extending it under specific circumstances.

The current period of 10 years is clear and hence predictable. The proposed variation of the OME period on the other hand is less predictable. With provisions for additional years based on the fulfilment of criteria related to HUMN, launch conditionality and the introduction of potentially new indications for already authorised orphan drugs. While the modulation of OME is designed to theoretically allow the exclusivity period to extend to 12 years, this is dependent on satisfying criteria which in any case are impossible to predict at the start of the approval

81 The methodology employed to estimate the number of patients affected by a retroactively applied Orphan Drug (OD) cut-off followed a series of steps. Initially, we identified the products that exceeded a seven-year time frame from the initial OD designation to marketing authorization (MA) for products that attained MA between 2018 and 2022, utilising the EMA approvals information. Following this identification, these drugs were aligned with the estimated prevalence data provided by the EMA, as documented in the initial orphan medicine assessment report. Subsequently, these prevalence figures were matched with the current population statistics of the EU to obtain the count of rare disease patients impacted by this retroactive OD cut-off. Through this analytical progression, a comprehensive estimation of the affected patient population was derived, reflecting the implications of the extended duration from OD designation to MA on the rare disease community within the European Union.

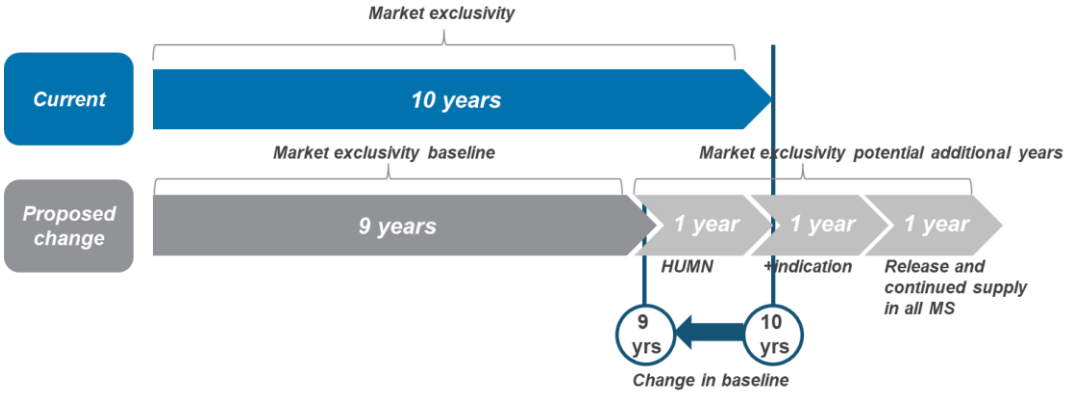
82 EMA (2020–2023). EPARs. Available at https://www.ema.europa.eu/en/medicines

process. The Commission's analysis does not include any focus on companies of different maturity but assumes they can all achieve these goals.

Drawing from interviews with small biotech companies, there are several reasons to question this conclusion.

The length of OMP exclusivity is seen as an important differentiator for Europe: The significance of the 10-year OME was notably highlighted through interviews both by emerging /small biotech companies and by VC as providing a competitive edge over the US, where the market exclusivity for orphan medicines stands at seven years. [83,84] This edge is important as it offsets some of the concerns regarding the complex and challenging European launch environment. The policy, and the impact of its change, needs to be seen within the context of the larger ecosystem – a longer exclusivity period is needed to offset the more challenging market access landscape, namely its longer approval process and its drawn out pricing and reimbursement negotiations which delay launches, leading to lower overall prices and subsequent revenue. Reduction of this protection minimises the offset, making the ecosystem less attractive.

Figure 16: Venture capital investors identified baseline change from the current regulatory environment vs the proposed changes in OMP.



Source: CRA summarisation of the proposed GPL and insights from interviews

Modulation is seen as uncertain, leading to investors focusing on baseline protections when making a decision: Investors and biotech companies are likely to view the potential additional years of exclusivity cautiously as they are contingent on meeting certain launch conditions. This caution is based on the early stage at which VC investment takes place, leading to a limited ability to predict launch outcomes. In fact, biotechnology companies, in interviews, suggest they themselves cannot predict whether they will meet launch criteria during product development and early clinical trials.

The requirements to satisfy modulation are not seen as practical as these incentives are only rewarded at the point of MA. For example, most mature pharmaceutical companies currently struggle to progress through pricing negotiations for all 27 Member States in a timely enough manner to launch in all of them within a reasonable time frame.[85] Both Tier 1 and 2 companies and VCs, in the interviews, highlighted that they do not have the infrastructure to achieve this.

83 CRA interview discussion with VC experts

84 FDA Designating an Orphan Product: Drugs and Biological Products. Available at https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products

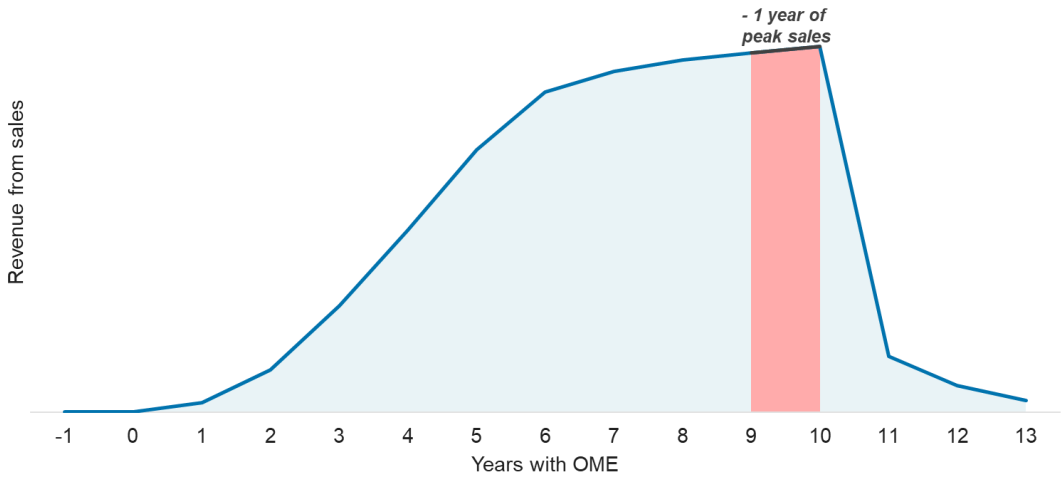
85 https://www.efpia.eu/media/636822/root-cause-unavailability-delays-cra-report-april-2022-final.pdf

Other modulation incentives are uncertain, as will be highlighted below, particularly modulations provided at launch, such as HUMN.

This will significantly reduce commercial value as investors frequently construct a Net Present Value (NPV) model when evaluating biotech investments. NPV models are a method of valuing an asset by calculating the present value of expected future cash flows, discounted at a rate reflecting the risk and time value of money.[86] Based on the insights gathered through the interviews, the reduction in OME from 10 to nine years could impact NPV models by:

- *Reduced revenue projections:* Shortening the OME period by a year could significantly reduce the projected revenues, especially as the later years of exclusivity are often when peak sales occur due to established market presence and optimised pricing strategies (Figure 17).
- *Asset evaluation:* With lower projected revenues, the overall valuation of the asset would be diminished. This is particularly impactful in regions like Europe, where the regulatory and market dynamics might already pose challenges to high valuations.
- *Lower rates of return:* The diminished asset value translates to lower projected rates of return on the investment. This is a critical factor for investors, as it directly impacts the attractiveness of the investment.

Figure 17: Investors' loss in the perceived value of the future asset with the nine years baseline (illustrative)



Source: CRA illustrative impact on revenue

It will be challenging to predict whether a product will achieve HUMN: The modulation based on HUMN introduces a level of complexity and uncertainty as this designation is only decided (or confirmed) at the point of MA. The proposed legislative framework suggests a shift towards favouring radical, innovative output for HUMN disease by offering differentiated market exclusivity incentives.

86 Investopedia (2022). Net Present Value (NPV): What It Means and Steps to Calculate It, Available at https://www.investopedia.com/terms/n/npv.asp

Box 4: Commission's definition of HUMN

The Commission defines an orphan medicinal product as addressing a high unmet medical need where it fulfils the following requirements:

- There is no medicinal product authorised for such condition **OR** the medicine demonstrates exceptional therapeutic advancement in addition to significant benefit.
- The use of the orphan medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population.

Source: Article 70 of the Proposal for a GPL[87]

However, there is a lack of clarity in distinguishing between HUMN and UMN, along with how this classification model will operate in practice. This will be clarified over time through further guidance from EMA but would still depend on complicated criteria. It seems also highly unlikely that a consensus on this guidance and criteria will ever be found between all stakeholders involved. An additional challenge emerges from the division of rare disease patients into groups of 'unmet medical need' and 'high unmet medical need', inadvertently positioning some rare diseases and their corresponding patient groups at a disadvantage.

The proposal to modulate OME based on criteria that are unclear early in the development process introduces an additional layer of uncertainty for investors. Although the Commission defines HUMN as separate from UMN based on the demonstration of "exceptional therapeutic advancement", there is significant uncertainty as to what this criteria will look like in practice.[88] Interviews with VC highlighted that the choice to invest in a small company developing orphan medicines typically occurs during late phase I or early phase II, which can be on average more than seven years prior to marketing authorisation, based on the average time it takes for therapies to reach MA from OD (Figure 12) – although many investors and emerging/small biotech highlight that earlier stages, such as drug discovery and preclinical development, are not possible without external investment, which can occur upwards of 10 years prior to MA. This further prompts investors to leverage a baseline case when evaluating any product. They are unwilling to build their investment models on additional regulation uncertainty. As a result, when investors are building a net present value (NPV) model for any given asset, they must assume that the base case will be the only protection awarded. In effect, this results in any drug evaluation under the proposed GPL missing the highest year of OMP protected sales (Figure 17).

To highlight the difficulty in determining whether a future asset will target HUMN, we analysed the disease condition of orphan medicines at the time of OD and their indication at the time of MA. Our examination of orphan medicines approved between 2018–2022 reveals that of 81 orphan medicines, the disease condition that the manufacturer submitted as their target differed

87 European Commission (2023). Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006. Available at https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52023PC0193

88 European Commission (2023). Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006. Available at https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52023PC0193

from their indication at MA in 59% of cases, typically narrowing to a more specific patient population following clinical trials, although this direction was not consistent across indication changes.[89] This finding underscores the challenge of predicting whether future medicines will target HUMN. It lends support to the argument that investors are likely to discount any potential additional years of exclusivity, as the uncertainty effectively diminishes the perceived future value of the asset. In the long term, this will harm innovation in the orphan space, as these smaller companies are disproportionately responsible for innovation.

Impact of HUMN on payers: Insights gathered from interviews with mature biopharma reveal a prevalent concern that payers might leverage the criteria for HUMN as a negotiating tool for lower prices. This scenario poses a significant challenge to the entire innovation value chain. Assets not meeting the HUMN definition could encounter lower prices, leading to diminished investment returns. This, in turn, could dampen the enthusiasm to invest in these assets, thus negatively impacting the overall investment climate within the EU orphan drug development space. The intertwining of the HUMN criteria with pricing negotiations might inadvertently create a financial disincentive for investing in orphan drugs that do not meet the HUMN criteria yet still address significant unmet medical needs. Such a scenario could potentially divert critical financial resources away from the development of orphan drugs, thereby undermining the broader objective of fostering innovation and addressing the healthcare challenges posed by rare diseases.

The proposal's aim to steer R&D investment towards more radical/exceptional innovations for HUMN diseases may not achieve the desired effect because of the inherent uncertainty and complexity it introduces. The reduction in baseline OME and the stringent conditions for extensions may deter investors, potentially impacting the EU's attractiveness for investment in orphan medicines. This could inadvertently impede progress in addressing high unmet medical needs, contrary to the intended objective of fostering innovation and addressing the healthcare challenges of rare diseases.

3.3. The impact of changes to regulatory data protection on emerging and small biotech companies

The European Commission has proposed multiple changes to the regulatory data protection (RDP) regimen, including a baseline reduction to all applicants and a new modulation system where additional protections will be awarded at or following MA for the achievement of certain criteria.

RDP serves as a crucial element for investors, safeguarding the opportunity to recoup their investments made in the biopharmaceutical domain. This is particularly important for medicines with long development timelines, which require additional protections after MA. RDP embodies a critical incentive that underpins biopharmaceutical investments' financial viability and attractiveness.

Drawing from interviews with smaller biotech companies and our data analysis, there are several reasons to believe that changes to RDP will have a particularly detrimental impact on smaller biotech companies:

Modulation of RDP incentives and considerations of smaller companies: The rules regarding RDP result in a baseline reduction in protections; however, there is an additional opportunity to extend RDP protection at launch based on UMN, undertaking comparative clinical trials and continuous supply across Member States. Although these incentives are only realised at MA, it is difficult to predict whether they will be perceived before launch. The Commission has

89 CRA analysis of EMA approvals data

included considerations for SMEs, meaning they have an additional year to comply.[90] However, SMEs (Tier 1 emerging biotechs) do not commercialise medicines, as shown for orphan medicines above. Once at the point of commercialisation, companies are inevitably larger organisations. Therefore, this allowance is of little value in the current environment and does not reflect the challenges of Tier 2 and Tier 3 companies in commercialising medicine across Europe.

Suppose companies receive less funding because of a reduction in RDP. In that case, they in turn will be less likely to meet some of the requirements for modulation, further reducing their attractiveness for investment in a cycle. This will particularly come about in small companies that already struggle with clinical trial costs and are less likely to be able to conduct more costly comparative trials. For example, an interview with a VC expert described that a company that could not raise its targeted funds had to scale back the size of its clinical trial due to insufficient funds, which led to a lower quality trial output and worse access outcomes.[91] Similarly, modulation of RDP based on UMN will negatively impact the amount of capital investments and is an unnecessary addition from their perspective. Similar to the challenges with determining the likelihood that an orphan drug will receive a HUMN designation at launch (see chapter 3.2.2), it is impossible to know until the point of MA whether an asset will achieve all the criteria required for UMN classification.

Investors will use the baseline to determine the length of RDP: To understand the full impact of GPL, we need to look at this from the viewpoint of potential investors as well as that of the biotech companies developing medications. Biotech VC works on the model that mature pharmaceutical companies will buy what they invest in – this is the key exit strategy. To get a sufficiently high return from this transaction, assets need to have strong intellectual property (IP) protections. A year's difference in any form of IP, such as RDP, substantially impacts an asset's revenues and, therefore, the return to a VC. Once a company's or asset's value goes down, VC will also respond accordingly and automatically lower the amount of money they are willing to invest as the potential return has decreased.[92]

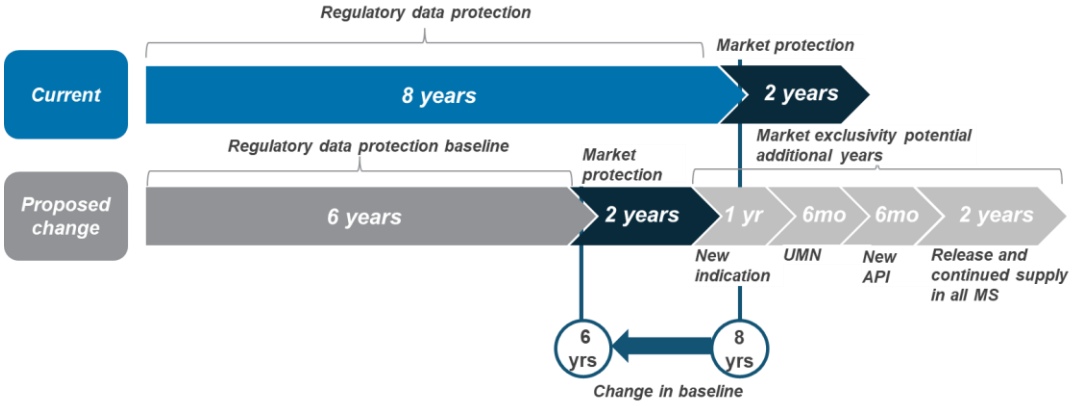
European biotech VC funds in interviews highlighted that they approach investment from a conservative angle to ensure a baseline return rather than the theoretical return from the completion of additional requirements offered through modulation. Therefore, they will assess potential investments using the baseline scenario of RDP at six years (previously eight years), where incentives are being reduced by the Commission, rather than enter investment decisions based on an assumption of other protections being awarded at approval (Figure 18). This aversion to uncertainty and conservative approach to investment leads to the proposed GPL diminishing the commercial value of all therapies, hindering the funding prospects for emerging and small biotech companies, and impeding the reach of new products to patients, thereby jeopardising innovation.

90 European Commission (2023). Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006. Available at https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52023PC0193

91 CRA interview discussion with VC experts

92 CRA interview discussion with VC experts

Figure 18: Venture capital investors identified baseline change from the current regulatory environment vs the proposed changes in RDP



Source: CRA summarisation of the proposed GPL and insights from interviews

Regulatory data protection is particularly important for smaller biotech companies: RDP was cited in the interviews with companies, trade associations and VC as a key factor in securing external investment into a new asset. This is especially pertinent for small biotech companies who do not have sufficient internal capital. Any reduction in RDP will disproportionately affect small and mid-sized companies that often depend on external investments that will be predictably diminished alongside any reduction in exclusivity protections such as RDP.[93]

The importance of RDP is intricately linked with the clinical trials process. Enrolling patients in clinical trials (CTs), especially for challenging conditions like cancer and Alzheimer's disease, can be a prolonged and difficult process.[94,95] This extended duration is a significant challenge for emerging and small companies, which may rely heavily on RDP to maintain a competitive edge. Therefore, if the CT environment in the EU stays the same, more small biotech companies will find themselves increasingly dependent on RDP. This situation could lead to a decrease in the development of innovative therapies, particularly affecting areas where there is a high need for new treatments.

Reduction and modulation requirements of RDP protection will most significantly hinder emerging and small companies and innovative products: This can be illustrated by looking at ATMPs. Although at launch the majority of ATMPs are owned by mature companies, this does not reflect the originators of ATMPs, of which Tier 1 (emerging) and 2 (small) companies make up a significant portion, as was highlighted previously (Chapter 2.3). RDP is often crucial for ATMPs since they get patented early. Without RDP they lack sufficient market protection due to limited patent protection. On average, ATMPs that received MA between 2018 and 2022 are left with 5.9 years of patent protection following MA (Figure 19). The proposed reduction of RDP from eight to six years could further deter innovation, especially considering the complex

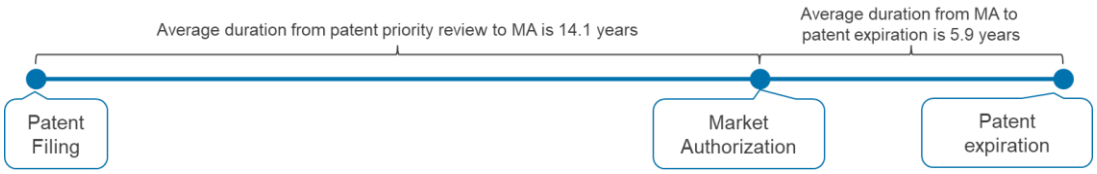
93 Kang, H. (2018). "A Start-Up's R&D Stages and the Evolution of Financing Sources: Evidence from the Biotechnology Industry". Entrepreneurship Research Journal. Available at https://www.degruyter.com/document/doi/10.1515/erj-2017-0159/html

94 Clement, C. et. Al (2019). "Challenges to and Facilitators of Recruitment to an Alzheimer's Disease Clinical Trial: A Qualitative Interview Study". *Journal of Alzheimer's Disease*. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6598018/

95 Sygna, K., Johansen, S. and Ruland, C. (2015). "Recruitment challenges in clinical research including cancer patients and their caregivers. A randomized controlled trial study and lessons learned". *Trials*. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4583740/

and lengthy development and approval processes of ATMPs. The modulation of incentives, coupled with a weakened commercial environment in Europe, directs investors and companies towards other regions, such as the US and China. This shift is supported by recent data, which shows that these regions outperform the EU in the number of ATMP clinical trials, indicating a potential re-focusing of resources and efforts away from the European market (Figure 8).[96]

Figure 19: ATMP patent duration (2018–2022)



Source: CRA analysis,[97] EMA, Global Data Patent Tracker

In interviews, this was also seen as relevant for other therapeutic areas – for example, mRNA platform therapies. Although the EMA does not consider mRNA therapies ATMPs, they represent a relevant recent breakthrough therapy in which the commercial model depends on RDP. Due to the speed of development, many patents filed by mRNA technology originators at the point of initial discovery are no longer sufficient to protect investment once they reach MA. These therapies are particularly reliant on RDP, and lowering baseline protections will only disincentivise further investment into new therapies.

Knock-on impact on biotech clusters and national innovation: Interviews with national associations reported that the GPL would have a negative impact on the development of clusters and European-grown innovation. A general perception is that Europe is less supportive of innovation. This perception may slow cluster growth by decreasing the security of investments and diminishing global competitiveness. In addition, it could make European clusters less attractive for talent and companies, both homegrown and international. This will potentially hamper collaboration and knowledge sharing, adversely affecting these innovation hubs' long-term growth and sustainability. This leads to another cycle where lagging investment leads to a lack of skills development which in turn triggers further slowing of funding.

The effects of these regulatory measures are significant, especially when considered in conjunction with the mandates of the EU Health Technology Assessment (HTA) Regulation. This significance is further amplified when these measures are integrated with other initiatives like the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation, regulations pertaining to Perfluoroalkylated Substances (PFAS), and the newly proposed revision to the Urban Wastewater Treatment Directive. These Regulations will have spillover impacts throughout the ecosystem and impact regional bio clusters and national ecosystems in addition to the larger European landscape. According to interviews, companies of all sizes in which novel technologies would be developed and scaled will be impacted by the decrease in emerging and small biotech. This includes an impact on CROs, CDMOs, and adjacent expert services, including financial and legal companies. As these support organisations, which are integral to the development of novel technologies,[98] have a smaller number of innovative companies to partner with, they will grow more slowly, damaging the

96 CRA analysis of GlobalData Clinical trials database

97 To determine the average remaining patent duration post-market authorisation, we identified approved ATMPs via the EMA database, focusing on gene, tissue, or cell-based medicines. Priority review dates from the European Patent Office, sourced from GlobalData, were then matched with EMA market authorisation dates to calculate the required durations. This list was narrowed to exclude any products that do not have an associated patent filing.

98 Ernst & Young Parthenon (2022). How CDMOs are leading innovation for pharmaceutical partners. Available at https://www.ey.com/en_gl/strategy/how-cdmo-companies-are-leading-innovation-for-pharmaceutical-partners

innovation infrastructure for the companies that choose to remain in Europe. Investigational medicinal product (IMP) and commercial manufacturing decisions are made based on proximity to innovative research hubs and the financial viability of investment in a given location.[99] Both of these will be negatively impacted by the introduction of the GPL, leaving regional hubs for development, both in research and manufacturing, as increasingly less attractive locations.

One of the main goals of the proposed legislation, as outlined by the Commission, is to prioritise investment into European life science; however, national associations have highlighted that decreasing incentives and increasing uncertainty will harm the development of new medicines and not aid them.[100]

3.4. Streamlining regulatory processes

The Commission proposes a set of measures to simplify, streamline and future-proof processes at the EMA with a specific focus on simplifying regulatory process and improving digitisation.

- **Simplifying regulatory process: changes include the abolishment of the renewal and the sunset clause. In addition to simplifying the structure of scientific committees at the Agency such as reducing the marketing authorisation applications (MAA) time frame, eliminating duplications in evaluations, and a new scheme for assessing the benefit–risk balance of combination products.**
- **Improving digitalisation: changes include provisions related to the electronic submission of applications of marketing authorisation and electronic product information (ePI) on authorised medicines.**

The proposed changes to streamline the governance and committee structure of the EMA could be beneficial for emerging and small biotech companies. The Commission argues that by focusing on the Committee for Human Medicinal Products (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC) as key scientific committees and bolstering them with expert advisory groups and broader engagement with patients, civil society and healthcare representatives, a foundation for enhanced collaboration and expedited decision-making is being laid.[101]

According to the Commission, a reduced approval time frame for standard MAA will benefit the innovation ecosystem by cutting the wait from 210 to 180 days and setting a 46-day window between the CHMP's opinion and the final MA decision, which will make EU regulatory timelines more competitive and predictable.[102] This, however, may be offset by not shortening the timeline for accelerated assessment (which stays at the current 150 days) and the

99 CRA (2022). Factors affecting the location of biopharmaceutical investments and implications for European policy priorities. Available at https://www.efpia.eu/media/676753/cra-efpia-investment-location-final-report.pdf

100 European Commission (2023). European Health Union: Commission proposes pharmaceuticals reform for more accessible, affordable and innovative medicines. Available at https://ec.europa.eu/commission/presscorner/detail/en/ip_23_1843

101 European Commission (2023). Executive summary of the impact assessment report: Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC. Available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52023SC0193

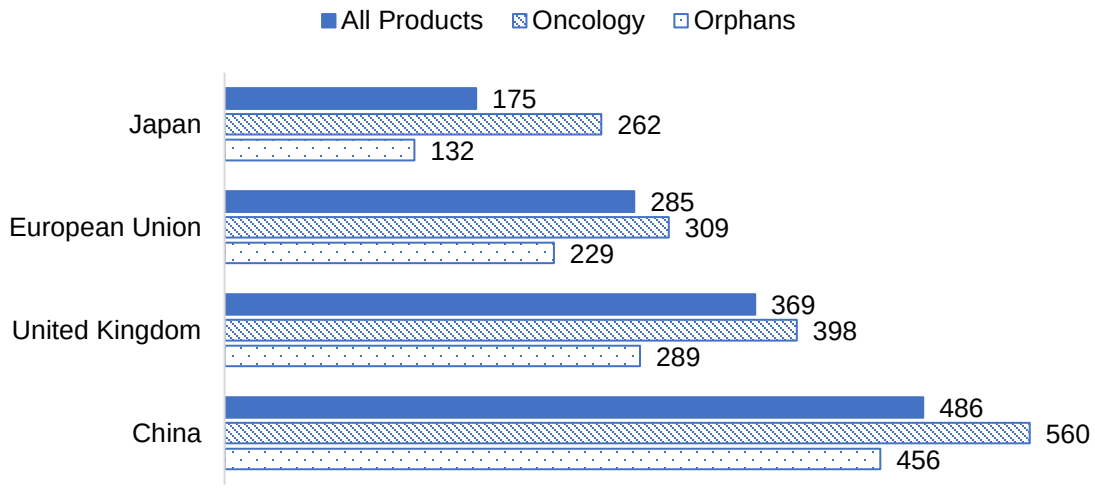
102 European Commission (2023). Proposal for a Regulation laying down Union procedures for the authorization and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency. Available at https://health.ec.europa.eu/publications/proposal-regulation-laying-down-union-procedures-authorisation-and-supervision-medicinal-products_en

introduction of the Environmental Risk Assessment, which may delay or prevent marketing approval.

Based on our interviews, these adjustments will benefit the biopharmaceutical industry at large, but particularly small and mid-cap companies. The quicker approval timeline and more straightforward decision-making process could lower barriers to market entry, making the pathway to approval less cumbersome. In interviews, companies highlighted that a major current barrier in the EU is the complexity of obtaining MA, which these changes will partially target. Moreover, these reforms are deemed necessary as the EU has been outperformed by other regions (see Chapter 2). However, companies are hesitant about the impact these changes will have as there are still significant delays in the reimbursement process due to the fragmented market access landscape where pricing and reimbursement negotiations must happen country by country.

The regulatory process is integral to the innovative biotech sector, but the EMA is falling behind other regulatory agencies: Navigating the regulatory landscape is particularly challenging for emerging and small biotech companies, who do not have the experience nor administrative capabilities of larger, mature biopharma. Thus, regulatory hurdles are common, often resulting in significant delays and high costs. The importance of developing a regulatory strategy early in the development process is essential, since errors in the early stages are less costly compared to those made closer to launch. In interviews, biotechnology companies highlighted key differences which make the approval process more challenging in the EU, such as a lack of communication channels, multiple approval committees for a single decision and insufficient pathways for expedited review. In turn, this makes the EMA approval process longer than that of other key agencies in Japan and the United States (Figure 20).

Figure 20: Median approval time longer than the FDA by regulator between January 2021 and June 2022 (days)



No. of dates used to calculate averages	FDA to EMA	FDA to PMDA	FDA to NMPA	FDA to MHRA
All products	66	24	5	34
Oncology	22	6	3	13
Orphans	19	17	2	11

Source: CRA analysis of IQVIA – Data relating to products in scope in European Access Hurdles Portal (2022)[103]

103 CRA (2023). European Access Hurdles Portal: initial results. Available at https://www.efpia.eu/media/677291/european-access-hurdles-portal-efpia-cra-report-200423-final.pdf

The gap between regulatory approval speeds is clear in key therapeutic areas such as oncology. In a dataset composed of 76 new anticancer drugs that were submitted for MAA between 2010 to 2019 at both the FDA and EMA, the review times were significantly shorter in the US.[104] Whereas it took 201 days (median) by the FDA, it took 136 days longer by the EMA (337 days, median).[105]

The timeline reductions in the overall approval times for standard MAA, from 210 to 180 days, and the time between CHMP opinion to final decision, from 67 to 46 days, are perceived positively by biotech companies interviewed – although there is a concern regarding whether these additional provisions will actually impact the approval times, as the EMA currently does not always meet its deadlines, with an average approval time of 426 days.[106] Additionally, the change in final decision duration may not be sufficient to impart change; at the moment the opinion due date is 65 days following CHMP opinion, although the average time between date of opinion and MA is 73 days (for products with a MA between 2018 and 2022), indicating that a large proportion of medicines need to wait longer than the allowed duration before receiving MA.[107] There are still many questions in the timeline, such as the absence of any communicated timelines for the Standing Committee.

The proposed guideline changes are targeted at issues that stakeholders highlighted in interviews, specifically in addressing the regulatory hurdle of needing approval from multiple committees. There were, however, additional concerns stressed particularly by Tier 1 and 2 companies, such as the failing Clinical Trials Regulation (CTR), which often relies on single Member States to progress clinical trials, and the inflexibility of the current system, which needs CT protocol changes to be made in series rather than in parallel like the FDA. These companies also reported issues with the EMA's agility in providing timely advice. This has led to delays in the past and actively causes significant financial strain on smaller companies. The regulatory and bureaucratic challenges might necessitate partnerships to facilitate market entry, underscoring the interconnectedness of the ecosystem in the pharmaceutical and biotech sectors – an indicator that works against the Commission's goal of promoting MA in Tier 1–Tier 3 companies.[108]

EMA expedited review pathways are insufficient: Enhancing patient access to crucial medicines via expedited regulatory pathways (ERP) is vital within the EU's pharmaceutical sector.[109] The EU offers several regulatory tools under the ERP umbrella, such as PRIME,

104 da Costa Gonçalves, F., Demirci, E., and Zwiers, A. (2022). A detailed analysis of expedited regulatory review time of marketing authorization applications for new anticancer drugs in the US and EU. *Clinical and Translational Science*, 15(8): 1959–1967.

105 da Costa Gonçalves, F., Demirci, E., and Zwiers, A. (2022). A detailed analysis of expedited regulatory review time of marketing authorization applications for new anticancer drugs in the US and EU. *Clinical and Translational Science,* 15(8), 1959–1967.

106 EFPIA (2023). Assessment of main provisions and key EFPIA recommendations on the revision of the pharmaceutical package. Available at https://www.efpia.eu/media/gy5j1nkt/efpia-recommendations-on-the-revision-of-the-pharmaceutical-package.pdf

107 CRA analysis of EPAR data published by the EMA

108 European Commission (2023). Proposal for a Regulation laying down Union procedures for the authorization and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency. Available at https://health.ec.europa.eu/publications/proposal-regulation-laying-down-union-procedures-authorisation-and-supervision-medicinal-products_en

109 EFPIA (2022). Expedited regulatory pathways: A toolbox to provide innovative medicines to patients. Available at https://www.efpia.eu/news-events/the-efpia-view/blog-articles/expedited-regulatory-pathways-a-toolbox-to-provide-innovative-medicines-to-patients/

Conditional Marketing Authorisation (CMA), and Accelerated Assessment (AA). However, the utilisation of these expedited pathways has been modest, with only a select number of products benefiting from them, showcasing a significant divergence from other regions. In the EU, only 9% of new active substances were approved through expedited review in 2021.[110] This is in comparison to 71% of new active substances in the US and 45% in Japan.[32] This is not a recent development; the EMA has lagged the FDA in the speed of approval and in establishing innovative pathways for drug approval. Between 2018 and 2021, 127 of 210 (60%) new drugs approved by the FDA qualified for at least one expedited program; this is in comparison to the 68 of 165 (41%) of approvals in the EMA.**[111]** The EMA fares slightly better when it comes to orphan drug approvals, although their absolute number of therapeutics eligible for an accelerated pathway is still lower than the FDA: 19/50 (38%) EMA vs 38/123 (31%) FDA.[112] In addition to more therapies being eligible for expedited approval, the speed of this approval is also faster in the FDA vs the EMA. Between 2010 and 2019, products that leveraged at least one expedited program – whether in drug development, review of MAA, or drug approval – the median time to review an authorisation application and reach drug approval in the US was 172 days, vs the EMA at 183 days.[113] Although the Commission is aiming to accelerate the time taken for approval, it does not consider how to optimise the pathways that have led to the FDA's regulatory success.

The Commission is tackling regulatory changes in a piecemeal fashion rather than addressing the root cause: As confirmed through interviews with biotechnology stakeholders across tiers, many of the Commission's proposed regulatory changes may lead to more efficient decisions and theoretically expedited access to medicines. However, they raise concerns regarding whether the evaluation is sufficiently thorough and includes all relevant experts. Emerging and small companies, many of which leverage novel technologies, highlighted that as therapies become increasingly specialised and scientific breakthroughs accelerate, more rather than less specialisation will be required from a regulatory perspective. This concern may be mitigated by the Commission's new provisions on joint scientific consultation,[114] but these same provisions may exacerbate current regulatory issues if there is not sufficient coordination between bodies, which may produce conflicting guidance, now that there is no longer a clear hierarchy between committees.

The addition of UMN criteria carries the same uncertainty impacting the RDP/OMP GPL changes: The Commission's prioritisation of medicines in areas of UMN/HUMN is carried over

110 EFPIA (2023). Assessment of main provisions and key EFPIA recommendations on the revision of the pharmaceutical package. Available at https://www.efpia.eu/media/gy5j1nkt/efpia-recommendations-on-the-revision-of-the-pharmaceutical-package.pdf

111 The number of novel therapies approved between 2018-2021 and expedited/priority reviews were collected from annual EMA human medicine highlight documents and FDA new drug therapy approval reports published by the center for drug evaluation and research. Expedited FDA programs include Fast Track Designation, Breakthrough Therapy Designation, Priority Review, and Accelerated Approval, expedited EMA programs include accelerated assessment, conditional marketing authorization and PRIME. This approach mirrors the methodology found in Hwang, T., Ross, J., Vokinger, K. and Kesselheim, A. (2020). Association between FDA and EMA expedited approval programs and therapeutic value of new medicines: retrospective cohort study. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7537471/

112 Hwang, T., Ross, J., Vokinger, K. and Kesselheim, A. (2020). Association between FDA and EMA expedited approval programs and therapeutic value of new medicines: retrospective cohort study. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7537471/

113 da Costa Gonçalves, F., Demirci, E. and Zwiers, A. (2022). A detailed analysis of expedited regulatory review time of marketing authorization applications for new anticancer drugs in the US and EU. *Clinical and translational science,* 15(8): 1959–1967. https://doi.org/10.1111/cts.13308

114 EFPIA (2023). Assessment of main provisions and key EFPIA recommendations on the revision of the pharmaceutical package. Available at https://www.efpia.eu/media/gy5j1nkt/efpia-recommendations-on-the-revision-of-the-pharmaceutical-package.pdf

to their proposed changes in the regulatory process.[115,116] Medicines addressing UMN are recommended to be prioritised for phased or rolling reviews and enhanced support over all other medicines. There is an additional acknowledgement of adapted trials and real-world evidence, although the extent of these incentives remains unclear.[117,118,119]

These changes are paired with an overall reduction in regulatory oversight and prioritisation of administrative streamlining. The changes include a single assessment for an active substance master file which will reduce redundancy and administrative burden, in addition to the abolishing of MA renewal after five years and the sunset clause. Biotechnology companies across tiers who were interviewed added that abolishing additional processes and documents will lead to greater efficiency in the overall regulatory processes; for example, allowing Member States to choose their package leaflet format will reduce unnecessary administrative burdens on the EMA. It is important to note that some national associations interviewed were cautious of the removal of MA renewal provisions; while this will lead to a reduction of administrative burden on manufacturers, it will increase the need for robust post-market surveillance to ensure ongoing safety and efficacy.

Finally, the Commission has proposed a new regulatory sandbox that it claims can be used to encourage the development of innovative solutions.[120] While biotechnology companies interviewed were optimistic about this prospect, some did note that careful oversight will be integral to ensuring patient and data safety. The proposed regulatory sandbox will aid in future-proofing the proposed framework and ensure the EMA will not fall behind other regions before the next legislation update. It provides the regulatory agency with a degree of flexibility to ensure that a pathway exists for novel therapies to gain approval where one might not currently exist. This will particularly aid emerging and small biotech companies that are at the crux of the development of innovative products, as evidenced by their role as key originators in the development of ATMPs (Figure 9). It is important to note that there is limited clarity on this sandbox, and it will be essential to ensure that the EU's regulatory standards remain consistent to avoid a system where different efficacy, quality and safety standards are established for certain novel medicines. Additionally, there needs to be careful monitoring of scope to ensure that the sandbox will be sufficiently capable of aiding novel therapies without becoming a preferential pathway for all medicines. This new bespoke plan for innovative medicines will

115 Stella Kyriakides (2023). Opening Remarks by Commissioner Stella Kyriakides at the Exchange of Views with the ENVI Committee – Revision of EU Pharmaceutical Legislation. Available at https://ec.europa.eu/commission/presscorner/detail/en/SPEECH_23_2472

116 European Parliament (2023). Initial appraisal of a European Commission Impact: Revision of the EU pharmaceutical legislation. Available at https://www.europarl.europa.eu/RegData/etudes/BRIE/2023/747464/EPRS_BRI(2023)747464_EN.pdf

117 Stella Kyriakides (2023). Opening Remarks by Commissioner Stella Kyriakides at the Exchange of Views with the ENVI Committee – Revision of EU Pharmaceutical Legislation. Available at https://ec.europa.eu/commission/presscorner/detail/en/SPEECH_23_2472

118 European Parliament (2023). Initial appraisal of the European Commission Impact Assessment: Revision of the EU pharmaceutical legislation. Available at https://www.europarl.europa.eu/RegData/etudes/BRIE/2023/747464/EPRS_BRI(2023)747464_EN.pdf

119 Of note is the fact that there are no specific provisions on the use of rolling reviews in the GPL; rather, there is a short note regarding their importance following the COVID-19 pandemic. This is important as rolling reviews were mentioned in the various impact assessments and in the opening remarks made to Parliament concerning the GPL.

120 European Commission (2023). Proposal for a Regulation laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency. Available at https://health.ec.europa.eu/publications/proposal-regulation-laying-down-union-procedures-authorisation-and-supervision-medicinal-products_en

provide the EMA increased flexibility into the future, but it is unclear to what extent this new sandbox is bound by other regulations proposed in the new GPL.

3.5. Additional regulatory requirements for EMA marketing approval- transparency of R&D funding and environmental risk assessment

The European Commission has proposed measures to increase transparency on the contribution of public funding to research and development costs and reduce the environmental impact of medicinal products:

- **Increase transparency: The proposal requires marketing authorisation holders (MAHs) to publish a report of any publicly provided direct financial support for research and development, with information easily accessible to the public on a dedicated web page. The Commission expects that transparency of public funding for medicines will help to maintain or improve access and affordability.**
- **Reduce environmental impact: The proposal strengthens the requirements and expands the scope (e.g., to cover the risks of antimicrobial resistance) for the environmental risk assessment (ERA) necessary for receiving marketing authorisation of a new medicinal product.**

Small and mid-cap biotech (Tier 2 and 3) companies voiced concerns over the added bureaucratic burden posed by environmental risk requirements and transparency in R&D funding. These requirements could demand additional investments and external consultancies to comply, potentially hindering the marketing authorisation process for companies with limited capacity. The Commission acknowledges that the transparency requirements regarding supply chain actors and environmental risk assessment will likely "represent a substantial burden on SMEs", but they do not identify R&D transparency as placing a similar burden. Furthermore, they argue that horizontal measures and a more harmonised regulatory system will counteract this burden.[121] However, these benefits are only assessed qualitatively.

It is unclear what the true impact of these changes will be, both on the entire biotechnology ecosystem as well as on specifically emerging and small biotechs and companies that specialise in the manufacturing of therapies. While the transparency initiatives and ERAs are welcome additions to a pharmaceutical industry with sustainability as a key pillar,[122] the additional paperwork burden may add an additional barrier to development for small companies. Additionally, in interviews, manufacturing-focused companies raised concerns surrounding the impact that these additional provisions will have on their operations. Specifically, they noted that there is significant uncertainty on what the consequences are when an ERA fails to meet regulatory standards. These unclear consequences may drive companies to accelerate the current manufacturing trend away from Europe and towards the US or China.[123] This is especially pertinent for ATMPs and other advanced therapeutics such as CAR-T where the manufacturing process is a major aspect of therapy.[124] These concerns have

121 European Commission. (2023, April 23). Impact assessment report and executive summary accompanying the revision of the general pharmaceutical legislation. Available at https://health.ec.europa.eu/publications/impact-assessment-report-and-executive-summary-accompanying-revision-general-pharmaceutical_en

122 EFPIA (2023). Assessment of main provisions and key EFPIA recommendations on the revision of the pharmaceutical package. Available at https://www.efpia.eu/media/gy5j1nkt/efpia-recommendations-on-the-revision-of-the-pharmaceutical-package.pdf

123 CRA interview discussion with company

124 Natalia Egri, Iñaki Ortiz de Landazuri, Clara San Bartolomé, J. Ramón Ortega, Marta Español-Rego, Manel Juan (2020). CART manufacturing process and reasons for academy-pharma collaboration. Available at https://pubmed.ncbi.nlm.nih.gov/31669547/

not been confirmed, as the Commission has not addressed many of the open questions concerning the GPL, although this uncertainty has already prompted many organisations to consider alternative manufacturing locations.

3.6. New incentive for addressing antimicrobial resistance (AMR)

The European Commission has proposed a new incentive to encourage and reward the development of priority antimicrobials. Novel antimicrobials meeting a set of criteria will be awarded a transfer exclusivity voucher (TEV) upon marketing authorisation. TEV awards an additional year of regulatory data protection for any asset within the voucher holder's portfolio, and the voucher can be either applied by the antimicrobial developer or sold to another manufacturer.

The Commission considers TEV to specifically benefit SMEs, considering the reward at the stage of regulatory approval to be an "early" reward and arguing that the promise of this award would support SMEs to attract private funding mechanisms, such as VC.[125] Therefore, some proportion of the voucher's value will be transferred to the SME developer. The Commission notes that TEV is intended to reward antibiotic developers specifically and notes that these are often SMEs.[126] However, this perspective on the benefit of TEV to SMEs does not consider the innovation pathway and cycle.

The development of novel antimicrobials is predominantly driven by emerging (Tier 1) and small (Tier 2) biotech companies (Figure 21). The TEV incentive is designed to boost the potential returns on investments, aiming to contribute to the growth of these companies. Emerging and small companies involved in antimicrobial development welcomed the TEV proposal. However, given that emerging and small biotech companies are financially precarious and often lack the required funds to develop their assets, this needs to be a package of push and pull incentives. There were also concerns expressed about the size of the TEV. Financial simulations suggest that the average cost of TEV incentives falls below Europe's fair share of contribution, leaving space for additional, country-specific support.[127] To make this field of R&D more attractive and provide supplementary support to small biotech firms, various incentives were suggested through the interviews. These included push incentives for early development phases that provide immediate financial support to cash-strapped emerging and small biotech companies or revenue guarantees that establish certainty for future returns to early-stage investors.

While in the interviews it was highlighted that the new incentive for antimicrobials is supportive of emerging and small companies involved in the development of antimicrobials, bringing predictability and a reward for investment, it was also noted that a discrepancy exists between the Commission's assertion that SMEs stand to benefit from TEV and the reality of how the innovation ecosystem operates. It is crucial to note that while emerging and small companies play a vital role in antimicrobial research,[128] antimicrobial research constitutes just a small

125 European Commission (2023, April 23). Impact assessment report and executive summary accompanying the revision of the general pharmaceutical legislation. Available at https://health.ec.europa.eu/publications/impact-assessment-report-and-executive-summary-accompanying-revision-general-pharmaceutical_en

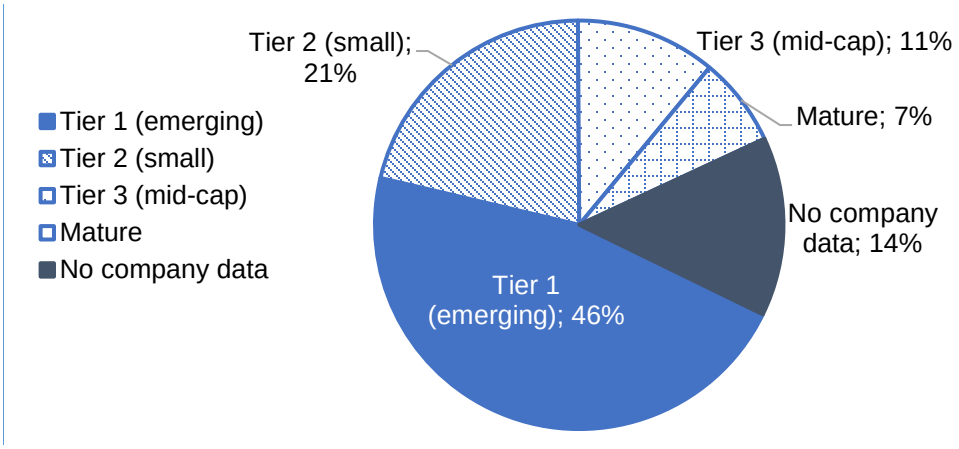
126 European Commission (2023, April 23). Impact assessment report and executive summary accompanying the revision of the general pharmaceutical legislation. Available at https://health.ec.europa.eu/publications/impact-assessment-report-and-executive-summary-accompanying-revision-general-pharmaceutical_en

127 BEAM Alliance (2023, March 13). Reflection paper: Call for a fair evaluation of the transferable exclusivity extension (TEE) vouchers. Available at https://beam-alliance.eu/wp-content/uploads/2023/03/2023-03-13-beam-fair-evaluation-tee-paper.pdf

128 World Health Organization (WHO) (2022). 2021 Antibacterial agents in clinical and preclinical development: an overview and analysis. Available at https://iris.who.int/bitstream/handle/10665/354545/9789240047655-eng.pdf?sequence=1

portion of the overall activities in the innovation cycle. As a result, the impact stemming from the proposed elements reviewed earlier in this report will have a much larger net negative impact on the innovation ecosystem and biotech sector in Europe generally, with associated repercussions on the innovation of novel antimicrobials.

Figure 21: R&D of novel antibiotics by company tier



CRA analysis of WHO pipeline report (2023)

4. Impact on the European innovation ecosystem and patient access to novel treatments

The revision of the European Commission's Pharmaceutical Package published in April 2023 builds on the pillars of the Pharmaceutical Strategy for Europe, adopted in 2020.[129] This strategy focuses on ensuring access to affordable medicines while addressing unmet medical needs, enhancing the sector's competitiveness, innovation, and sustainability, improving crisis preparedness, preventing medicine shortages, and strengthening the EU's global presence in pharmaceuticals. The proposed new Regulation and Directive aim to streamline approval processes, modify incentives for new medicines, provide a clearer definition of unmet medical need, condition RDP extension on the supply of medicines across EU Member States, and more closely align pharmaceutical regulations with environmental legislation.[130] The proposed GPL seeks a delicate balance between fostering innovation and competitiveness and ensuring patient access and affordability. Achieving this equilibrium is challenging, as focusing solely on access and affordability could potentially undermine the innovation ecosystem, limiting the development of future medicines.

Summary

The current proposals within the GPL include some positive proposals, such as the regulatory sandbox and efforts to encourage the development of antimicrobials, but these do not offset the changes to regulatory incentives that will negatively affect Europe's innovation ecosystem. To address these weaknesses in the GPL we need to consider:

- The investment potential of European biotechnology innovation and the need for an international competitive baseline of incentives and clear, predictable criteria for modulation
- Innovation maturation through collaboration and partnership, and the need for the incentives to align at each tier of biotech company
- European capacity, resilience and agility that helps to build international bio-clusters at the national level, supporting an ecosystem that includes CROs and CDMOs, and aligned with industrial strategy
- A set of incentives that support patient access to innovative treatments by encouraging a sustainable environment for clinical trials, and the development of novel medicines, rather than indirect mechanisms for controlling costs and managing national budgets

4.1. Investment potential of European biotechnology innovation

The European innovation ecosystem has many key strengths, including a strong scientific foundation, high quality human resources and a strong regulatory system. However, as set out in Chapter 2, there are weaknesses in terms of funding, particularly the depth of the VC community compared to that of the US. There are numerous reasons for this, but the fragmented European market and the barriers to accessing the home market for nascent

129 European Commission (2020). A pharmaceutical strategy for Europe. Available at https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en#:~:text=Adopted%20on%2025%20November%202020,needs%20while%20addressing%20market%20failures

130 European Commission (2023). Reform of the EU pharmaceutical legislation. Available at https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en

players play a key role. VCs are experienced in managing the inherent risk associated with investing in biotechnology, identifying potential for growth and providing tools for success. However, additional regulatory uncertainties will make this assessment more challenging, inevitably negatively impacting valuation and the willingness to invest. As set out in the previous chapters, the GPL adds exactly this type of additional uncertainty to investments:

- *Whether the OD will be in place when the medicines are applying for marketing authorisation*: OD is seen as an important signal regarding the likelihood of achieving orphan status and, therefore, affects the likely success of the medicine from a regulatory and commercial perspective.
- *The length of the regulatory protections arising from OMP and RDP both depend on many additional factors*: Investors already need to factor in the likelihood that a product will successfully achieve its clinical endpoints, the degree to which it will be superior to existing treatments on the market, and the competitive landscape. They would now also need to consider whether the therapy area will be categorised as HUMN in the future, whether the company will successfully complete comparative trials, and if there is any possibility that the company will achieve the launch considerations. Investors are likely to consider these extensions as highly uncertain and likely to simply reduce their assumptions via a reduced baseline consideration.
- *The modulation of protections and tiering of unmet need at launch similarly will add additional complicating factors to market access considerations in the Member States*: The impact on timing and protection are significant issues in terms of the modelling of commercial value, but perhaps an even bigger element is the price that an innovative medicine achieves. From the investor's perspective, there is a considerable risk of being categorised as a "low" unmet need, as this would mean the product would be priced relative to existing, potentially off-patent competitors. This is a risk that companies face today; however, products under the new GPL will be even less likely to achieve preferred regulatory status, leading to a reduced commercial life and a lower price. This increases the risk for investors – who cannot know when they make the investment whether the products will satisfy the regulatory constraints. This will be particularly those focusing on complex novel treatments with long development times that rely on RDP.

Based on the Impact Assessment and recent Parliamentary commentary, it appears that emerging and small biotech companies, and institutional investors, were not sufficiently consulted during the development of the GPL. In many cases, the companies interviewed for this report were aware of GPL but not of the detailed changes under consideration nor how these changes would impact their operations. In discussing the GPL's impact with these companies, it is clear that there exists a major concern, particularly in the fragility of the innovation ecosystem in Europe; the opportunities for emerging and small companies are already decreasing in Europe, and there is significant concern that this trend will accelerate with these new provisions.

To address the concerns and strengthen the European innovation ecosystem – one of the stated aims of the European Commission's changes to the GPL – we need to look at the regulatory incentives from an investor's perspective. This requires a baseline level of incentives that competes with other regions of the world, considering the fragmented nature of the European commercial marketplace. The regulatory incentives can be modulated, but they need to account for the timeline and partnership models used in developing novel medicines, which are based on clear criteria that can be assessed and the impact quantified years from the launch of the medicine.

4.2. Innovation maturation through collaboration and partnership

The current innovation cycle in Europe is complex. Emerging (Tier 1) and small (Tier 2) biotech companies play a key role but will only prosper if supported by public and private investment. To progress through the development stages, companies that originate novel therapies require support from VC, who will only invest if they can see a growth plan. They must then push towards accessing funding through IPOs or partnering with mature pharmaceutical organisations. In turn, the mature companies commercialise the drug, use the same profits to fund innovation in emerging and small biotech companies and realise VC return on investment. This cycle is fragile. Changes proposed in the GPL will impact how companies work together, affecting emerging and small companies to a greater extent compared to larger, mature ones. This could impact how partnering and collaboration works:

- The length of OD will affect the attractiveness of working with early-stage companies as there is additional uncertainty on the value of OD if there are additional time constraints that could lead to the expiration of designation. This could exacerbate the trend of focusing on investing in companies closer to commercialisation.
- The pressure on companies to have geographical presence in different markets to combat the fragmentation of the European innovation ecosystem will lead to additional barriers to commercialisation, which in turn will affect companies' negotiating power. In other words, the commercial attractiveness of a product is determined by whether it can be marketed across Europe; therefore, this will encourage investment in larger companies and increase the barriers that smaller companies face when trying to raise investment.
- The shrinking market receptivity to innovation will affect the European regional market pull. This perception will affect investment decision-making if Europe is not seen as a region supporting innovation. For example, one reason companies give for undertaking IPOs in the US is closeness to the key market for commercialising a successful medicine. If the regulatory process is seen as adding an additional barrier to successful commercialisation in Europe, this will only exacerbate the attractiveness of seeking IPO in the US.

Putting these impacts together suggests that the GPL will make it harder for emerging and small biotech companies to attract capital and to partner and collaborate with other key stakeholders in the innovation ecosystem. In all, the changes brought by the Commission's GPL will result in less investment in emerging and small companies while disincentivising mature companies from investing in areas due to higher uncertainty. These changes will result in a deterioration of the investment cycle and the eventual move of biotech companies out of Europe.

To address these concerns, the proposed changes need to work from the perspective of companies across tiers and consider the impact on partnerships that deliver new medicines to patients. The current SME definition used within the GPL is not fit for purpose in the life sciences industry. Instead, the rules should support smaller companies, encouraging those that wish to develop their medicines and eventually commercialise them.

4.3. European capacity, resilience and agility

Investing in innovation is highly risky and unlikely to succeed; it also takes many years and involves many complex processes. There needs to be a stable and predictable environment for innovation that still can evolve to reflect the technologies of the day.

Achieving this prospect requires confidence in the regulatory system, and the belief that innovation is recognised and encouraged. Many of the interviewees reported that they were concerned regarding the balance of the GPL; although inevitably a mixture of favourable and less favourable changes, the current proposals send the message that innovation is not valued to the same degree as it previously was.

Furthermore, there is a lack of targeted efforts to directly support the innovative biotech sector within the proposals, with a large proportion of the change committed to minimising incentives through reductions in baseline OMP and RDP. Although intangible, investor confidence could be the largest and most immediate repercussion of the proposal – with consequences felt even before the implementation of a final legislation.

The impact of the proposed GPL changes extends beyond investors and innovators, affecting various elements of the entire biotech ecosystem, including supporting industries such as CDMOs and CROs, as well as legal and financial expert services and intellectual property management. According to the Europabio-WifOR report, the biotech sector contributed significantly to the European economy, with a Gross Value Added (GVA) of €34.5 billion, escalating to €78.7 billion when considering indirect and induced effects between 2008 and 2018. This sector supported not only 223,000 direct jobs but also facilitated an additional 710,500 jobs along the value chain.[131] National associations have underscored the importance of considering the wide-ranging implications of the GPL on job and talent retention across the biotech sector in Europe. The proposed changes could lead to a decrease in VC investment, particularly affecting emerging and small biotech companies. This in turn would reduce the number of projects and collaborations for CDMOs and CROs. The reduction in demand for services would directly impact employment within these organisations, and the ripple effects of these changes would extend to national biotech ecosystems, impacting their functioning and growth. Therefore, GPL's proposed changes risk impacting not only direct employment within core biotech companies but also the broader employment ecosystem, including the range of supporting industries that contribute to the vitality and innovation of the biotech sector in Europe.

To address these concerns, the policy on regulatory incentives needs to align with the European Commission policy on supporting innovation and development of smaller companies. For example, the Commission has proposals for a regulation establishing new strategic technologies for the Europe platform (STEP). This would support for the development and manufacturing of deep and digital technologies including biotechnologies, and the strengthening of their value chains to meet the digital transitions. This is to be welcomed but will not be sustainable if companies supported through these programmes do not grow within the European innovation ecosystem.

4.4. Patient access to innovative treatments

Although the direct impact of the changes in the GPL will be on the innovation ecosystem, these changes will ultimately impact patients. The weakening of the innovation cycle will result in fewer medicines developed in Europe, leading to an estimated loss of 45 orphan medicine products (12%)[132] and 50 RDP dependent products (over 22%) in the next 15 years.[133] This impact will be primarily due to funding difficulties for emerging and small biotechnology companies, as VC firms are less incentivised to invest, and mature pharmaceutical companies look towards other regions to partner in the development of their products. This impact is clear even when considering the impacts of individual components; for example, the proposed

131 Measuring the economic footprint of the Biotechnology Industry in Europe (WifOR Study). Available at https://www.europabio.org/measuring-the-economic-footprint-of-the-biotechnology-industry-in-europe-wifor-study/

132 Neez, E. and Hutchings, A. (2023, August). Revision of the Orphan Regulation: Estimated impact on incentives for innovation of changes proposed by the European Commission. *Dolon.* Available at https://www.efpia.eu/media/tigiq5g5/revision-of-the-orphan-regulation-estimated-impact-on-incentives-for-innovation-of-changes-proposed-by-the-european-commission.pdf

133 Dolon. (2023, November). Revision of the General Pharmaceutical Legislation: Impact Assessment of European Commission and EFPIA proposals. Available at https://dolon.com/wp-content/uploads/2023/11/Revision-of-the-General-Pharmaceutical-Legislation-GPL-Impact-Assessment_vFinal.pdf?x23572

seven-year cap on OD could have impacted 1.9 million EU rare disease patients if applied retroactively over the last five years. The biggest impact will be felt throughout the innovation ecosystem following the synergetic impact of the proposed changes, and it is difficult to quantify the overall effect.

The short-term impact will be a reduced ability of Europeans to participate in clinical trials, as innovative products are developed in other regions hosting emerging and small companies. However, over time the impact will ripple through the innovation ecosystem. Mid-cap companies will be driven towards regions with more favourable, stable launch incentives, such as the US, due to the degradation of protections that are currently offsetting the challenging market access dynamics in Europe. Finally, mature multinational pharmaceutical companies will direct their investments and partnerships towards regions where these companies are soon to be concentrated, as a majority of their portfolio continues to be made up by products originated at smaller organisations.

This could change the view of Europe as a launch market. Some interviewees reported that Europe will soon no longer be the second option for launch, leaving European patients with diminishing numbers of innovative medicines. This could transition Europe to becoming the third launch choice, following the US and China, and even possibly following other smaller countries that are taking action to establish an environment to improve access to innovative medicines.[134]

To address the concerns, we need to focus on regulatory incentives to encourage innovation and attract investment into Europe's innovation ecosystem rather than an indirect mechanism of controlling costs and managing national budgets that can better be managed by other means.

134 See, for example: Australia-Canada-Singapore-Switzerland-United Kingdom (Access) Consortium. (2021, June). Access Consortium Strategic Plan 2021-2024. Available at https://www.tga.gov.au/sites/default/files/2022-09/access-consortium-strategic-plan-2021-2024.pdf