DOLON

Revision of the Orphan Regulation: Estimated impact on incentives for innovation of changes proposed by the European Commission

Prepared by

Emilie Neez
Adam Hutchings

Funding and Contributions

This report was commissioned and funded by the European Federation of Pharmaceutical Industry Associations (EFPIA). The conceptual framework, model structure and parameters were developed by Dolon, with input from EFPIA. Dolon did not have access to any non-public manufacturer information or company-specific data. The use of specific parameter values in the model does not constitute an endorsement of these data by EFPIA.

August 2023

Contents

Executive summary

Despite the tremendous progress in the care of patients with rare diseases afforded by the 2000 European Orphan Medicinal Product Regulation, a revision of the orphan incentives framework is underway, as part of an overhaul of the general pharmaceutical package. In this study, we build on a risk-adjusted net present value model previously developed to assess the potential impact on innovation of regulatory changes put forward by the European Commission. We find that the provisions relevant to orphan medicines proposed by the Commission in April 2023 would hamper the development of 45 products in Europe in 2020-2035 (or a decrease in innovation of 12%). More profound changes, such as further shortening orphan market exclusivity and tightening criteria for obtaining an orphan designation, would amplify detrimental effects.

Introduction

The 2000 European Regulation on Orphan Medicinal Products ('Orphan Regulation') was introduced to stimulate progress in the care of rare diseases. Its enactment underlined a political commitment to equity in health care (i.e., all individuals suffering from a disease should have the same chance to benefit from a treatment, regardless of prevalence). It also recognised that the inherent characteristics of rare diseases challenge the normal functioning of the pharmaceutical innovation model, and as such require dedicated incentives to (somewhat) level the playing field. Incentives introduced include, most significantly, the 10-year orphan market exclusivity (OME), as well as protocol assistance, fee waivers and aid for research.

The Orphan Regulation delivered against its goal to stimulate pharmaceutical research and development (R&D) thanks to incentives. As of February 2023, 146 orphan medicines had an active marketing authorisation in Europe[1]. A previous Dolon analysis – on which the present study builds – estimated that about half of the orphan medicines developed in 2000-2017 would not have been economically viable in Europe in the absence of the Orphan Regulation[2].

Despite this apparent success, the European Commission intends to revise the Orphan Regulation, alongside the General Pharmaceutical Legislation and Paediatric Regulation, as part of its Pharmaceutical Strategy for Europe. The latest development in the initiative was the publication of the Commission's proposal for a new Directive and a new Regulation in April 2023[3]. Materials reiterate the key concern that innovation is insufficient in areas of greatest unmet medical needs. Accordingly, tools to better align incentives with areas of unmet need are deployed, with the view to more effectively direct innovation. (Other important concerns regard patient access, affordability, European industrial competitiveness, environmental protection and antimicrobial resistance.)

This report aims to estimate the impact on incentives for innovation in Europe of the legislative changes proposed by the Commission. We first describe the modelling approach adopted, before presenting findings and discussing implications.

Analytical approach

The analytical approach is based on a risk-adjusted Net Present Value model, which reflects how developers make investment decisions

When making investment decisions throughout the R&D process, developers estimate expected revenues and costs across the medicine's life cycle, assess the risk of failing to obtain a marketing authorisation (e.g., because of insufficient efficacy or safety concerns), and consider the time from investment to returns. Developers routinely rely on modelling, such as risk-adjusted Net Present Value (rNPV), to quantify these four dimensions and synthesise them into a single value[4]. Broadly, the higher the rNPV, the better the

[1] EMA (2023). List of European Public Assessment Reports (EPAR). Downloaded from here
[2] Dolon (2020). Estimated impact of EU Orphan Regulation on incentives for innovation. Available here
[3] European Commission (2023). Reform of the EU pharmaceutical legislation. Available here
[4] The rNPV framework should not be confused with cost-plus pricing: rNPV is a tool used by industry to inform investment decisions (i.e., used before marketing authorisation), while cost-plus pricing has been proposed as an alternative pricing

investment proposition. Conversely, a negative rNPV indicates a poor investment; development would generally not be pursued. As such, rNPV modelling is a simple and efficient tool to compare different investment propositions.

This study relies on rNPV because it analytically reflects how developers respond to the incentives framework[5]. It thus captures how changes to specific legislative provisions, the regulatory framework or in the pricing and reimbursement (P&R) landscape might affect developers' behaviour. It also aligns with previous work we conducted on the topic, which was validated by external experts[6].

Importantly, the modelling exercise focuses on Europe. Although R&D programmes and markets are necessarily global, Europe is considered in analyses as a standalone entity with the view to best tease out the effect of regulatory changes in Europe.

The reader is invited to refer to Dolon's past publication for a full description of the rNPV concept and of the modelling approach adopted[7]. The appendix provides a summary of key input parameters considered.

We revised the base case, which represents the investment proposition given the current environment, to better approximate the real economic picture for orphan medicines in Europe

In our 2020 publication, we developed a base case aimed at representing the investment proposition for orphan medicines in Europe given the current incentives package. Revenue estimates were derived from bottom-up estimates of patient numbers and net prices, informed by the academic literature. Despite feeling relatively comfortable with our data and assumptions, we ran into a conundrum: our model estimated an average annual revenue of €316 million, which contrasts with the average yearly turnover of €56 million reported by Technopolis (based on IQVIA data)[8]. At the time we made several hypotheses on the cause of this discrepancy, including that we overestimated net prices and the share of the prevalent population receiving access to the innovative treatment.

Accordingly, we revised the base case in the present study to better represent the real, observed turnover, with the view to have a more accurate representation of the current economic picture for orphan medicines in Europe. Revising the base case entailed updating assumptions on the list-to-net price and lowering the number of patients treated with any given medicine.

Several additional changes were made. A previous error in phase III costs attributed to Europe was corrected. Cost of goods and selling, general and administrative costs were amended to rely on evidence-based estimates (instead of assumptions), thanks to a new analysis of companies' annual reports. The delay between expiry of OME and introduction of generics or biosimilars was better represented. The expected drop in market share following loss of OME was increased, to reflect the increased extent of competition expected in the future.

Scenario 1: Our first scenario analytically represents proposed changes to the orphan incentive framework outlined in the Commission's new pharmaceutical package

This first scenario analytically represents the proposals outlined by the Commission in April 2023. We consider two key changes: the introduction of a cap on the validity of an orphan designation and the modulation of OME. Other changes (e.g., increased scientific support for products addressing HUMN,

approach (i.e., used after marketing authorisation). Cost-plus pricing diverges from industry's approach to price medicines according to their value; it also fails to appropriately consider risk and cost of capital

[5] Whilst some developers rely on different models than rNPV, approaches all consider revenues, costs, risk and time, making them conceptually largely interchangeable.

[6] The modelling approach used for the 2020 publication was reviewed by two independent experts, Jorge Mestre-Ferrandiz and Mikel Berdud (of the Office of Health Economics)

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

[8] Technopolis & Ecorys for the European Commission (2019). Study to support the evaluation of the EU Orphan Regulation. Available from here

adaptation of the definition of an orphan condition) are not captured, as their effect is less defined and/or expected to be relatively lesser.

The Commission has proposed to cap the duration from initial orphan designation to marketing authorisation to 7 years; products exceeding this time frame for R&D would lose the designation and associated benefits. This cap intends to "stimulate timely product development" of orphan medicines, under the premise that developers would be able to speed up clinical trials[9]. However, we posit that developers already minimise R&D duration as much as feasible while still meeting regulators' demands and health technology assessment bodies' expectations. Therefore, we model that a quarter of products would lose orphan designation because of the 7-year-cap, based on an analysis of EMA data on the lag from original designation to regulatory approval for products authorised for a first indication in the past three years.

Second, the Commission introduced the concept of OME modulation according to product characteristics. We reflected the Commission's duration of OME by category of products and made informed assumptions on the share of products expected to receive each duration, as described in **Error! Reference source not found.Error! Reference source not found.**.

Category of products	OME (scenario 1)	Share of products	Comment
Products addressing a high unmet medical need (HUMN)	10 years	20%	The share of products estimated to qualify as addressing HUMN reflects the Commission's own assumption[10].
New active substances	9 years	55%	This proportion was calculated as the share of products that do not fall within other categories.
Re-purposed and well-established use products	5 years	20%	We assumed that the share of such products would remain about constant from historical data[11], although there might be dynamic effects from the erosion of incentives.
Multiple indications	11 years	5%	The Commission proposes that HUMN products and new active substances would receive one additional year of OME per additional indication, with a limit of two years. The share of products is an assumption.

Table 1. *OME modulation in scenario 1*

The additional year of OME given to HUMN products and new active substances as a result of "Union market launch" was overlooked in the absence of a detailed specification of what might constitutes "launch" and impossibility of the target. Considering the aforementioned proposals from the Commission and our assumptions, we calculated the average duration of OME to be 8.5 years (compared to slightly over 10 years currently).

[9] European Commission (2023). Impact assessment report and executive summary accompanying the revision of the medicines for rare diseases and children legislation. Available here
[10] European Commission (2023). Impact assessment report and executive summary accompanying the revision of the medicines for rare diseases and children legislation. Available here
[11] 19% of products between 2000-2017 were known active substances or approved based on well-established use. Technopolis & Ecorys for the European Commission (2019). Study to support the evaluation of the EU Orphan Regulation. Available from here

Scenario 2: We modelled a second scenario aimed at assessing the impact of a larger reduction of OME duration and of an additional change to the orphan designation eligibility criteria

We also analysed the impact of a second, hypothetical set of changes to orphan provisions. This scenario builds on the first one, but differs in two key aspects. First, we assume a shorter duration of OME for each product category (as described in the table below), which results in an average OME duration of 6.4 years. Second, we consider the effect of updating eligibility criteria for the orphan designation, so that the *cumulative* prevalence across indications would be considered (rather than prevalence for each indication as is currently the case). We analytically represent this second change as a 15% decrease in the average number of indications per orphan medicines, as a result of a change in manufacturer investment behaviour aimed at safeguarding orphan designation.

Category of products	OME (scenario 2)	Share of products (as per scenario 1)
Products addressing a high unmet medical need (HUMN)	8 years	20%
New active substances	6 years	55%
Re-purposed and well-established use products	5 years	20%
Multiple indications	10 years	5%

Table 2. *OME modulation in scenario 2*

Results and discussion

The revised base case suggests that the investment proposition for orphans in Europe is more marginal than originally suggested

As described in the previous section, we revised the base case, which represents the investment proposition for orphan medicines in Europe given the current context, with the view to better reflect real-world dynamics. Results presented below show that, when more closely approximating the real revenue achieved in Europe by orphan medicines and accounting for the risk of development and cost of capital, the average rNPV is only €22 million (vs. €38 million in our initial analysis) .

While according to economic theory a positive rNPV would support investment, in practice developers are looking for rNPVs significantly greater than zero. In this context, a rNPV of €22 million is very marginal. As in our 2020 report, we attribute continued innovation in the rare disease space despite limited incentives to optimism from developers and a *de facto* subsidisation of global orphan innovation by the US market.

Figure 1. *The current economic picture for orphan medicines in Europe*

This result contrasts with the perceived 'over-compensation' of orphan medicine developers. This perception is likely driven by the handful of products achieving 'blockbuster' status, when in fact the *average* orphan medicine faces a tight pricing and reimbursement environment.

Regulatory changes proposed by the Commission would decrease the amount of orphan innovation expected in Europe by 12%, which equates to a 'loss' of 45 products between 2020-2035

Our first scenario was geared to represent the changes proposed by the Commission. It shows that shortening OME and introducing a 7-year validity for the orphan designation would decrease innovation expected *based on European incentives* by 12%. Building on the Commission's estimate that 375 orphan medicines would be approved over the next 15 years[12], this translates to a loss of 45 orphan medicines between 2020-2035 – which could deprive about 1.5 million European rare disease patients of a novel treatment option, and the continent of about €4.5 billion in R&D spending.

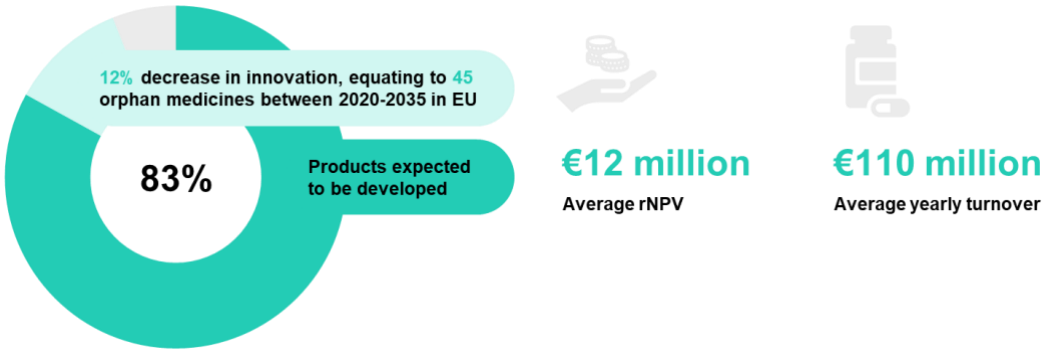

Figure 2. *Impact on orphan innovation in Europe given changes proposed by the Commission*

Our results contrast the Commission's assessment that regulatory revisions would increase the number of medicines addressing HUMN by 10%, on the basis that they would receive longer OME. Although our modelling didn't disaggregate the case of HUMN, it calls this finding into question. Products addressing a HUMN would receive 10 years OME at baseline; extended OME would only occur in the event of Union launch within two years, which is unlikely until root causes to impaired patient access are tackled[13].

These insights emphasise the critical role of dedicated incentives, paired with scientific progress and a positive commercial environment, in driving innovation in rare diseases[14]. Losing about a fifth of future orphan medicines represents a significant dip in innovation and contrasts with the Commission's ambition to boost therapeutic options for rare disease patients, as well as the Union's aspiration to remain a leading industrial hub[15].

Of course, investment decisions and the resulting innovation are necessarily global. The pace of innovation in rare diseases may not diminish if other geographies contribute a disproportionate share of incentives. This implies that future innovation benefiting European patients would depend on the goodwill of other countries – goodwill that may be eroding, as exemplified by the recent introduction of negotiations in the US Medicare within the Inflation Reduction Act.

[12] European Commission (2023). Impact assessment report and executive summary accompanying the revision of the medicines for rare diseases and children legislation. Available here
[13] Charles Rivers Associate for EFPIA (2020). The root cause of unavailability and delay to innovative medicines: Reducing the time before patients have access to innovative medicines. Available here
[14] Dolon for EFPIA (2021). Addressing unmet needs in extremely rare and paediatric-onset diseases: how the biopharmaceutical innovation model can help identify current issues and find potential solutions. Available here
[15] European Commission (2020). A pharmaceutical strategy for Europe. Available here

More extensive regulatory updates, such as further reductions of OME duration and more stringent criteria for orphan designation eligibility, would have a significantly more damaging effect on innovation in Europe

We considered an alternative, hypothetical scenario, whereby regulatory changes introduced would be more extensive (shortening OME duration by a further couple of years vs. scenario 1 and restricting eligibility to the orphan designation for products with multiple indications). Results show a decrease in the amount of innovation expected in Europe by 36% compared to that expected within the current incentives framework and by 28% vs scenario 2. Assuming again a baseline of 375 orphan medicines developed between 2020-2035, this scenario entails foregoing 135 products, novel treatment options for over four million European patients and €13 billion of pharmaceutical R&D outlay. This underlines the dramatic influence of the policy environment on innovation. Again, it should be underlined that our modelling consider Europe as the analytical unit, hence actual, *global* innovation would be impacted differently.

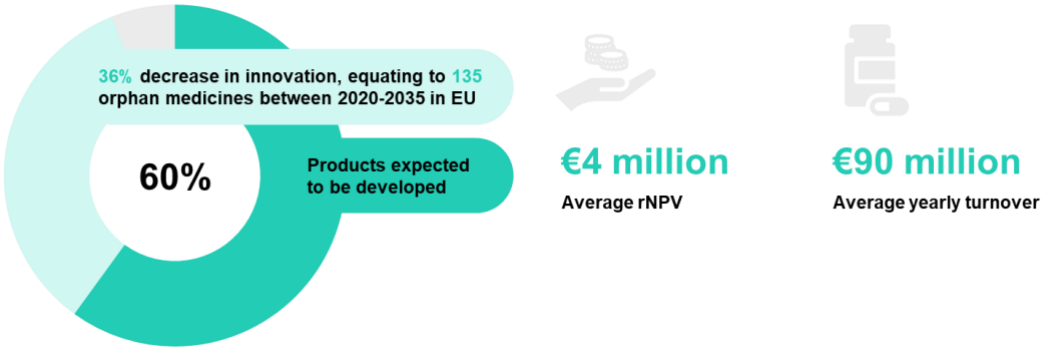

Figure 3. *Impact on orphan innovation in Europe given regulatory updates*

Results should be interpreted in light of the limitations of our methodological approach

As described in our 2020 report, the rNPV modelling approach we adopted is constrained by its reliance on averages (which may mask real-life heterogeneity) and limited data availability to inform model inputs and parameter distributions. The scarcity of evidence to inform model inputs prevented us from exploring different product archetypes (e.g., ATMPs, products addressing HUMN), which would have added beneficial granularity. Similarly, we were not able to evaluate the "shape" of innovation, or, in other words, to assess whether the Commission's proposals stand to direct innovation where it is most needed.

In addition, the retrospective nature of analyses, dictated by the reliance on retrospective data, may not fully capture rapid changes in the orphan landscape (such as the specificities of advanced therapy medicinal products). Finally, the European scope adopted, which we find warranted given the scope of the Regulations of interest, may overstate the importance of Europe within the global market.

Although individual results should be treated with the appropriate scepticism, collectively they underly the dramatic effect that constraining incentives is likely to have on innovation in Europe – and thus, on patients.

Conclusion

In her opening remarks introducing the revision of the EU Pharmaceutical Legislation, Commissioner Stella Kyriakides stated that "[the Commissions'] political vision is to build an ecosystem for medicines that is both industry-friendly and puts patients at the centre; one in which availability, access, and affordability of medicines are ensured, and go hand in hand with industrial competitiveness"[16]. In this balancing act, it seems that the Commission chose to chip away at incentives for innovation – though it needs not be a zero-sum game.

[16] European Commission (2023). Opening Remarks by Commissioner Stella Kyriakides at the Exchange of Views with the ENVI Committee - Revision of EU Pharmaceutical Legislation. Available here

Appendices

Appendix 1. *Key rNPV model inputs used in the base case*

rNPV model input	Average	Source / note
Revenue		
Prevalence	1.24 per 10,000	Calculation based on Medic et al. (2017), as in previous Dolon publication
Number of indications per medicine	1.4	Assumption aligned with previous Dolon publication
Peak market share	57%	Assumption aligned with previous Dolon publication
Drop in market share post IP/OME loss	30%*	Assumption, updated to reflect increased competition expected
OME duration	10.5 years*	Calculation reflecting products with multiple indications and paediatric extension
Price	€58,000*	Calculation based on Medic et al. (2017) prevalence to price curve, assuming 40% average drop from list to net price
Costs		
Phase I-III costs (global, out-of-pocket)	€263 million*	Wouters et al. (2020); calculation based on data reported in supplementary materials
Share attributed to Europe	34%	EFPIA public data
COGS	21% of revenue*	Analysis of data reported by 9 companies with significant orphan portfolios
SG&A	21% of revenue*	Analysis of data reported by 9 companies with significant orphan portfolios
Time		
Time to patient access	13 years	Jayasundara et al. (2019)
Cost of capital	10.5%	Wouters et al. (2020)
Risk		
Probability of successful marketing authorisation	17%	Wong et al. (2020)

*Updated compared to previous Dolon publication

Appendix 2. *Changes in inputs between base case, scenario 1 and scenario 2*

Input	Base case	Scenario 1	Scenario 2	Rationale
Revenue				
OME duration	10.5 years	8.5 years	6.4 years	As described in table 1 and 2 above
Number of indications	1.4	1.4	1.2	Assumption of 15% drop in number of indications in scenario 2
Price	€58,000	€53,000	€53,000	Assumption of 33% drop in price for products losing orphan designation, as in previous Dolon publication
Risk				
Probability of success	17%	16%	16%	Assumption of 10% drop in success of phase III and approval for products losing orphan designation, as in previous Dolon publication

References

Charles Rivers Associate for EFPIA (2020). The root cause of unavailability and delay to innovative medicines: Reducing the time before patients have access to innovative medicines. Available: https://www.efpia.eu/media/554527/root-causes-unvailability-delay-cra-final-300620.pdf

Dolon (2020). Estimated impact of EU Orphan Regulation on incentives for innovation. Available: https://dolon.com/dolon/wp-content/uploads/2020/10/Estimated-impact-of-EU-Orphan-Regulation-on-incentives-for-innovation.pdf

Dolon for EFPIA (2021). Addressing unmet needs in extremely rare and paediatric-onset diseases: how the biopharmaceutical innovation model can help identify current issues and find potential solutions. Available: https://www.efpia.eu/media/602878/addressing-unmet-needs-in-extremely-rare-and-paediatric-onset-diseases-how-the-biopharmaceutical-innovation-model-can-help-identify-current-issues-and-find-potential-solutions.pdf

EMA (2023). List of European Public Assessment Reports (EPAR). Available: https://www.ema.europa.eu/en/medicines/download-medicine-data

European Commission (2020). A pharmaceutical strategy for Europe. Available: https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en

European Commission (2023). Impact assessment report and executive summary accompanying the revision of the medicines for rare diseases and children legislation. Available: https://health.ec.europa.eu/publications/impact-assessment-report-and-executive-summary-accompanying-revision-medicines-rare-diseases-and_en.

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

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

Jayasundara et al. (2019). Estimating the clinical cost of medicine development for orphan versus non-orphan medicines. *Orphanet Journal of Rare Diseases*, 14(1). Available: https://pubmed.ncbi.nlm.nih.gov/30630499/

Medic et al. (2017). Do payers value rarity? An analysis of the relationship between disease rarity and orphan medicine prices in Europe. *Journal of Market Access & Health Policy*, 5(1), p.1299665. Available: https://pubmed.ncbi.nlm.nih.gov/28473888/

Technopolis & Ecorys for the European Commission (2019). Study to support the evaluation of the EU Orphan Regulation. Available: https://health.ec.europa.eu/system/files/2020-08/orphan-regulation_study_final-report_en_0.pdf

Wong et al. (2018). Estimation of clinical trial success rates and related parameters. *Biostatistics,* 20(2), pp.366–366. Available: https://pubmed.ncbi.nlm.nih.gov/29394327/

Wouters et al. (2020). Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009–2018. *JAMA*, 323(9), p.844. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7054832/