DOLON

Revision of the General Pharmaceutical Legislation: Impact Assessment of European Commission and EFPIA proposals

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Executive Summary

The European Commission has proposed revisions to the Pharmaceutical Legislation, with the view to bolster innovation in areas of unmet medical need, enhance the sector's global competitiveness, ensure timely, equitable and affordable access to medicines across the European Union (EU) and expand environmental protection. To this end, the Commission has (non-exhaustively) proposed to modulate the duration of regulatory data protection (RDP) based on conditions of need, access and evidence, to streamline regulatory procedures, to introduce a unified definition of unmet medical need and to create references to environmental policies. These proposals are informed by an Impact Assessment conducted by Technopolis.

This update represents a once-in-a-generation opportunity to strengthen the European biopharmaceutical ecosystem, if fit-for-purpose policy options are implemented in response to the ambitious goals set. That is why the European Federation of Pharmaceutical Industries and Associations (EFPIA) commissioned the present Impact Assessment, which aims to complement the evidence base supporting proposed policy revisions developed by Technopolis. This assessment was conducted independently, with EFPIA Members' role being confined to validating assumptions based on their expertise.

This study relies on risk-adjusted net present value modelling (rNPV) – which analytically represents how biopharmaceutical companies make investment and launch decisions and is consistent with previous studies – to assess the potential impact of legislative changes.

EU innovation.

Key changes proposed by the Commission (mainly, RDP modulation) are estimated to halve the average rNPV for products relying on RDP in Europe. From an EU perspective (i.e., presuming that global investment decisions are influenced proportionately by Europe), this would translate to the loss of 50 of the 225 products relying on RDP that are expected to be developed over 2020-2035 (a 22% drop). Conversely, EFPIA proposals would maintain incentives for innovation in Europe.

Competitiveness.

As a consequence of these reduced incentives to develop medicines, Europe would play a lesser role in driving global innovation: we estimate that the European share of global biopharmaceutical research and development (R&D) spend would fall to 21% in 2040, compared to 32% currently.

Small and medium enterprises (SMEs).

It appears that SMEs, which already face a more challenging investment proposition than large enterprises, would be disproportionately impacted by legislative revisions. Under Commission proposals, only about a tenth of products relying on RDP would be economically viable in Europe.

Environmental provisions.

Proposed links with environmental regulations (many of which are under revision) would compound the detrimental effect of RDP modulation on innovation by worsening the investment proposition for new medicines. While it is difficult to predict exactly the economic impact of environmental proposals at this stage, a scenario in which R&D and manufacturing costs are increased (+5%, +20% respectively), would lead to a loss of 124 of the 225 expected new medicines relying on RDP within the next 15 years.

Access.

We estimate that launch is already financially unsustainable (negative return on investment) in countries covering 6% and 8% of the EU population for large companies in prevalent and rare diseases (respectively), or 21% and 38% for SMEs. Decreasing RDP duration further hampers the economic case for launch, casting doubt over the soundness of the logic of diminishing RDP duration with the view to enhance breadth of access.

Contents

Introduction

Policy context

In its Pharmaceutical Strategy for Europe adopted in 2020, the European Commission outlined four key pillars for EU sectorial action: ensuring access to affordable medicines while addressing unmet medical needs; supporting competitiveness, innovation and sustainability; enhancing crisis preparedness and preventing medicine shortages; and ensuring a strong EU voice in the world[1]. The flagship initiative within the Strategy is the revision and consolidation of the current Pharmaceutical Package, which comprises the General Pharmaceutical Legislation, Orphan Regulation and Paediatric Regulation. Accordingly, the Commission adopted in April 2023 a proposal for a new Regulation and a new Directive[2].

The draft legislative texts includes some changes which may have profound implications.

- **Regulatory approval.** The Commission wishes to shorten standard timelines to EU approval and bolster the Priority Medicines (PRIME) programme.
- **Incentives.** The Commission proposes to reduce baseline RDP duration for new medicines from eight to six years, with various possibilities for recoupment: EU market launch and supply (+2 years); addressing unmet medical need (+6 months); comparative clinical trials (+6 months); new therapeutic indication (+1 year; as current) – with a cap of 12 years.
- **Unmet medical need.** The Commission introduces a unified definition for unmet medical need, which would be a condition for RDP extension and determine eligibility to specific regulatory pathways (such as PRIME and conditional marketing authorisation). The definition encompasses three criteria that must be fulfilled for an unmet medical need to be recognised: 1) life threatening or seriously debilitating condition; 2) lack of available treatment or remaining high mortality or morbidity; and 3) decrease in mortality or morbidity brought by the new therapy.
- **Access conditionality.** The Commission intends to encourage access by making a two-year extension of RDP conditional on the release and continuous supply of medicines in all 27 Member States within two years of marketing authorisation (or three years for SMEs).
- **Links to environment, chemicals, and water policy.** The Commission suggests better linking pharmaceuticals to existing and forthcoming environmental legislations, with the view to more extensively manage the environmental risk associated with their production. Proposals include the possibility of refusal of marketing authorisation on environmental grounds, introduction of environmental risk assessments (ERA) for antimicrobials and legacy active pharmaceutical ingredients (API), substance restrictions (e.g., PFAS), and measures related to packaging waste and wastewater. The appendix provides a more detailed overview of the proposed environmental measures.

In response to the Commission's Pharmaceutical Strategy, EFPIA has outlined a set of alternative policy proposals to meet the same goals. These proposals include streamlining regulatory procedures, strengthening RDP provisions, adopting a patient-centric approach to unmet medical need, implementing a suite of solutions aimed at tackling the root causes of impaired patient access, and ensuring the feasibility of environmental provisions[3].

[1] European Commission. (2020). A pharmaceutical strategy for Europe. Available here

[2] European Commission. (2023). Reform of the EU pharmaceutical legislation. Available here

[3] EFPIA. (2023). Assessment of main provisions and key EFPIA recommendation on the revision of the pharmaceutical package. Available here

Technopolis Impact Assessment

The Commission's proposed revisions build on findings from the Impact Assessment conducted by Technopolis, which focuses on the economic and social impacts of different sets of policy changes[4].

- **Impact of changes to incentives.** Technopolis models the revenue lifecycle of an archetypal product relying on RDP as its last form of protection, based on IQVIA data. By shifting annual revenues to match the timing of loss of exclusivity, they suggest that RDP modulation would result in a €89 million loss in profits for originators.
- **Impact of unmet medical need definition.** By linking RDP modulation to a definition of unmet medical need, Technopolis anticipates gains to society in the form of one or two additional unmet medical need products per year.
- **Impact of access conditionality.** Technopolis estimates the social impact of linking RDP duration to patient access by making two years of RDP conditional on launch and continuous supply in all 27 Member States (unless a waiver is obtained). Assuming that two thirds of manufacturers would be able to comply with the condition, 90% of the EU population is measured to gain access to newly launched medicines within three years of marketing authorisation, up from ~63%.
- **Impact of environmental requirements.** Technopolis qualitatively assesses environmental impact and suggests that measures will reduce the likelihood of potential disruptions to ecosystems and human health and lead to greater environmental awareness but may result in high costs and administrative burden.

Although these analyses build on robust data, they present shortcomings in their conceptual framing: modelling assumes that investment decisions are static rather than dynamic and does not take into consideration the knock-on impact of legislative changes on developers' portfolio investment decisions.

Report objectives

The update of the Pharmaceutical Legislation represents a once-in-a-generation chance to strengthen the European ecosystem, if fit-for-purpose policy options are implemented in response to the ambitious goals set. The changes proposed by the Commission stand to have a profound impact on manufacturer's investment and launch decisions, and hence on innovation and patient access. It is essential that legislative updates be grounded in a robust evaluation of their potential impact, rooted in the dynamics of the pharmaceutical industry.

Accordingly, this report presents an Impact Assessment aimed at complementing Technopolis' findings. Importantly, the approach is designed to dynamically reflect how pharmaceutical companies make real-life investment and launch decisions. Subsequent sections detail the methodology, present results and highlight implications from the modelling results.

[4] European Commission. (2023). Impact assessment report and executive summary accompanying the revision of the general pharmaceutical legislation. Available here

Analytical Approach

Overarching approach.

Our Impact Assessment adopts a risk-adjusted net present value (rNPV) approach, which dynamically represents the impact of the policy environment on investment and launch decisions

Pharmaceutical R&D is characterised by expensive clinical, non-clinical and quality research, long development timelines and a high risk of failure. That is why, when pharmaceutical companies make investment decisions, they balance the expected revenue with the financial risk entailed by the R&D process. In a nutshell, the expected revenue must sufficiently exceed the predicted outlay on R&D costs (including clinical trials) across all successful and unsuccessful development programmes within a set timeframe. Similarly, when making launch decisions, companies compare the marginal overheads associated with distributing in an additional country with the revenue upside. The central importance of financial analysis in decisions taken up to launch was confirmed in a recent analysis commissioned by the Dutch Ministry of Health, Welfare and Sports[5].

These investment decisions are routinely helped by financial analysis, most commonly relying on rNPV modelling (or a close variation). An rNPV model neatly summarises the strength of the investment proposition in a single figure by combining inputs relevant to the four key dimensions of pharmaceutical investment:

- **Revenue** expected based on the size of the patient population, achievable price (at net level) and duration of the market exclusivity period;
- **Costs** of R&D, production (COGS), and administration (SG&A);
- **Risk** of failure (i.e., risk of not obtaining a marketing authorisation);
- **Time** from initial investment to revenue (which is critically important for investors).

An rNPV greater than zero theoretically indicates an opportunity worth pursuing, although companies and investors generally require a much larger value to consider investment.

rNPV provides a strong conceptual framework to evaluate the impact of legislative provisions. Indeed, it yields a simple and easily comparable quantification of the strength of the economic proposition for investment or launch. It permits the capture of how environmental changes (including changes to intellectual property (IP) protections, to regulatory requirements, or to pricing and reimbursement (P&R) frameworks) are factored in decision-making within the pharmaceutical industry, hence affording a dynamic assessment. Finally, it aligns with previous work we conducted on the topic[6,7], as well as other studies on similar topics[8].

Two variations of the rNPV model are used and further described in subsequent sub-sections.

- The first variation models the **impact on innovation** by considering the investment proposition at the time of initiation of clinical development.
- The second variation models the **impact on access** by assessing the economic case for launch across Member States at the time of marketing authorisation.

[5] LEK Consulting, RAND Europe and SiRM. Special report commissioned by Dutch Ministry of Health, Welfare and Sports. (2022). The financial ecosystem of pharmaceutical R&D: An evidence base to inform further dialogue. Available here

[6] Dolon. (2020). Estimated impact of EU Orphan Regulation on incentives for innovation. Available here

[7] Dolon. (2023). Revision of the Orphan Regulation: Estimated impact on incentives for innovation of changes proposed by the European Commission. Available here

[8] For example, an analysis of the impact of the Inflation Reduction Act in the US. LEK. (2022). How the Inflation Reduction Act Will Impact the Biopharmaceutical Industry. Available here

Impact on innovation.

We estimate the impact on innovation of proposed changes for the average medicine relying on RDP as the last form of IP protection in Europe

The first variation of the model helps quantitatively assess the impact on innovation of key legislative changes proposed by the Commission and EFPIA. As stated above, it computes the investment proposition at the start of phase I of R&D.

Importantly, this model focuses solely on the cohort of products which rely on RDP as their last form of IP protection[9] (henceforth 'RDP products'; this cohort represents a third of all approved products[10]), so that we best isolate the effect of RDP modulation. This also aligns with the scope of Technopolis' analyses. Furthermore, the model's geographic scope is Europe, to best align with the reach of the legislative provisions considered. In practice, this means that we only include revenue generated and costs incurred in Europe in the model.

Inputs for the models come from a mix of sources, including Technopolis' Impact Assessment, the published academic literature and EFPIA resources (which do not include product-specific or confidential data). Where publicly available evidence is not available, assumptions are made based on Dolon expertise and validated with EFPIA Members.

We superimpose a Monte Carlo simulation onto the rNPV model to best represent the significant heterogeneity of pharmaceutical development and revenue. Put simply, the Monte Carlo simulation samples values around the inputted average based on a prespecified distribution and variance. We run 10,000 iterations of the model (i.e., consider 10,000 hypothetical investment cases) and use as outputs the average rNPV across all of these iterations and share of iterations with positive rNPV. Please refer to our past publication for a full description of model specifications[11].

We use this model in multiple analyses (which are further described below).

- First, we estimate the impact of Commission and EFPIA proposals (relative to regulatory processes, RDP and access) on incentives for innovation in Europe, compared to the current ecosystem.
- Second, we extrapolate from these results the implications of Commission proposals on Europe's place within global innovation.
- Third, we consider specificities of SMEs to differentiate the impact of Commission proposals by the size of company.
- Fourth, we add in the potential impact of links to environmental regulations.

EU innovation. We estimate the impact of Commission and EFPIA proposals on incentives for innovation within Europe

To estimate the impact of legislative proposals, we vary modelling inputs to reflect the current situation ('base case'), Commission proposals and EFPIA counterproposals. The appendix provides a summary of key input parameters considered in the analyses.

Current situation. The base case represents the status quo (i.e., incentives provided within the current legislative package) for products which rely on RDP as their last form of protection

Input parameters are selected to reflect the current investment proposition for RDP products (see Appendix I for full inputs specification).

[9] In other words, we focus on products that exclusively rely on RDP for IP protection. It should be noted that RDP also provides a critical form of IP protection for products where the patent provides longer exclusivity than RDP, as patents are more uncertain and challengeable.

[10] See Table 3 p. 38. European Commission. (2023). Staff Working Document – Impact Assessment report. Available here

[11] Dolon. (2020). Estimated impact of EU Orphan Regulation on incentives for innovation. Available here

Analytical Approach

Revenue.

We leverage the revenue curve for 'archetypal' RDP products reported by Technopolis, which suggests peak European sales of €158.7 million, reached the year prior to loss of exclusivity[12]. Average duration of RDP protection is set at 10.1 years, based on IQVIA data reported by Technopolis[13]. This average corresponds to eight years of data exclusivity, two years of market protection, and (where obtained) an additional year for products with a new therapeutic indication that is deemed to bring offers enhanced clinical benefits over existing options[14].

Costs.

We consider costs of phase I, II and III based on the published academic literature but exclude pre-clinical costs (as our model adopts the vantage point of an investor considering investment at clinical stage). Costs reported by Wouters et al. (2020) are converted to euros and adjusted for inflation. Out-of-pocket (i.e., neither risk-adjusted nor discounted) clinical costs amount to about €450 million globally[15]. As R&D costs are global, we assign a proportion to Europe; in the absence of specific data, this proportion is aligned with the share of Europe within global R&D expenditure (approximated as Europe, US, Japan and China) in 2020, based on data reported by EFPIA (32%)[16].

Yearly costs incurred at the time of marketing authorisation and health technology assessment are set at half of annual outlays for phase III trials. Annual R&D costs post marketing authorisation are set at $1.5 million for Europe, in line with an assumption previously made[17]. COGS and SG&A are derived from figures reported by top 20 largest pharmaceutical companies in their 2022 annual reports (29% and 24% of revenue respectively).

These data reflect costs incurred by average medicines and are not specific to RDP products. To confirm the validity of applying these figures to our cohort, we researched the characteristics of RDP products, based on a historical list of 37 products which saw RDP expire as their last form of IP between 2016-2021 in France, Germany, Italy and Spain (as a proxy)[18]. We do not find evidence that RDP products have systematically different R&D compared to the average medicine (in terms of duration, costs or risk), and conclude that approximating RDP products to average products is acceptable [19].

Risk.

We refer to the academic literature to compute the probability of success at each phase: 66% success at phase I, 58% at phase II and 59% at phase III[20].

Time.

We use publicly available data to estimate average time from investment to patient access: 8 years from phase I to end of phase III[21], 426 days from EMA submission to marketing authorisation[22] and 517 days from authorisation to ultimate patient access[23].

Discounting is set at 10.5%, to be consistent with previous Dolon publications and published literature[24, 25].

Commission proposals. We analytically represent key changes (relative to regulatory approval and RDP modulation) outlined in the Commission's proposal

This scenario reflects changes to revenue, costs, risk and time induced by key legislative provisions proposed by the Commission. Commission proposals of interest include those related to regulatory approval and modulation of RDP (including according to the unmet medical need definition and access conditionality). Appendix II presents all input parameters amended compared to the current situation. Note that we do not consider links to environmental regulations here, but do so in a subsequent, separate analysis.

Regulatory approval.

The Commission proposes to expedite the standard marketing authorisation procedure[26]. However, because gains in speed to approval are likely to be counteracted by increased ERA demands, we do not alter the time from submission to marketing authorisation. The Commission has also proposed to bolster the use of PRIME, which we (optimistically) model as an increase by 10% of the probability of success of marketing authorisation[27].

Modulation of RDP.

The Commission advises to reduce baseline RDP duration from eight to six years (supplemented by two years of market protection as currently). Possibilities for extension are introduced, which we consider to estimate the average duration of RDP.

- EU-wide market release and continuous supply within two years of regulatory approval is assumed not to be achieved by any product, as to date no RDP product has been successfully launched in all Member States[28]. EFPIA companies have committed to file P&R applications for newly approved medicines within all Member States no later than two years after market authorisation, provided local systems allow it[29], but this is not sufficient to guarantee release and continuous supply, given that access outcomes ultimately lie within individual countries' purview.
- Addressing an unmet medical need is modelled to be achieved by 20% of products, in line with Technopolis[30] and EFPIA estimates[31].
- The comparative clinical trials condition is expected to be fulfilled by half of products, based on Technopolis' assessment and published literature[32].
- One-year extensions for new indications bringing significant therapeutic benefits are estimated to be applicable to 10% of products, in line with current practice[33].

[12] Interestingly, these sales are estimated based on public, list prices, as stated in the Technopolis assessment. Actual revenue, reflective of net prices as well as clawbacks and other schemes aimed at managing country expenditure, is likely to be (significantly) lower.

[13] European Commission. (2023). Staff Working Document – Impact Assessment report. Available here

[14] This additional year of protection for indication expansion is not automatic and only granted in relevant cases where the regulator agrees the standard is met.

[15] Wouters, McKee & Luyten. (2020). Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA, 323(9):844-853. Available here

[16] EFPIA. (2023). The Pharmaceutical Industry in Figures. Available here

[17] See Dolon reports on the impact of revisions to the Orphan Regulation, available here and here

[18] Data on file. List of products extracted by IQVIA from ARK Patent Intelligence for the 2022 study 'Protection Expiry and Journey into the Market: Pharmaceutical products in Europe', available here

[19] Discussion with EFPIA Members highlighted that RDP products tend to be the most difficult and lengthiest to develop. In the absence of published literature to support this, we used industry averages for time and cost of R&D, as well as risk. These estimates are thus likely conservative ones.

[20] Wong, Siah & Lo. (2019). Estimation of clinical trial success rates and related parameters. Biostatistics, 1;20(2):273-286.

[21] Wong, Siah & Lo. (2019). Estimation of clinical trial success rates and related parameters. Biostatistics, 1;20(2):273-286.

[22] Lythgoe et al. (2022). Cancer Therapy Approval Timings, Review Speed, and Publication of Pivotal Registration Trials in the US and Europe, 2010-2019. JAMA Netw Open, 5(6):e2216183.

[23] IQVIA. (2023). EFPIA Patients W.A.I.T. Indicator 2022 Survey. Available here

[24] See Dolon reports on the impact of revisions to the Orphan Regulation, available here and here

[25] Wouters, McKee & Luyten. (2020). Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA, 323(9):844-853. Available here

[26] Timelines for the accelerated assessment procedure are to remain unchanged per the Commission's proposal; EFPIA asks for a maximum duration of 120 day.

[27] This assumption builds on a previous publication by the Office of Health Economics, which suggested that removal of protocol assistance by the EMA would lead to "a decrease of 10% of development success rates (i.e., phase III, regulatory review)". Protocol assistance and PRIME are not fully comparable, but in the absence of a more appropriate source, we adapt this assumption. Office of Health Economics for EUCOPE. (2020). Economic and financial challenges of developing orphan medicinal products: Does the European Regulation tackle them. Available here

[28] Table 14 of Technopolis's Impact Assessment shows that, within the 78 products with RDP expiry 2016-2024, the maximum number of countries where a product was launched was 20, achieved by 12.8% of the sample. No timeframe is specified. Available here

[29] EFPIA. (2022). Addressing patient access inequalities in Europe: The Industry commitment to file pricing and reimbursement applications across Europe and the European Access Portal. Avai lable here

[30] European Commission. (2023). Staff Working Document – Impact Assessment report. Available here

[31] EXON analysis commissioned by EFPIA (2023). Forthcoming publication

[32] Naci et al. (2020). Generating comparative evidence on new drugs and devices before approval. The Lancet, 395(10228), 986-997.

[33] As evidenced by the fact that the average duration of RDP is 10.1 years. European Commission. (2023). Staff Working Document – Impact Assessment report. Available here

Analytical Approach

EFPIA Commitment to File.

In the absence of specific data on the costs incurred by companies to complete country-level P&R processes, we assume that costs incurred between approval and patient access would be increased by 50% as a result of EFPIA's Commitment to File, following discussion with EFPIA Members.

We do not consider the Commission's proposal for a Transferable Exclusivity Voucher (TEV) in our modelling. That is a consequence of our methodological approach: we focus on product-level incentives for innovation for products which rely on RDP for IP protection. This exclusion should not be misconstrued as suggesting that TEVs as novel pull incentives have limited value or importance for sustainable R&D in antimicrobials.

EFPIA counterproposals. A second scenario aims at evaluating EFPIA's counterproposal to strengthen the innovation ecosystem

Similarly, we amend the model inputs to evaluate the impact of EFPIA's counterproposals on the investment proposition for RDP products in Europe (inputs described in Appendix II). The same changes as in the previous scenario are introduced with regards to regulatory approval and EFPIA's Commitment to File.

EFPIA proposes for the RDP baseline to be strengthened rather than shortened, for conditions connected to access conditionalities not to be introduced and for the unmet medical need definition to be linked to a more significant incentive. Accordingly, we model the RDP baseline as being prolonged by two years compared to current status (i.e., 10-year baseline). We consider addressing an unmet medical need and conducting comparative clinical trials to lead to a year-long extension of RDP each (instead of 6 months as in the Commission's proposal). We also infer that a patient-centric definition of unmet medical need would lead to broader eligibility, meaning that 50% of products would receive this year-long extension. As is currently the case, we reflect that 10% of product would receive a year-long RDP extension for an additional indication bringing significant therapeutic benefits and that all products would benefit from two years of market protection. Collectively, these changes amount to IP protection lasting 13.1 years on average.

Implications. We leverage direct outputs from the rNPV model to estimate impact on health and country-level R&D spend

From the direct outputs delivered by our rNPV model (change in share of products expected to be developed in Europe and in average rNPV vs. baseline), we extrapolate implications:

- On health benefits, by leveraging an estimate from the academic literature that every "$2,000 spent on pharmaceutical research and development increases population health by one statistical life-year"[34];
- On country-level R&D spend, by applying the drop in expected innovation in Europe, adjusted for the share of products impacted (i.e., the third of all products that rely on RDP for data protection), on observed R&D spend by EU country[35].

Competitiveness. We extrapolate the implications of Commission proposals on Europe's place within global innovation

We perform an analysis to understand the impact of Commission proposals on Europe's standing within the global R&D landscape. To that end, we leverage historical data to calculate the share of global R&D spend (equated to spend within Europe, the US, Japan and China) that Europe (EU27 + Switzerland + UK) is currently responsible for, as well as average compound annual growth rates within each country/region to 2030 and 2040 by making the assumption that all countries/regions will continue to grow at the same rate over the next two decades as that observed over the last one, with the exception of China. For China, we presume that after a period of "catch-up" to 2025 (arbitrary), the growth rate will be lower and equal to that achieved by the US. In addition, we apply the drop in European innovation yielded by our rNPV model to the predicted value of R&D spend. We apply this drop from 2028, assuming adoption of the Directive and Regulation in 2026 and an 18-month implementation period. In other words, we reflect the fact that R&D spend will continue to grow in Europe, but at a slower pace than could have been expected in an unchanged ecosystem. Importantly, we do not model the estimated impact of the Inflation Reduction Act on US R&D spend.

The case of SMEs. We consider specificities of SMEs to differentiate the impact of Commission proposals by the size of company

SMEs play a singular role in the innovation ecosystem, significantly contributing to breakthrough innovation. At the same time, their requirement for continued financing from external investors renders them particularly sensitive to the effect of the policy environment: any decreases in the investment proposition they offer directly affects their ability to attract capital, threatening their existence in the short term. Similarly, changes in the environment influence SMEs' ability to secure strategic partnerships that routinely allow products to be further developed, manufacturer and distributed.

This uniquely important yet precarious position of SMEs makes them of interest for our Assessment. We repeat the analyses described in the 'EU innovation' section above, tweaking inputs to reflect the case of SMEs. In the absence of specific, robust data from the published literature, we only modify the cost of capital, which we (conservatively) infer to be 50% higher for SMEs than that incurred by large companies (also see Appendix III).

Environmental regulations. We add in the potential impact of links to environmental regulations

In addition to proposals relative to regulatory processes and RDP, the Commission puts forward extensive environmental proposals, as well as links between the pharmaceutical legislation and other requirements regarding the environment, chemicals and water policy, which are not captured in our main analysis described above. These include increased scope and impact of ERAs, the possibility of refusal of marketing authorisation on environmental grounds, and links to a revised REACH regulation[37] and One Substance, One Assessment initiative[38].

Many of the regulations referenced in the draft Regulation or Directive are themselves undergoing revisions, hence there is significant uncertainty as to the extent and nature of the new obligations to be introduced. In addition to this uncertainty, there is a lack of identified quantitative evidence on the implications of environmental requirements. Accordingly we posit that increased obligations would translate to a 5% increase in R&D costs and 20% increase in COGS as a result of the more extensive ERA requirements and constraints on substances involved in manufacturing and packaging (see Appendix IV). It should be noted that some of the proposed changes could have more profound impacts on industry's activity: an EFPIA-commissioned analysis of the impact of a ban of per- and polyfluoroalkyl substances (PFAS) suggests that all EU production might be curtailed by this measure alone[39].

[34] Philipson & Durie. (2021). Issue Brief: The Evidence Base on The Impact of Price Controls on Medical Innovation. Working paper No. 2021-108. Becker Friedman Institute for Economics at UChicago. Available here

[35] EFPIA. (2023). The Pharmaceutical Industry in Figures. Available here

[36] EFPIA. (2023). The Pharmaceutical Industry in Figures. Availa ble here

[37] European Commission. (2023). Chemicals legislation – revision of REACH Regulation to help achieve a toxic free environment. Available here

[38] ECHA. (2020). In support of the EU chemicals strategy for sustainability: One substance – one assessment. Available here

[39] EPPA. (2023). Socio-economic analysis of the potential restriction of the per- and polyfluoroalkyl substances (PFAS) used in the production, packaging and delivery of human medicinal products. Available here

Analytical Approach

Impact on access.

We scrutinise the economics of launching in all 27 Member States, with the view to examine the feasibility of the Commission's proposed launch conditionality and the impact of reduced RDP.

A second version of the NPV model adopts the perspective of a biopharmaceutical company having just obtained marketing authorisation and considering market launch decisions. As in the previous model, it focuses on products that rely on RDP for IP protection and is European in scope. This NPV model is designed to be schematic, in the absence of reliable public data (e.g., net drug prices), but to help broadly understand whether launch in all Member States is financially viable. Model structure and inputs are described below and summarised in Appendix V.

Revenue.

The model considers two disease archetypes (a prevalent disease and a rare disease), characterised in Table 1. Prices are adjusted for each country, and anchored on German prices, based on a published pharmaceutical price index[40]. Patient populations are estimated based on the population in each country[41], disease prevalence and an assumption on the share of prevalent patients that would actually receive the therapy. We assume 10 years of RDP protection in the base case, 8.5 years given the Commission's proposals and 12 years given EFPIA's proposals. We also assume a 50% drop in patients treated with the branded originator product and 10% drop in originator price occurs at loss of exclusivity, leveraging Technopolis' data on normalised sales for originator products[42].

Costs.

COGS are estimated to account for 29% of revenue based on a review of company annual reports. SG&A costs are differentiated between small and large companies: SMEs are assumed to have annual overheads varying between €5 million and €20 million based on country size, while large companies are assumed to have yearly SG&A varying between €2 and €10 million. That is because we consider that marginal overheads are spread across more products in larger companies than smaller ones.

Time.

We consider time to patient access varying from zero to three years, based on the EFPIA WAIT indicator[43].

The model is structured to yield a binary prediction as to whether launch in a given country is expected, based on a positive vs. negative NPV at the time of regulatory approval.

Table 1. Key assumptions relative to revenue estimates

Archetype	Prevalence	German price (used as anchor)	Peak share of prevalent patients treated
Prevalent disease	1,000 per 10,000	€2,000	1%
Rare disease	1 per 10,000	€100,000	15%

[40] TLV. (2022). International price comparison 2021: An analysis of Swedish pharmaceutical prices in relation to 19 other European countries. Available here

[41] Eurostat. Data browser. Available here

[42] European Commission. (2023). Impact assessment report and executive summary accompanying the revision of the general pharmaceutical legislation. Available here

[43] IQVIA. (2023). EFPIA Patients W.A.I.T. Indicator 2022 Survey. Available here

Results & Discussion

EU innovation.

We find that the changes proposed by the Commission have significant detrimental impacts on the investment proposition within Europe, while those proposed by EFPIA maintain the status quo.

Results relative to the impact on innovation in Europe of the Commission proposals and EFPIA's counterproposals are presented in Table 2. Our modelling suggests that the changes proposed by the Commission would decrease the amount of innovation expected in Europe by 22%, which equates to a 'loss' of 50 products between 2020-2035 compared to what would have been expected without a revision of the regulation. The key driver of this negative impact is the shortened duration of RDP; a secondary driver is the increase in costs incurred by industry as a result of the Commitment to File.

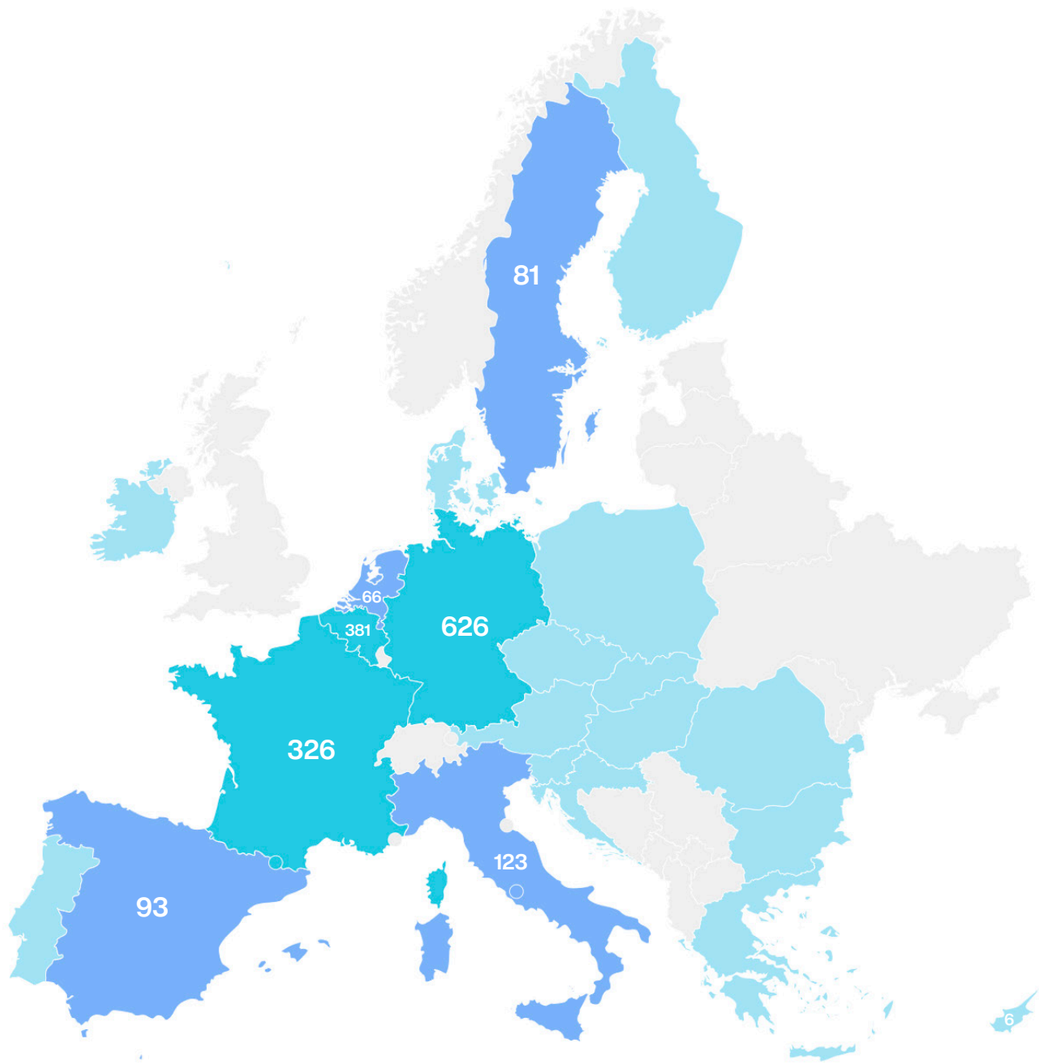
Conversely, changes proposed by EFPIA stand to drive little change on incentives for innovation compared to those provided by the current ecosystem. It should be noted that this result reflects two opposite influences on the investment proposition entailed by EFPIA counterproposals: on the one hand, the EFPIA Commitment to File (aimed at enhancing access) increases costs for developers in the short term; on the other hand, EFPIA's proposal to strengthen RDP expands IP protection in the long term. The rNPV methodology, which discounts all future costs and revenues, places more emphasis on the short-term expense associated with the Commitment to File than the long-term benefits of lengthier IP.

Table 2. Incentives for innovation in Europe for products relying on RDP given the current legislative ecosystem, Commission proposals and EFPIA counterproposals

Model results	Current ecosystem	Commission proposals	EFPIA counterproposals
Average rNPV	€10.1 million	€4.6 million	€10.3 million
Change vs. current ecosystem	-	-55%	+2%
Innovation expected by 2035	225 products	175 products	221 products
Change vs. current ecosystem	-	50 products "lost" (22%)	4 products "lost" (2%)

The 'loss' of 50 products by 2035 given Commission proposals corresponds to up to 16 million life years lost in Europe, as well as up to €2 billion of R&D activity within EU countries potentially at risk (detailed in Figure 1).

Figure 1. Estimated annual R&D activity lost as a result of Commission proposals



Results & Discussion

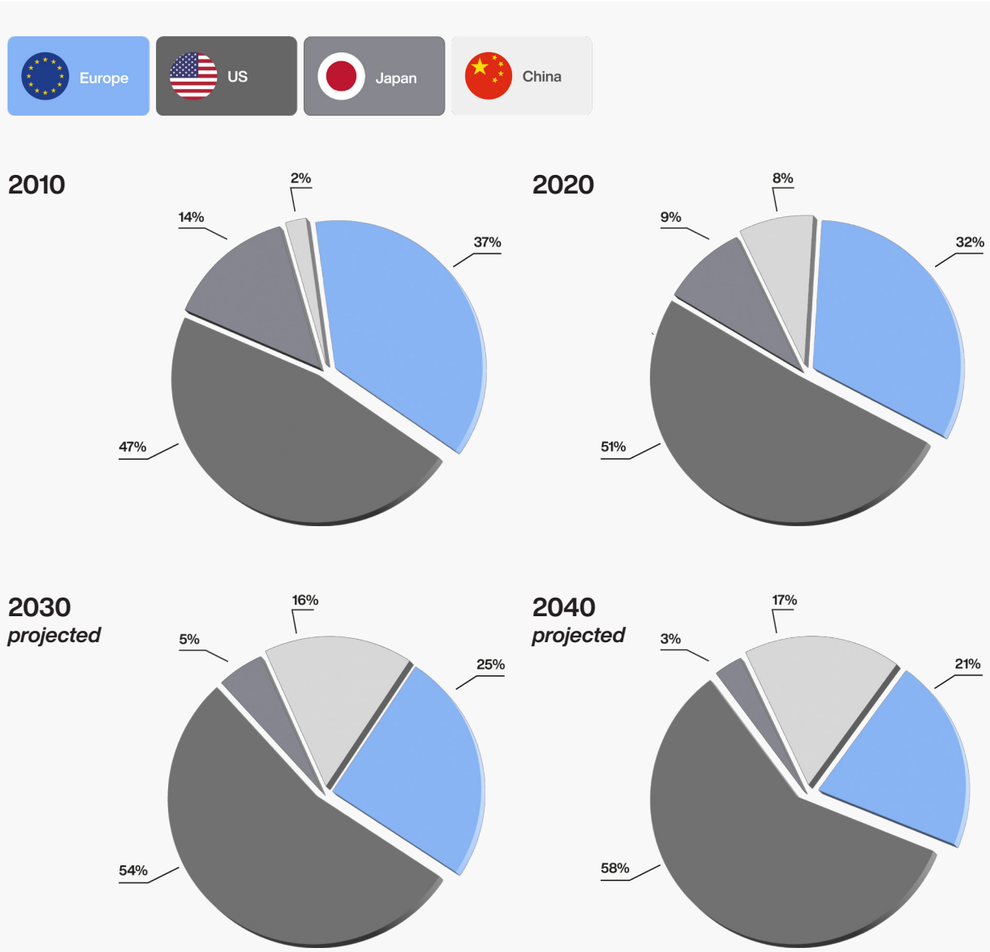
Competitiveness.

Over time, Europe may come to play a lesser role in driving global innovation

Reductions in incentives to invest in biopharmaceutical innovation, as well as reducing the amount of new medicines approved in Europe, is also expected to reduce the intensity of biopharmaceutical R&D in Europe. The estimated 22% reduction in medicines developed by 2035 is expected to translate into reduced expenditure on R&D in Europe.

Figure 2 shows that Europe might contribute to just 21% of global R&D spend by 2040, compared to 32% currently, as a result of a slower growth in R&D activity compared to that achieved by other regions.

Figure 2. Share of pharmaceutical R&D spend between Europe, US, Japan and China



SMEs.

SMEs, which offer a weak investment proposition within the current environment, are expected to see their attractiveness further lessened by Commission proposals.

As described in the methods section, we make a single tweak to represent the investment proposition offered specifically by SMEs: we increased the cost of capital by 50%. This lone change is sufficient to have significant impact in our modelling: the average base case rNPV falls from €10.1 million to -€4.2 million. While this result should be interpreted cautiously, given the scarcity of inputs specific to SMEs, it does suggest that the investment proposition for RDP products in Europe developed by SMEs is precarious even within the current legislative environment.

When considering the changes proposed by the Commission, average rNPV falls to -€6.1 million, suggesting a further deterioration of the attractiveness of SMEs within Europe. Following these changes, it is estimated that only about one in ten SME-developed product would be economically viable.

Environmental regulations.

Links to environmental requirements paired with other Commission proposals are likely to profoundly and negatively affect incentives for innovation in Europe.

Table 3 summarises outputs related to the impact of Commission proposals (regulatory approval and RDP modulation) coupled with increased environmental demands.

Our modelling suggests that, should linkages between the Pharmaceutical Legislation and environmental regulations result in significant increases in development and manufacturing costs, European's incentives for innovation would be impacted. More specifically, we find that increases of 5% in R&D costs and 20% in COGS, on top of other changes directly embedded in the legislation, could translate to up to half of the RDP products no longer being economically viable in Europe within the next 15 years.

Table 3. Incentives for innovation in Europe for RDP products given the Commission proposals and links to environmental links requirements

Model results	Current ecosystem	Commission proposals	Commission proposals and environmental links
Average rNPV	€10.1 million	€4.6 million	-€0.7 million
Change vs. current ecosystem	-	-55%	-106%
Innovation expected by 2035	225 products	175 products	101 products
Change vs. current ecosystem	-	50 products "lost" (22%)	124 products "lost" (55%)

Results & Discussion

Access.

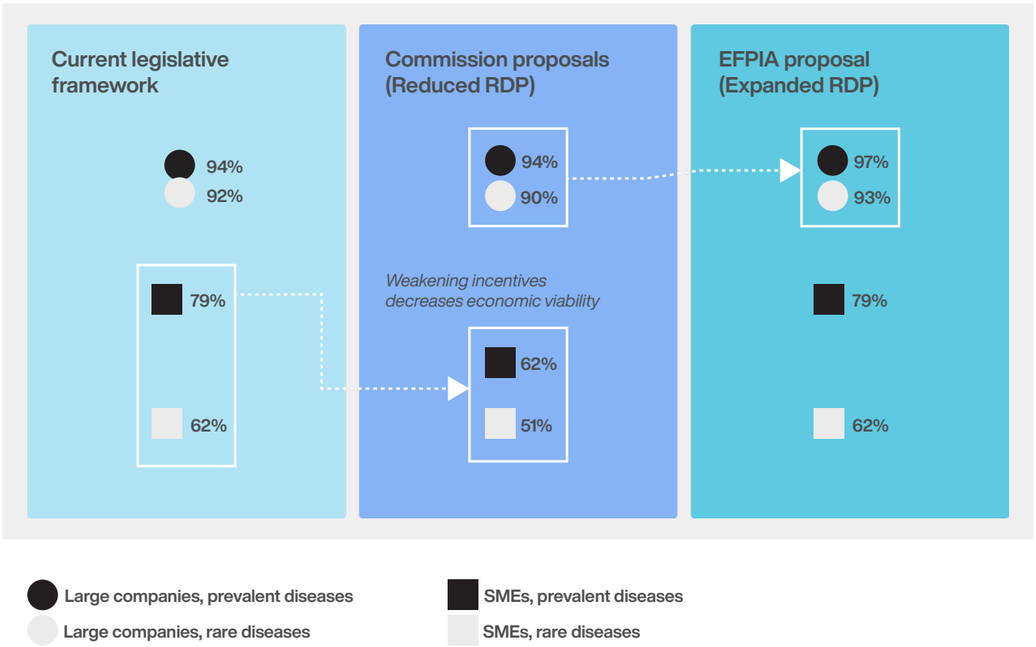
Reducing RDP duration makes filing across all Member States more challenging for industry, especially for SMEs.

Our final analysis shifts perspective to focus on the dynamics of launch across all Member States. Results are presented in Table 4; they should be seen as conceptual and indicative, rather than as a direct reflection of reality.

We identify two takeaways from these results:

- Even within the current legislative framework, it is challenging for companies to reach the entirety of the European population while ensuring a sustainable return on investment. This is particularly the case for SMEs and more pronounced for rare diseases than more prevalent ones.
- IP incentives have a direct impact on the economic viability of launch. The logic is clear: extended market protection improves the economics of supplying a medicine in a given country, including where the patient population is small and/or prices are constrained. Conversely, reduced market protection decreases the economic proposition for launch.

Table 4. Share of EU population living in a country where launch is economically viable



Limitations.

Results should be interpreted carefully, in light of our study's methodological limitations.

Predicting the impact of legislative changes as profound as those proposed to be introduced by the Commission, in a field as complex as the biopharmaceutical industry, is notoriously challenging. Limitations inherent to our methodological approach and relative to limited data availability (especially the lack of specific data for products dependent on RDP as their last form of protection) should be kept in mind as major caveats when interpreting results[44]. Crucially, our reliance on historical averages likely improperly represents the evolution of the biopharmaceutical industry in the coming decades. Nonetheless, while the exact magnitude of the impact might come to be different, the direction of the impact will not change.

While pharmaceutical investment decisions are fundamentally global in nature; our model isolates the impact of European legislative changes on European innovation. It is possible that the 50 products aforementioned may not be lost in practice, if other regions disproportionately contribute to global incentives for innovation. In particular, historically the US pharmaceutical market has been perceived to underwrite investment in biopharmaceutical innovation and subsidise new product development in other regions, including Europe. However, with the introduction of tougher price negotiation requirements in the Inflation Reduction Act, it is less likely that drops in incentives in Europe will be offset by increased expenditure in the US.

Conclusion

Although the revision of the Pharmaceutical Legislation is a laudable initiative to seek equal and affordable access, increase innovation and make the regulatory framework future proof, proposed provisions do not appear well tailored to achieve the stated objectives. This should not be misinterpreted as a net gain for society: decreasing the attractiveness of investment in Europe stands to have long-term consequences on the region's ability to innovate, ultimately impacting patients and citizens alike. Europe must create an ecosystem that actively nurtures innovation and encourages greater investment from pharmaceutical companies in pioneering therapeutic advancements.

[44] For a more thorough description of limitations, please see Dolon reports on the impact of revisions to the Orphan Regulation, available here and here

Appendices

Appendix I. Innovation model: Key rNPV model inputs used in the base case

Input	Value	Details
Revenue		
Average yearly turnover	€158 million peak revenue	▪ As reported in the Technopolis report, based on IQVIA data[45] ▪ Evolution over time (e.g., time to peak sales, drop in revenue at loss of exclusivity) based on the revenue curve for archetypal RDP products reported by Technopolis ▪ Specific to RDP cohort
Costs		
R&D costs	€150 million out-of-pocket costs globally, adjusted for inflation	▪ Sourced from the academic literature and based on recent estimates[46]; they are not sponsored by industry ▪ Adjusted for inflation and converted from US dollars to euros ▪ As R&D costs are global, a proportion was assigned to Europe; in the absence of specific data, this proportion is aligned with the share of revenue generated in Europe based on data reported by EFPIA (32%)[47] ▪ Assumption that average R&D costs are applicable to the RDP cohort
Launch year costs (approval and HTA)	€12.8 million	▪ Assumed to be half of the yearly phase III costs, in the absence of available data, based on the knowledge that launch years tend to be most expensive
Other costs (COGS and SG&A)	29% of revenue on COGS; 24% of revenue on SG&A	▪ Derived from a Dolon analysis of figures reported by the top 20 largest pharmaceutical companies in their annual reports ▪ Assumption that average COGS and SG&A costs are applicable to the RDP cohort ▪ Note: COGS may differ by product type (e.g., may be much higher for specialised therapies like ATMPs and plasma-derived products)
Risk		
Probability of success	Ph I: 66% Ph II: 58% Ph III: 59%	▪ Referred to the academic literature to estimate the probability of success at each phase[48] ▪ Assumption that the probability of success for the average RDP product is the same as industry averages

[45] European Commission. (2023). Impact assessment report and executive summary accompanying the revision of the general pharmaceutical legislation. Available here

[46] Wouters, et al. (2020). Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. Available: here

[47] EFPIA. (2023). The Pharmaceutical Industry in Figures. Available here

[48] Wong, Siah & Lo. (2019). Estimation of clinical trial success rates and related parameters. Biostatistics, 1;20(2):273-286. Available: here

Time		
R&D duration and time to access	Ph I-III: 8 years EMA approval 426 days Approval to patient access: 511 days	▪ Referred to the academic literature to estimate the time to approval[49], and used data from the EFPIA W.A.I.T. indicator to determine time from approval to access[50] ▪ Assumption that time to access remains the same for RDP products as other products*
IP protection	10.1 years	▪ Corresponds to eight years of data exclusivity, two years of market protection, and an additional year for products with a new therapeutic indication that offers enhanced clinical benefits over existing options
Discounting	10.5%	▪ Consistent with previous Dolon publications and published literature[51, 52]

Appendix II. Innovation model: Changes in inputs between base case, Commission's proposals and EFPIA's counterproposals

Input	Base case	Commission proposal	EFPIA proposal	Rationale
Launch year costs (approval and HTA)	€12.8 million	€19.2 million	€19.2 million	▪ 50% increase in costs in approval year to reflect EFPIA's commitment to file
Probability of success (Ph III to approval)	79.5%	87.45%	87.45%	▪ To reflect the Commission's proposal to shorten standard timelines and bolster PRIME, we include a 10% increase in probability of approval
IP protection	10.1 years	8.5 years	13.1 years	▪ Commission proposal assumes a 6-year RDP baseline, 20% of products meet the UMN definition (+6mo), 50% of products have comparative trials (+6mo), 0% of products launch and supply in all States, a +2y market protection and +1y RDP for new indications ▪ EFPIA proposal assumes a 10-year RDP baseline, 50% of products meet a broader UMN definition (+1y), 50% of products have comparative trials (+1y), there is no launch conditionality, +2y market protection and +1y RDP for new indications

[49] Wong, Siah & Lo. (2019). Estimation of clinical trial success rates and related parameters. *Biostatistics*, 1;20(2):273-286. Available: here

[50] IQVIA. (2023). EFPIA Patients W.A.I.T. Indicator 2022 Survey. Available here

[51] See Dolon reports on the impact of revisions to the Orphan Regulation, available here and here

[52] Wouters, et al. (2020). Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. Available: here

Appendices

Appendix III. Innovation model: changes in inputs for the case of SMEs and analysis of environmental regulations

Input	Base case	Base case (SMEs)	Commission proposals (SMEs)	Rationale
Cost of capital	10.5%	16%	16%	▪ Assumption that cost of capital is 50% higher than for large companies

Appendix IV. Innovation model: changes in inputs for analysis of impact of environmental regulations

Input	Base case	Commission proposals, including environmental regulations	Rationale
R&D costs	€150 million out-of-pocket costs globally, adjusted for inflation	€157.5 million out-of-pocket costs globally, adjusted for inflation	▪ Estimate of a 5% increase in R&D costs as a result of more extensive ERA requirements and constraints on substances involved in manufacturing and packaging
Other costs (COGS and SG&A)	29% of revenue on COGS	34.8% of revenue on COGS	▪ Estimate of a 20% increase in COGS as a result of more extensive ERA requirements and constraints on substances involved in manufacturing and packaging

Appendix V. Access model inputs

Input	Value	Details
Revenue		
Prevalence	▪ Prevalent disease: 1,000 per 10,000 ▪ Rare disease: 1 per 10,000	▪ The model considers two disease archetypes (a prevalent disease and a rare disease ▪ Prevalent patient population calculated based on country population[53]
Peak share of prevalent patients treated	▪ Prevalent disease: 1% ▪ Rare disease: 15%	▪ Assumption
Time to access	▪ Variable by country	▪ Derived from WAIT indicator and set at maximum 3 years[54]
German price (used as anchor)	▪ Prevalent disease: €2,000 ▪ Rare disease: €100,000	▪ Price adjusted for each country based on price indexes[55]
Costs		
COGS and SG&A	▪ COGS estimated at 29% of revenue ▪ Large company: annual SG&A varying between €2-10 million ▪ Small company: annual SG&A varying between €5-25 million ▪ Small yearly expense for ongoing R&D costs	▪ COGS based on Dolon analysis of company annual reports ▪ SG&A based on country size ▪ Note: COGS may differ by product type (e.g., they may be much higher for specialised therapies such as ATMPs and plasma-derived medicinal products
Time		
RDP duration	▪ 10 years (base case, but varied upwards / downwards in Commission / EFPIA scenarios)	▪ Varying RDP duration based on scenario, with 50% drop in market share and 10% drop in price at loss of exclusivity
Discounting	▪ 10.5%	▪ Consistent with previous Dolon publications and published literature[56, 57]

[53] Eurostat, data browser. Population change – Demographic balance and crude rates at national level. Available: here

[54] IQVIA. (2023). EFPIA Patients W.A.I.T. Indicator 2022 Survey. Available here

[55] TLV. (2022). International price comparison 2021. Available: here

[56] See Dolon reports on the impact of revisions to the Orphan Regulation, available here and here

[57] Wouters, et al. (2020). Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. Available: here

Appendices

Appendix VI. Five mechanisms proposed by the Commission to lessen the environmental impact of medicinal products

Measures proposed	Summary
Possibility of refusal of marketing authorisation on environmental grounds (Articles 47, 195, 196)	Introduction of possibility to refuse, suspend, revoke, prohibit supply or withdraw a marketing authorisation on environmental ground (e.g., if ERA is incomplete is incomplete/ insufficiently substantiated, or if risks identified have not been sufficiently addressed)
Introduction of manufacturing covered in the ERA for antimicrobials (Recital 72, Article 22)	ERA scope extended to cover risk of AMR selection during entire lifecycle of antimicrobials, including manufacturing inside and outside the EU
Introduction of ERA for legacy APIs (Recital 71, 72, Article 23)	Requirement for medicines authorised before October 2005 to complete an ERA; prioritisation of medicines using a risk-based approach
Increased interlinkages with other environmental legislation (Recital 69, 71, Articles 22, 23)	Need for applicants to consider environmental procedures of other EU legal frameworks that may apply to medicines
Medicinal products with environmental concerns subject to medical prescription (Article 51)	Subjection of medicinal products to medicinal prescription if they are an antimicrobial or contains an active substance which is persistent, bioaccumulative and toxic (PBT); very persistent and very bioaccumulative (vPvB); persistent, mobile and toxic (PMT); or very persistent and very mobile (vPvM)

Appendix VII. Increased interlinkages with non-pharmaceutical legislations

Measures proposed	Details
European Chemicals Agency's EU Chemicals Strategy for Sustainability	
One substance, one assessment[59]	Risk assessment and risk management of the same chemical to be consistent across all sectors, despite different uses, levels of exposure and benefit-risk evaluation in different sectors
Per- and polyfluoroalkyl substances (PFAS)[60]	Ban of all PFAS, with the exception of APIs, with a very broad definition of PFAS
REACH legislation revision[61]	Additional obligations and restrictions in REACH processes; treatment of severe health issues to fulfil criteria for essential use of chemicals, but treatment of non-severe health issues will not be deemed essential
Classification, labelling and packaging of chemicals[62]	Revision of Regulation and introduction of new hazard classes for endocrine disruptors and PBT/vPvB or PMT/vPvM chemicals
Regulation on synthetic polymer microparticles[63]	Medicines exempt from the broadening ban on microplastics, but requirement to report usage of a broader category of microplastics, including synthetic polymer microparticles
European Food Safety Authority Opinions	
Titanium dioxide (TiO2)[64]	Use of TiO2 banned in food, which affect oral medicines; Commission to review potential alternatives in Feb 2025
N-nitrosamines impurities[65]	EMA to request more supporting safety science for Nitroso Drug Substances Related Impurities (NDSRIs) to confirm lower safety risk
Zero Pollution package	
Urban wastewater treatment directive (UWWT)[66]	Extended producer responsibility specifically for the pharmaceutical sector (e.g., 'polluter pays principle')
Proposal on protection of surface and groundwater against new pollutants[67]	Updated list of water pollutants to include pain medicines, antimicrobials and hormones; all APIs included and closely monitored
Other	
Packaging and packaging waste directive[68]	Future requirement for recyclability of primary and secondary packaging; immediate removal of certain medicines if they do not comply to recyclability criteria by 2035
Corporate Sustainability Reporting Directive[69]	Mandatory reporting, with sector specific reporting standards
Animal use for scientific purposes[70]	Call for full phase-out across the pharmaceutical sector, with accelerated transition to non-animal testing
EU Taxonomy Regulation[71]	Creation of an EU classification system for sustainable activities, of criteria for pharma companies to be considered "environmentally sustainable" and of company reporting rules (e.g., biodegradability of APIs)

58 European Commission. (2023). Reform of the EU pharmaceutical legislation. Available: here

59 ECHA. (2022). In support of the EU chemicals strategy for sustainability: One substance – one assessment. Available: here

60 ECHA. (2023). ECHA publishes PFAS restriction proposal. Available: here

61 European Commission. (2023). Chemicals legislation – revision of REACH Regulation to help achieve a toxic-free environment. Available: here

62 ECHA. (2023). Understanding CLP. Available: here

63 European Commission. (2023). Commission Regulation (EU) .../... amending Annex XVII to Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards synthetic polymer microparticles. Available: here

64 European Commission. (2022). Re-evaluation. Available: here

EMA. (2020). Nitrosamine impurities. Available: here

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EMA. (2023). Ethical use of animals in medicine testing. Available: https://www.ema.europa.eu/en/human-regulatory/research-development/ethical-use-animals-medicine-testing#:~:text=The%20European%20Medicines%20Agency%20(EMA, the%20European%20Union%20(EU).

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European Commission. (2023). EU taxonomy for sustainable activities. Available: https://finance.ec.europa.eu/sustainable-finance/tools-and-standards/eu-taxonomy-sustainable-activities_en#:~:text=The%20Taxonomy%20Regulation%20was%20published,to%20qualify%20as%20environmentally%20sustainable.

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