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Estimated impact of EU Orphan Regulation on incentives for innovation

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Executive Summary

The 2000 Regulation on orphan medicinal products (OMP) was introduced to mitigate the significant scientific and economic challenges inherent to the development of therapies for low-prevalence conditions with high unmet medical need and of medicines unlikely to attract investment. It established a set of incentives aimed at stimulating investment in rare diseases, by supporting development processes (through research grants and protocol assistance) and heightening potential economic returns (through orphan marketing exclusivity).

The strengths and weaknesses of the OMP Regulation are currently being evaluated by the European Commission. The innovation accrued as a result of the Regulation is an important element of this evaluation. The present study intends to contribute evidence on the current economic case for investment in OMP and on the impact of the Regulation, and thus hopes to contribute to a debate that ought to be evidence-based.

This study adopted a business economics approach to evaluate the impact of the OMP Regulation on innovation. We used a risk-adjusted Net Present Value (rNPV) approach to dynamically reflect how incentives direct investment, and thus impact innovation. rNPV modelling yields an economic measure which summarises in a single figure the value *today* of all future cashflows, given the high risk of development failure. It is routinely used across industries to inform investment decisions given expected investment, time, risk, and revenue, and as such allowed to analytically represent how companies respond to legislative provisions.

We found that over half (74) of the 142 OMPs developed between 2000–2017 would not have been economically viable in the absence of the Regulation. The study showcases the extent to which the Regulation has stimulated innovation in orphan medicines.

This result differs from the Technopolis Group's, relayed in the European Commission's Staff Working Document, which suggested that the Regulation only stimulated the development of 21 OMPs (confidence interval: 18–24) and had a relative impact of about 20%[1]. The Technopolis Group's study relied on "*a basic statistical analysis of the number of marketing authorisations for orphan medicines as compared to those for non-orphan products*". Authors first assumed that the number of OMPs would have grown at the same rate as non-OMPs without the Regulation, then observed that OMPs were approved at a faster rate over the period 2012–2017, and finally attributed the difference in OMPs actually approved vs. those expected given non-OMP market trends to the Regulation.

[1]Technopolis Group, 2020

We see a number of shortcomings with this approach, both conceptual and technical. Firstly, a statistical approach, such as the authors undertook, does not represent the causal relationship between incentives and investment. Secondly, we question their assumption that, in the absence of Regulation, OMPs would have been developed at the rate of non-OMPs: the OMP Regulation was introduced precisely because orphan medicines were not being developed at a rate even close to non-OMPs. Comparing instead the number of orphan medicines developed pre-Regulation versus post-Regulation suggests that the Regulation has stimulated an increase in orphans in the range of 51% to 94%. The authors suggested that undertaking a business economics analysis, such as we have presented in this report, was curtailed by methodological limitations.

In addition, we estimated that the mean rNPV for OMPs stands at €37.6 million, given the *status quo*. In other words, one might expect a mean risk-adjusted net benefit of €37.6 million over 30 years when investing in an OMP. This makes for a weak case for investment: target rNPVs have been set at $100 million[2] and $200 million globally[3] in the literature. In addition, manufacturers compare investment propositions across products and disease areas; investors weight options across industries. For manufacturers and investors to direct investment to orphan medicines, the risk-adjusted return needs to be commensurate with that from other types of medicines or alternative investments.

This result therefore suggests that investment in OMP development remains a marginal economic decision in most cases. While this study bears limitations, as all modelling exercises, it is clear that OMPs do not offer a straightforward investment proposition. Far from the OMP Regulation over-incentivising biopharmaceutical companies, our study indicates that investment decisions in OMPs remain precarious, despite legislative provisions aimed at mitigating the market failures linked to low prevalence, high unmet need conditions.

Maintaining a positive incentive framework is essential to advancing therapeutic innovation towards effective preventative medicines and treatments for rare diseases, strengthening equitable health systems, and fostering a productive biopharmaceutical industry in Europe. Our study demonstrates the large impact that the Regulation has had on OMP availability in Europe, and highlights the risk of investment moving away from rare diseases should the removal of incentives diminish the economic viability of OMPs. Consequently, it is critical that any consideration of reform of the Regulation should be informed by a robust understanding of the relationship between incentives, investment, innovation and patient access.

[2]Towse *et al*., 2017; Sertkaya *et al*., 2014
[3]Sharma and Towse, 2011

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Glossary of Abbreviations

ATMP	Advanced Therapy Medicinal Products
COGs	Cost Of Goods
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
G-Ba	German Federal Joint Committee
HTA	Health Technology Assessment
IP	Intellectual Property
NPV	Net Present Value
OD	Orphan Designation
OME	Orphan Marketing Exclusivity
OMP	Orphan Medicinal Product
POS	Probability Of Success
P&R	Pricing and Reimbursement
R&D	Research and Development
rNPV	Risk-adjusted Net Present Value
SE	Standard Error
SG&A	Selling, General and Administrative
SME	Small and Medium-sized Enterprise
SPC	Supplementary Protection Certificate
SWD	Staff Working Document

Introduction

The biopharmaceutical business model is founded on three fundamental components: innovation (driven by a large investment in research and development (R&D)), time (from patenting of a promising molecule through regulatory approval to patent expiry), and risk (clinical failure during development and commercial failure post approval). At each point of the development process, manufacturers must not only weigh the product's clinical promise, but also consider its economic viability given the current and forecasted environment. This business case is influenced by the incentive framework established by policymakers, including intellectual property (IP) rights, R&D incentives, regulatory processes, and pricing and reimbursement (P&R) rules. In light of the complexity and uncertainty associated with investment decisions, incentives play a critical role in shaping the amount and direction of R&D investment and hence, the nature of innovation that accrues.

The development of orphan medicinal products (OMPs) is particularly sensitive to incentive frameworks due to the specific challenges inherent to rare diseases. Lack of disease knowledge, novel or unproven surrogate endpoints, and small and highly heterogeneous patient populations impact R&D time and affect the risk of trial failure compared to more common, better understood conditions[4]. Small patient populations also limit the revenue potential of products that successfully reach the market. The impact of these challenges on economic viability are such that, prior to 2000 and in the absence of legal, political and economic incentives, only 8 therapies were approved in Europe for the 6–7,000 known rare diseases[5].

The Regulation (EC) No 141/2000 on OMPs (henceforth: 'Regulation') was introduced in 2000 by the European Commission to encourage investment in treatments for rare diseases by increasing incentives to a level that would justify investment. Central to the Regulation was the goal to remedy market failure: the EU estimated that, for rare diseases, the revenues to be expected for a small patient population would be insufficient to undertake the risks and expenses of developing an OMP. Accordingly, orphan marketing exclusivity (OME), centralised regulatory processes, and scientific and financial assistance for R&D were instituted.

In the European Commission Staff Working Document (SWD) published on 11 August 2020, which presents an evaluation of the Regulation (alongside the Paediatric Regulation), it was concluded that the Regulation has played an important role in addressing market failure, successfully stimulating innovation and progressing care in many overlooked conditions. Between 2000 and 2017, 1,956 products were granted an orphan designation and 142 orphan-designated products obtained a marketing authorisation[6].

Despite the value brought to patients and health systems from this innovation, concerns about prices, patient access and sustainability of expenditure have increased scrutiny of rare disease treatments in recent years. In the SWD, the Commission noted that there are large remaining unmet medical needs and perceptions of overcompensation of some products. Furthermore, the SWD relayed an estimate by the Technopolis Group that only 21 of the 142 products developed between 2000–2017 are directly attributable to the Regulation, thus questioning the efficiency of the incentives. The Commission is now contemplating revisiting the Regulation in order to "recalibrate" the incentives.

[4]Nestle-Parr *et al.*, 2018; Kempf *et al.*, 2018 [5]Office of Health Economics, 2010. Note that the Technopolis Group Orphan Study estimated that there were 15 to 70 "orphan-like" products before 2000. The Technopolis Group estimated that there were 15 products approved for rare diseases based on data published by Orphanet. They estimated that there were 70 "orphan-like" products before 2000 by analysing the products which had received an orphan designated in the United States and were available (i.e. had sales reported by IQVIA) in a European country. Note however that criteria to obtain an orphan designation differ between the US and the EU: not all medicines designated as orphans in the US are eligible for the designation in the EU. [6]Technopolis Group Orphan Study, 2020. 1,552 orphan designations were active at the time of the Technopolis Group analysis.

A meaningful debate on changing the Regulation must examine how economic incentives impact scientific innovation. In particular, two questions stand out:
- How do companies and their investors prepare decisions on whether to develop an OMP?
- How would decisions to develop today's authorised OMPs have been affected if the incentives provided by the OMP Regulation had not been there?

Our study aimed to contribute to the debate by considering these questions analytically. We examined how companies and investors prepare decisions to develop OMPs given the incentives landscape and market dynamics, adopting a business economics perspective to estimate the Regulation's impact on innovation.

Analytical Approach

Conceptual approach to investment decisions

When making investment decisions, companies must not only consider the scientific promise of a medicine, but also its economic viability. Companies considering investing in OMPs – like in any other industry – need to ask four main questions:
- How much would I be expected to invest?
- What level of revenues can I expect if I succeed, and for how long?
- What are the probabilities of success / risks of failure?
- How long do I need to wait before revenues start coming in? This last question is especially important: the longer the investor has to wait, the higher the rewards must be, to make the investment viable.

Note that incentives, such as those provided by the Regulation, impact responses to all these questions. As such, incentives translate into new medicines by affecting the economic viability of a potential development programme and shifting the investment decision from 'No-Go' to 'Go'.

Risk-adjusted Net Present Value

The most commonly used method to estimate the economic viability of an investment over time (and compare it to other investment opportunities) is the Net Present Value (NPV) approach. This method combines the expected investment amount, the expected revenues and the "waiting time" into a single monetary amount aimed at informing decision-making.

As failure is an inherent feature of medicines development, the pharmaceutical industry employs a variation on classical NPV model: a *risk-adjusted* NPV model (rNPV). The rNPV estimates the value today of all future cashflows, *given the risk of failure*. rNPV models are commonly employed in the biopharmaceutical industry to inform decision-making for early stage (pre-clinical) R&D investments, Go/No-Go decisions at each development stage, and in-licensing decisions[7]. (Whilst there is some variation in the methods used by companies to inform development investment decisions, rNPV modelling is a consistent component.)

Basically, the rNPV model sequentially:
- Estimates the amount to be invested (e.g. R&D costs, commercialisation costs);
- Predicts the level and duration of the expected revenues (based on expected patient numbers and price);
- Adjusts the expected revenues to account for the probabilities of success (for example, a 50% chance of success reduces the rNPV by half);
- Accounts for the 'cost of waiting' for the revenue: i.e. the "discount rate"[8].

[7]Svennebring and Wikberg, 2013; Rogers *et al*., 2005; Woo *et al*., 2019 [8]The discount rate further reflects the fact that investors have other competing opportunities for their funds and have a preference for earlier returns on investment.

Discount rates are applied to reflect the fact that investors have alternative options for their money, beyond financing biopharmaceutical development, and these alternative investments would likely provide an economic return (opportunity cost).

The outcome of the rNPV needs to be positive before a reasonable investor can commit to the costs and risks of developing an OMP. The higher the rNPV above zero, the better the investment proposition and the more likely that investment is to be prioritised over other investment opportunities. In this analysis, products are assumed to be economically viable if their rNPV is greater than zero.

rNPV should not be confused with cost-plus pricing. In the former, a value-based price estimate is used to inform whether investment in a potential medicine is likely to be economically viable, accounting for risk of failure and opportunity cost. The latter is a proposed approach to pricing that breaks the link between value and price, and does not account for risk of development or opportunity cost.

Table 1. Differences between the rNPV approach and cost-plus pricing

	rNPV approach	Cost-plus pricing
Use	By pharmaceutical companies when making investment decisions for early stage medicines, go/no-go decisions during development, and in-licensing decisions	Proposed by payers as a way to establish a price for a new medicine as an alternative to value-based pricing
Time	Pre-clinical development – *expected price at launch* is a variable that informs the investment decision, not an output from the analysis	After drug approval
Perspective	*Ex-ante* – when making investment decisions companies do not know whether or not the drug will be successful. Risk is a critical component of an rNPV model, as is the discount rate (the opportunity cost of capital)	*Ex-post* – cost-plus pricing is proposed as a pricing approach to use once a product is approved. Accordingly, it does not account for the risk of development, nor the opportunity cost of the investment (discount rate)
Role in setting price	Not used directly in pricing. Companies do not revisit the original rNPV price parameter estimate at the time of pricing, instead undertaking an up-to-date and more accurate value-based price assessment (i.e. reflecting the true value of the product as witnessed in trials, rather than the expected value of the medicine at the pre-clinical stage)	Not used by companies. Companies price based on the value of the product in the context of global P&R systems

Estimating investment, risks, rewards and time

Model parameters

As described above, all rNPV models account for investment needed, expected rewards, risk of investment and time lag between investment and return[9]. **Table 2** details how each of these aspects of investment were reflected in the model. Full details of model parameters are included in the Appendix.

[9]Note that the tax rate was not considered

Table 2. rNPV model parameters

Key Inputs		
Investment	Development expenses & post-launch costs	Annual preclinical costs (€)
		Annual phase I costs (€)
		Annual phase II costs (€)
		Annual phase III costs (€)
		Cost of approval phase (€)
		Annual ongoing R&D costs (€)
		Cost of goods (% of revenues)
		SG&A expenses (% of revenues)
	Duration of phases	Preclinical (years)
		Phase I (years)
		Phase II (years)
		Phase III (years)
		Approval (years)
		HTA (years)
Rewards	Market data	Treated patient population (n)
		Annual population growth (%)
		Peak market share, before effective market protection loss (%)
		Ramp time to peak market share (years)
		Market share, post effective market protection loss (%)
		Annual price per patient (€)
		Drop in price post market protection loss (%)
		Annual price erosion (%)
		Revenue multiplication factor, to scale from EU5 to EU28 (%)
		Average number of indications per OMP
		Duration of market protection, including IP/SPC/OME (years)
Risk	Probability of success	Preclinical (%)
		Phase I (%)
		Phase II (%)
		Phase III (%)
		Approval (%)
Time	Cost of capital	Cost of capital

Sources for input parameters

rNPV model parameters were based on information available in published literature. The model adopts a 'top-down' approach to estimating key input parameters, using (where available) reported averages for the cohort of 142 orphan products approved since 2000. Accordingly, inputs come from aggregate data and are not specific to individual OMPs approved to date. To reflect the scope of the Technopolis study, this analysis looks into products authorised between 2000 and 2017.

When identifying sources, peer-reviewed academic articles and European Commission reports were prioritised where possible. Relevant articles were identified through comprehensive and structured literature reviews. The Technopolis Group Orphan Study was used extensively. In the absence of available quantitative estimates, assumptions were made by the authors. The European Federation of Pharmaceutical Industries and Associations (EFPIA) and some of its members provided feedback on the sources and parameter values selected. Please note that Dolon did not have access to any manufacturer or product specific data: no non-public information was shared by EFPIA or its members to inform input parameters.

Geographic scope

Our study focused on Europe. Though medicine investment decisions and patient populations are global, the assessment was adjusted to reflect European-specific contributions to incentives, thus aligning with the scope of the OMP Regulation.

A portion of global development costs was assigned to Europe. To do so, we identified the pharmaceutical R&D expenditure in Europe, USA and Japan from a public EFPIA report[10]. We assumed that these three geographies account for the majority of global R&D expenditure. We used the latest complete data presented in the report (2015) and further assumed that the distribution of R&D across regions has remained stable since then. With this method, we estimated that Europe accounts for about a third (34%) of global R&D investment.

Similarly, only revenue generated in European countries was considered. Revenue from the EU5 (France, Germany, Italy, Spain, United Kingdom) was modelled in detail, and a multiplication factor was then applied to extrapolate total European sales from those of EU5. The multiplication factor was assessed by comparing orphan expenditure reported by a recent publication in the EU5 to that in all 22 European countries in 2014[11]. Using this approach, we assessed that 80% of European revenue is generated in EU5 countries. This approach reduced the challenge of assessing the complex and varying P&R systems across European countries.

Investment

We estimated the investment necessary, on average, to bring a medicine to patients. We reviewed the academic literature for estimates of *cash* R&D expenditure (that is, money spent by a company, excluding discounting and risk adjustment). The literature on biopharmaceutical R&D economics is large with a broad range of estimated costs. We used an estimate from a recently published paper by Wouters *et al.*[12]. Data in supplementary materials allowed us to estimate direct and indirect out-of-pocket expenditure specifically for orphans. From this source, investment (for each product, successful *or unsuccessful*) from phase I to III was evaluated at slightly over €260 million globally *accounting neither for risk of failure nor discounting*. (This means that, when accounting for product failures and capitalisation, development costs for a medicine sits at nearly €1 billion.) This assessment by independent academic authors sits at the lower end of the spectrum of published costs, and was chosen to be deliberately conservative[13].

[10]EFPIA, 2018 [11]Deticek *et al*., 2018 (Figure 4) [12]Wouters *et al*., 2020. Note that the main body of the paper does not report orphan-specific figures. Our estimates of orphan R&D expenditure is based on an analysis of the supplementary data provided alongside the article. The paper collected both direct and indirect R&D costs defined as follows: "*Direct research and development expenses included all resources directly allocated to a particular agent. Indirect research and development expenses, which included personnel and overhead costs, were sometimes reported as a lump sum across all drug development programs. If so, we applied the same percentage of direct research and development costs attributable to a particular agent to estimate indirect costs for the same agent.*" [13]Note that EFPIA members did not endorse this number; industry reviewers suggested that this figure may underestimate true development costs.

We estimated orphan-specific duration of development phases (i.e. trial duration) from Jayasundara *et al*.[14]. We adjusted the duration of phase III studies to account for the proportion of OMPs which obtain a marketing authorisation based on phase II data. Duration from the preclinical phase to phase III was estimated at 11 years.

We estimated costs incurred after approval of the product. In the absence of robust published data, we reviewed the distribution of spend from a sample of orphan drug companies' annual reports. Manufacturing costs (or cost of goods (COGs)) were inferred to represent 32% of revenue and overheads (or selling, general and administrative costs (SG&A)) 22% of revenue. Post-launch evidence generation costs were conservatively assumed to be €1.4 million per year in Europe, in line with an assumption by the Office of Health Economics[15].

Risk

We built the model to estimate rNPV at the time of entry in clinical development. Accordingly, we assumed 100% success for the preclinical phase. We extracted probabilities of success for each phase of clinical development from Wong *et al*. (2019)[16]. We selected the study for its high quality and availability of orphan-specific estimates. We used Thomas *et al*. (2016) to inform the probability of successful approval. From this source, probability of success from phase I to marketing authorisation was estimated at 17.2%.

Revenue

Treated patients

To estimate the patient population, we calculated the average prevalence for orphan products from Medic *et al*. (2017) and the Technopolis Group Orphan Study (2020). Both sources yielded an average prevalence of 1.24 per 10,000 people. We multiplied that figure by the total EU5 population (324 million)[17] to obtain the average prevalent population in the EU5 per orphan indication.

Table 3 details adjustments made to account for the number of prevalent patients who receive treatment with an OMP, accounting for diagnosis, access, and treatment received. To note: these estimates are for patients receiving funded treatment – we excluded considerations of patients receiving treatments through 'compassionate use' or trial programmes. Patient compliance with treatment was estimated at 80%[18]. Market share for the product modelled was assumed to be 60% on average of the patients receiving an active treatment. Market share was estimated based on an analysis of the average number of competitors per indication (as there are 142 OMPs across 107 unique orphan indications, we inferred an average 1.33 products per indication).

Table 3. Estimation of patient numbers

Assumptions informing patient numbers		
Diagnosed patients	60%	Assumption
Population in which treatment is reimbursed	65%	Malinowski *et al.*, 2018
Patients receiving approved treatment (vs. best supportive care)	80%	Assumption

[14]Jayasundara *et al*. [15]OHE, 2020 [16]Cf. table 4. Note that we disentangled the phase III probability of success by using the Thomas *et al*. (2016) probability of successful approval [17]Eurostat, 2020 [18]Published studies suggest compliance rates of 58–65% (Dwyer *et al*., 2014; Hromadkova *et al*., 2012; Candrilli *et al*., 2011). We adopted a more conservative estimate

Price

The ex-factory price of OMPs has been observed to be correlated with the size of the patient population for which they are indicated. To reflect this, in our analysis the average price of an OMP was determined as a function of prevalence, according to an equation derived from the literature. Specifically, the equation was obtained by fitting a logarithmic function to the price-prevalence curve reported by Medic *et al*. for German prices[19]. German prices were adjusted to a European average using data presented by Medic *et al*. (30% decrease), and further adjusted to reflect confidential discounts and rebates (20% decrease)[20].

Prices in Europe are value-based: they reflect the benefits brought to patients and health systems. In addition, prices have been shown empirically to be correlated with prevalence, which reflects theoretical arguments for adjusting the value-based price according to prevalence[21]. As value-based factors are hard to explicitly link to price and prevalence is the cornerstone of the OMP legislation, rarity was taken as a proxy determinant of OMPs' prices for the purpose of this analysis. This represents a simplification of the complexity of price negotiations.

Patent and marketing exclusivity protection

The duration over which revenue is obtained from a medicine is largely determined by the length of patent, or more broadly, intellectual property (IP). While medicines are protected by some form of IP, generic or biosimilar copies of the medicine cannot be introduced (however the product can still face competition from other branded medicines or generic versions of different molecular entities). For the purposes of this analysis, we sought to estimate the average total duration of IP protection for OMPs, incorporating all forms of IP. We adapted the concept of 'effective market protection' from the *Study on the Economic Impact of Supplementary Protection Certificates*[22]. We calculated the average duration of effective market protection from marketing authorisation using data from the Technopolis Group Orphan Study[23], as detailed in **Table 5** (in appendix). We estimated that *on average*, products benefit from 13 years of effective market protection post approval. While this means that effective market protection is *on average* longer than OME (which lasts 10 years), it does not entail that the protection provided by OME is redundant *for individual products*. Indeed, 21.9% of OMPs did not have IP or supplementary protection certificate (SPC) protection at the time of OME expiry and 29.5% had no IP/SPC at the time of marketing authorisation. For at least half of approved OMPs, OME therefore plays a key role.

An important simplification from our model relates to the protection provided by IP/ SPC vs. OME. Whilst in practice OME provides additional protection compared to IP (by preventing market entry of *similar* products covering the same indication unless they prove to provide additional benefits, rather than only barring entry of *identical* molecules), our model equated the protection provided by IP/ SPC and OME. The model thus only accounted for competition from generics, biosimilar, or similar molecules at the time of loss of IP/SPC or OME, whichever occurs last. (Note, however, that some competition within an indication was accounted for, including during OME, by adjusting peak market share to the average number or products per indication.) This simplification was necessitated by data limitations: available evidence does not allow to estimate the additional protection awarded by OME compared to IP/SPC.

[19]Medic *et al*., 2017. See appendices for a reproduction of the curve [20]The 20% list-to-net gap was assumed based on indications from the literature: Espin *et al*. (2018) estimate the gap to be 17% in 2021 and Morgan *et al*. (2017) propose that discounts are most commonly over 20% of the list price [21]Berdud *et al*., 2020 [22]Copenhagen Economics, 2018 [23]Technopolis Group Orphan Study, 2020.

Market protection was thus modelled as preventing generic entry. However, competition from other innovative products was modelled to occur, including when market protection was in force. As described in the 'Treated patients' section above, we adjusted products' market share to reflect that there are on average 1.33 approved OMPs for each unique orphan indication.

We made further assumptions regarding outcomes at the time of loss of market protection. We hypothesised that only small molecule medicines would see generic entry at loss of IP/SPC/OME, whereas biologics and advanced therapy medicinal products (ATMPs) would not face biosimilar entry. (Small molecules represent 64% of OMPs authorised in 2000–2017, biologics 24% and ATMPs 12%[24].) Assumptions on biosimilar competition reflect the retrospective nature of the assessment and are not meant to reflect future market dynamics. Generic entry for small molecule products was assumed to lead to a 50% drop in market share within a year, but not to impact prices (i.e. manufacturer maintains price and loses market share to lower price generics). Further, for all product types (small molecules, biologics, and ATMPs), we assumed a 5% price drop at loss of IP, reflecting mandatory re-assessment and price re-negotiations in some countries. The scarcity of data on the impact on price and sales volumes of generic entry prevented an evidence-based assessment of these parameter values. Assumptions made are conservative: it is likely that prices fall significantly more at the time of market protection expiry.

Time

Discount rates in the model were set at 10.5%, in alignment with two important studies: DiMasi *et al*. and Wouters *et al*.[25]. Note that this is a conservative estimate of the cost of capital: Berdud *et al*. (2020) report that "the cost of capital for investments in OMPs is in the range of 11%–14% (Rollet *et al*., 2013) whilst for the pharmaceutical industry in general, it is estimated to be in the range of 9%–12% (Schuhmacher *et al*., 2016; DiMasi *et al*., 2016)."

Model structure

A Monte Carlo simulation was performed to account for uncertainty surrounding model inputs. During a Monte Carlo simulation, values are sampled at random a number of times (10,000 in this analysis) from the input probability distributions and within its confidence interval[26]. Results of each sample (iteration) are recorded and, once all iterations are completed, averaged together to provide a probabilistic estimate.

Monte Carlo outputs were the mean and median rNPV across all 10,000 simulations, as well as the probability that products would be developed. The model time horizon was set to 30 years, covering the full life-cycle of products, from R&D to IP expiry.

[24]Technopolis Orphan Study, 2020 [25]DiMasi *et al*., 2016; Wouters *et al*., 2020 [26]Probability distributions were selected based on the literature when available (Briggs *et al*., 2011) or on author assumptions. Appendices provide details of the distribution and confidence intervals for all parameters.

Estimating the economic case with and without the Regulation

Current situation (base case)

The first scenario was intended to reflect the incentives granted by the 2000 OMP Regulation (i.e. the current OMP landscape in Europe). In other words, the model aimed to reflect the R&D incentives and market dynamics observed in the past 20 years as accurately as evidence allows.

'No Regulation' scenario

We created an alternative scenario to create a counterfactual to the incentive landscape observed since 2000, instead representing what the rare disease incentives landscape might have looked like had the OMP Regulation not been enacted.

To that end, we changed specific model parameter values to represent direct and indirect effects of the foregone Regulation. Incentives granted by the OMP Regulation encompass 10 years of marketing exclusivity in the EU (restricting market access to similar products in the same therapeutic indication), European Medicines Agency (EMA) fee waivers, EMA protocol assistance and EU grants for research. We reflected the absence of these incentives as per the table below (**Table 4**).

We also accounted for the indirect effect of the hypothetical lack of the Regulation. At the time of introduction, European policymakers highlighted that the Regulation alone would be insufficient to spur innovation and increase access to rare disease medicines. EU competencies encompass regulatory and legislative matters, while countries retain control over pricing and reimbursement and taxes. Some Member States thus created additional (explicit and implicit) country-specific incentives linked to orphan designation to further the effect of the Regulation. Examples of linked incentives at the Member State level are the automatic recognition of added benefit for OMPs by the Federal Joint Committee (G-BA) in Germany, exemptions from clawbacks in Italy and lower mandatory discounts in Spain. Within this analysis it was presumed that many of these incentives were consequences of the Regulation and would not have been implemented in its absence.

Table 4. 'No Regulation' modelling approach

		Key Inputs
Direct effects	No OME	Lower average duration of effective market protection
	No EMA fee waivers	Higher costs of approval
	No protocol assistance	Lower likelihood of phase III success Lower likelihood of successful approval
	No EU research funds	Higher preclinical costs
Indirect effects	Secondary effects on P&R outcomes at country-level	Lower price
	Reduced incentives for additional indications	Lower average indications per product

We calculated the impact of the absence of OME on effective market protection. In the absence of the Regulation, we estimated that effective market protection would be reduced by 3.5 years (see **Table 5** for details of calculation).

We assumed a 10% lower probability of phase III trial success and regulatory approval in the absence of OMP Regulation, reflecting the absence of scientific advice (this aligns with assumptions in a similar analysis by the Office of Health Economics[27]). We assumed 10% higher costs in the pre-clinical phase, because of a decrease in EU funds for basic research. This is likely an overestimate of the impact of EU research funding.

We assumed that the requirement within the Regulation for OMPs to demonstrate added clinical benefit where alternative treatments exist ("significant benefit") is recognised within Member State P&R processes by granting in general a price premium versus the already marketed comparator. Conversely, we hypothesised that the absence of the demonstration of significant benefit (which acts as a signal of added benefits) would have led to lower prices (33% reduction). No evidence suitable to inform this parameter was identified in the published literature. This assumption was explored in scenario analyses.

Lastly, we assumed a slightly lower average number of orphan conditions (1.2 vs 1.4) targeted per product, given the reduced incentive to expand indication to new patient populations.

Results

Current economic incentives for OMP investment

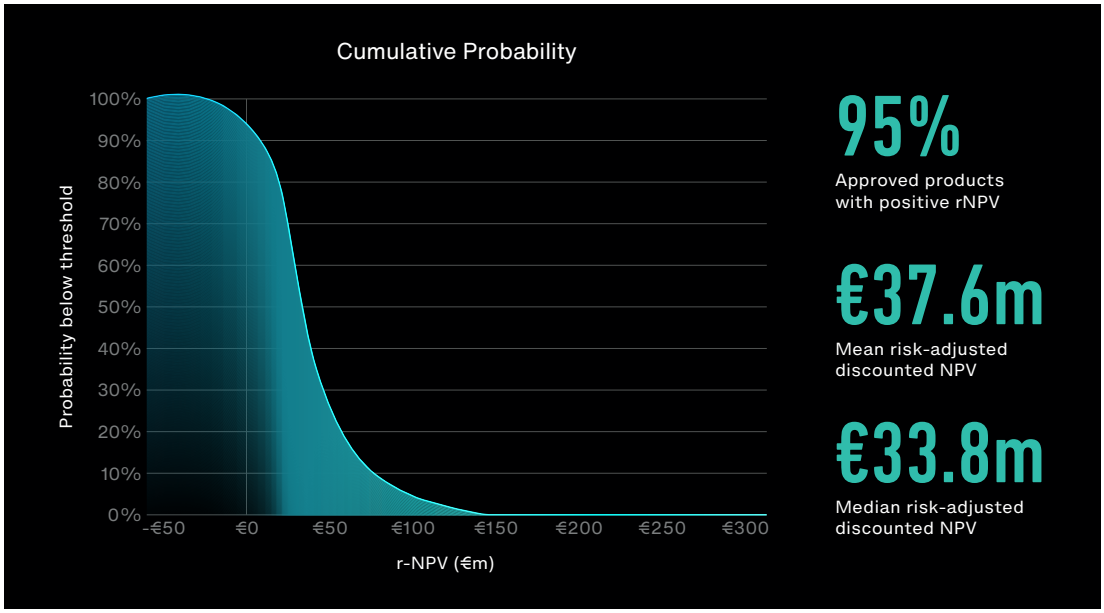
We first explored the output for the base case. Our model predicted that 95% [95% confidence interval: 93%; 97%] of the products that were approved between 2000–2017 would have been expected to have a positive rNPV at the time of the investment decision (**Figure 1**). That is, given the current incentive framework, 135 products would have been considered to be economically viable, and thus developed. In reality 142 products were actually developed and approved. We interpreted this result as indicating that current incentives are well-calibrated to promote the OMP innovation that has been witnessed over the past 20 years.

Mean and median rNPV were quite low. We estimated the mean rNPV across OMP products at €37.6 million [€37.0; 38.1 million], with a median of €33.8 million [€33.2; 34.3 million]. These estimates are in line with those obtained in a similar modelling exercise conducted by the Office of Health Economics[28], which estimated a base case mean rNPV ranging from €34.6 to €55.5 million (2018 euros)[29].

Results were sensitive to the probability of success, treated patient numbers and the discount rate (see **Figure 3**, in the appendix, for further details).

[27]Berdud *et al.*, 2020 [28]Berdud *et al.*, 2020 [29]Of note, the model here presented also accounted for competition and higher R&D costs, explaining the slightly lower base case mean rNPV

Figure 1. Base case outputs (reflecting the current incentive framework)



Economic incentives without the Regulation

When considering the 'No Regulation' scenario, we predicted that only 61 (45%) of products would have been developed had the Regulation not been enacted. Hence 74 (55%) of products would not have been developed because of a lack of economic viability in the absence of the Regulation. In other words, 74 products (or 55%) can be attributed to the advent of the Regulation.

In the absence of the Regulation, our model estimated the mean rNPV at -€0.22 million [-€0.44; 0 million] and the median rNPV at -€1.75 million [-€1.97; -1.54 million].

We performed a deterministic sensitivity analysis for the 'No OMP Regulation', as for the base case. We found that the number of patients treated, probability of success and duration of R&D were most influential (**Figure 5** in the appendix presents full results). We also conducted scenario analyses, aimed at exploring the extent to which results are affected by assumptions around the impact of the absence of the Regulation. We found that assumptions on the effect of protocol assistance and on price differentials bear an impact on results (**Table 10** in the appendix presents all results).

Figure 2. Impact of the absence of the OMP Legislation on innovation, patients and R&D investment

Note that the estimate of patients and R&D investment impacted by the absence of Legislation is obtained by multiplying the number of products predicted to be foregone by the number of patients diagnosed and development costs (preclinical to phase III), respectively. These estimates should be taken as directional.

Discussion

A business economics perspective

Our study aimed to examine the balance of economic incentives to invest in orphan medicines under two scenarios: the reality of the existing legislative landscape created by the OMP Regulation over the last 20 years, and a second hypothetical scenario in which the Regulation was never enacted.

We used an rNPV methodology as the basis of our analysis. This type of model analytically reflects how companies could make investment decisions, balancing expected revenue with cost, time, and risk associated with R&D. As such, it is a well-established economic tool to explore the viability of an investment given a specific regulatory environment. Similar rNPV approaches have been extensively adopted in the academic literature, including in assessments of the economics of developing OMPs[30], of incentives for antibiotic development[31], of the impact of price decrease on R&D investment in the US[32], and of the consequence of policy changes on medical devices development[33].

We extended the rNPV analysis by using Monte Carlo simulation, thus enabling us to account for the uncertainty in input parameters. The Monte Carlo approach is well recognised for its ability to computationally consider uncertainty. For example, it is used as a method to incorporate the uncertainty of clinical data when evaluating the benefit-risk ratio of medicines during regulatory processes[34] and has been proposed as a tool to maximize information from clinical trials[35].

[30]OHE, 2020 [31]Towse *et al*., 2017 [32]Abott and Vernon, 2007 [33]Reed *et al*. 2007 [34]Wen *et al*., 2014 [35]Bonate, 2000

Current incentives for OMP development

The base rNPV analysis attempted to reflect how current incentives, as provisioned by the OMP Regulation, shape the investment proposition. We estimated that the mean rNPV for OMPs stands at €37.6 million. In other words, one might expect a mean risk-adjusted net benefit of €37.6 million over 30 years when investing in an OMP under the current Regulation.

While according to economic theory any positive rNPV should be sufficient to justify investment, in practice it is likely that manufacturers seek rNPVs significantly greater than zero. Most investors will require an NPV of several tens of millions of euros as a minimum[36]. In the economic literature, target rNPVs have been set at $100 million[37] and $200 million globally[38]. In addition, manufacturers compare investment propositions across products and disease areas; investors weight options across industries. For manufacturers and investors to direct investment to orphan medicines, the risk-adjusted return needs to be commensurate with that from other types of medicines or alternative investments.

Our results therefore suggest that investment in the orphan space remains a marginal economic decision in most cases; the economic case for investment, is on average, weak, even in the presence of the incentives within the current Regulation[39]. This finding may help to explain the fall in orphan designation observed in the past few years[40].

Impact of the OMP Regulation on innovation

The 'No Regulation' scenario explored investment incentives in the absence of the 2000 OMP Regulation and hence the number of products attributable to the Regulation. We found that over half (74) of the 142 products developed between 2000–2017 would have been unlikely to have been economically viable in the absence of the Regulation.

This result differs to analyses reported in the Technopolis Group Orphan Study. Two methods were applied within the Orphan Study to assess the level of innovation attributable to the Regulation:

- a primary statistical analysis that predicted that 21 of 131[41] OMPs can be attributed to the Regulation;
- a secondary incentives-based analysis that suggested that the Regulation increased OMP development by 17%–23%.

The authors described the primary approach as "*a basic statistical analysis of the number of marketing authorisations for orphan medicines as compared to those for non-orphan products*". The authors nevertheless suggested that a business economics analysis, such as we have presented in this report (albeit at aggregate level), would have been preferrable:

"*Ideally, the analysis would have used company data on R&D costs, production and marketing costs, pricing and revenues from individual products. Such information could show how these factors influence the decisions of companies to start or continue the development process of new orphan medicines, and how the rewards (public research, protocol assistance, fee waivers, market exclusivity) influence these decisions. Unfortunately, such information is scarce and not sufficiently available in the public domain to model the decision-making process.*"

[36]Informal conversations with pharmaceutical manufacturers suggested that a mean rNPV higher than $100 million is usually required to consider investment. [37]Towse *et al*., 2017; Sertkaya *et al*., 2014 [38]Sharma and Towse, 2011 [39]Furthermore, the orphan market has been described as "immature" and thus sensible to changes in incentives. See Solà-Morales, 2019 [40]European Medicines Agency, 2019 [41]The Technopolis Group excluded the 11 products which have been withdrawn since obtaining a marketing authorisation

Instead, they looked at the number of OMPs approved from 2000 to 2017 and compared the trend in approvals versus those for non-OMPs (all other medicines approved). They observed that orphan and non-orphan product approvals had similar growth rates from 2000 until 2011, but that growth rates diverged from 2012 to 2017. The authors assumed that, without the Regulation, the number of OMPs would have grown at the same rate as non-OMPs. In fact, OMPs were approved at a faster rate over that period, and they attributed the difference – 21 OMPs (19%) – to the Regulation (range 18 [16%] to 24 [22%]).

We see a number of significant limitations to this approach, both conceptual and technical. We agree that the business economic approach is preferable, as it reflects the causal relationship between incentives and OMP investment. A statistical approach, such as the authors undertook, does not account for causation and relies on observed association only, with the high risk of confounding that is inherent in such an approach.

In particular, we question their assumption that, in the absence of Regulation, OMPs would have been developed at the rate of non-OMPs. The OMP Regulation was introduced precisely because orphan medicines were not being developed at a rate even close to non-OMPs.

Indeed, if a basic statistical analysis is to be done to assess the impact of the Regulation, then the more logical comparison should be between the number of orphan medicines developed pre-Regulation versus post-Regulation. Estimates of the number of orphan-like medicines developed in the two decades preceding 2000 range from 8 (Office of Health Economics) to 15 – 70 (Technopolis Group Orphan Study)[42]. This compares with 142 OMPs in the 18 years that followed the introduction of the Regulation. This would suggest that the legislation has stimulated an increase in orphans in the range of 51% to 94%.

A second analysis is presented in the Technopolis report to address the same question of the amount of innovation stimulated by the Regulation. This seeks to assess the additional level of incentive provided in the Regulation by quantifying the increased potential revenue due to the 3.4 years of additional IP from OME. The authors conclude that this equates to 17%–23% increase in incentive, suggesting the finding aligns with the primary statistical analysis. Nevertheless, this analysis bears a significant limitation in that it does not account for the other direct and indirect incentives within the legislation, namely EMA fee waivers, EMA protocol assistance, EU grants for research and Member State incentives linked to orphan designation. The analysis therefore (largely) underestimates the incentives provided by the Regulation and therefore the innovation afforded by it.

To our knowledge, the Technopolis Group Orphan Study is the only study comparable to ours in its objective. We did not find similar empirical evaluations of the impact of Orphan Regulations on innovation in the United States or in Japan. In the United States, one study evaluated the impact of *price control* policies on innovation, across therapy areas, using an NPV approach akin to ours[43]. It estimated that "cutting prices by 40–50% in the US will lead to between 30 and 60% fewer R&D projects being undertaken (in early-stage development)".

[42]Technopolis Group, 2020 and Office of Health Economics, 2010. Note that the Technopolis Group Orphan Study estimated that there were 15 to 70 "orphan-like" products before 2000. The Technopolis Group estimated that there were 15 products approved for rare diseases based on data published by Orphanet. They estimated that there were 70 "orphan-like" products before 2000 by analysing the products which had received an orphan designated in the United States and were available (i.e. had sales reported by IQVIA) in a European country. Note however that criteria to obtain an orphan designation differ between the US and the EU: not all medicines designated as orphans in the US are eligible for the designation in the EU. [43]Abbott *et al*., 2007

Predicted revenue vs. realised revenue

Beyond the results from the two core scenarios, our model yielded an interesting additional insight: we observed a difference between the average (undiscounted, non risk-adjusted) annual revenue predicted by our rNPV model and the observed annual turnover for OMPs reported in the Technopolis Group Orphan Study. Based on reasonable assumptions about prevalence (from estimates used by the EMA, adjusted for diagnosis and market share) and price (Medic *et al*., adjusted for confidential discounts), our model predicted average annual sales of €316 million across Europe. In contrast, the Technopolis Study estimates an average OMP revenue of €56 million per annum (over the period 2008–2017), with approximately half of OMPs earning less than €10 million per year and only 14% of OMPs exceeding €100 million in annual revenue.

To reconcile these results, we made several hypotheses. It may be that, historically, companies have systematically over-estimated the potential revenue from OMP investment opportunities in Europe. In reality, OMPs may reach fewer patients than published prevalence data would suggest, perhaps due to diagnosis and reimbursement challenges. A publication by experts from the metabolic disease European Reference Network states that only about 50% of diagnosed patients treated in a network centre received an active treatment[44]. It is also possible that net prices (after discounts) are lower than is presumed in the published literature. Alternatively, the gap between predicted and realised revenue may also be an artifact of modelling averages, whereby the average masks a wide distribution, possibly with a long right-hand tail.

Another hypothesis is that investments are made in OMPs with the hope of achieving 'blockbuster' status. In that view, the incentive for investment does not lie in the revenue brought by an *average* OMP but in the hope that the product will turn out to be an *outlier* in terms of turnover – one of the 14% of OMPs that achieves sales in Europe in excess of €100 million per year. It follows that high-revenue OMPs may perform an important economic role in enticing investment. Proposals to cap OMP revenue for fear of 'over-compensation' could thus have a disproportionate impact on future investment.

Limitations

The study's results should be interpreted in light of its limitations.

The model was based on aggregate data, not product-level information, as specified previously. Reflecting averages for the cohort of products may have limited consideration of heterogeneity.

The study was further constrained by data availability. We relied on numerous assumptions, in the absence of available published evidence. As with all models, assumptions increase uncertainty around results, heightening the possibility of bias. We aligned our assumption on the impact of protocol assistance with that of the Office of Health Economics[45], and therefore relay their acknowledgement that the assumption might overestimate the impact of protocol assistance. Assumptions were reviewed by external experts (Jorge Mestre-Ferrandiz and Mikel Berdud, as stated in the front page disclaimer) to mitigate bias.

[44]Heard *et al*., 2020 [45]Berdud *et al*., 2020.

The choice of parameter distributions in probabilistic analyses was informed by author expertise as true distributions of parameters were unavailable. This was especially true as the choice of distributional form was informed by secondary rather than primary data, as in this model. Even though distributions were chosen according to published guidance and deterministic analysis were aligned with probabilistic results, it is possible that some parameters' distributions have been mis-specified, leading to bias in probabilistic estimates. Moreover, confidence intervals around the mean value were seldom available in the literature. Instead, some degree of uncertainty was accounted for in the model by assuming a 95% confidence interval ranging ±20% from the mean. This strategy to assume a fixed level of deviation from the mean could have over- as well as under-estimated variation around some parameters.

Our assessment was retrospective in nature. It reflected the development challenges, market dynamics (e.g. around generic and biosimilar entry), and regulatory rules observed in the past 20 years. Our results clearly show that a reduction to incentives would have a large detrimental effect on innovation available to patients. Nevertheless, results should not be applied prospectively without considering other changes to the orphan landscape. For example, it should be noted that the EMA issued in November 2016 an important guidance update[46] which made reassessment of orphan designation at license extension possible. This regulatory change in itself may have already led to a reduction of orphans authorised (the number of orphans approved fell to 9 in 2019, compared to an average of 16.75 in the four preceding years)[47]. Another example relates to trends in reimbursement: as the outlook for market access becomes more challenging in Europe, it could be that worse sales outcomes for newer products eventually work their way into rNPV-based business development decisions.

Last, the study adopted a European perspective, which may have overestimated the impact of the Regulation on innovation. Our presumption was that the European Commission strives to make the European market attractive for pharmaceutical development in its own right. In other words, we propositioned that pharmaceutical innovation ought to be sustainable within Europe, thus making the European scope appropriate. Nevertheless, investment decisions are necessarily global, and investments unprofitable in the European market may be underwritten by other countries, such as the United States.

Conclusion

Maintaining a positive incentive framework is essential to advancing therapeutic innovation towards effective cures for rare diseases, strengthening equitable health systems, and fostering a productive biopharmaceutical industry in Europe. Our study aimed to analytically reflect the relationship between incentives and investment, accounting for the cost, risk and time-lag inherent to pharmaceutical development.

Despite the study's limitations, it is clear that OMPs do not offer a straightforward investment proposition. Far from OMP Regulation over-incentivising biopharmaceutical companies, our study suggests that investment in OMPs remains precarious, despite legislative provisions aimed at mitigating the market failures linked to low-prevalence, high unmet need conditions.

Our study demonstrates the large impact that the Regulation has had on OMP availability in Europe, and highlights the risk of investment moving away from rare diseases should the removal of incentives diminish the economic viability of OMPs. Consequently, it is critical that any consideration of reform of the Regulation should be informed by a robust understanding of the relationship between incentives, investment, innovation and patient access.

[46]European Medicines Agency, 2016 [47]European Medicines Agency, 2019.

Appendices

Input parameters

Current economic incentives (base case)

Table 5 and **Table 6** present inputs used to populate the base case and 'No Regulation' scenario, respectively. Data inputs that feed directly into the model are highlighted in green. Inputs used in interim calculations are not highlighted. Note that while each input variable is accompanied by uncertainty, values reported below represent the inputs' point estimates (means). **Table 6** only lists parameters which differ from the base case.

Table 5. Base case input parameters

Category	Input	Value	Source
Duration of phases (yrs)	Preclinical	1	Paul *et al.*, 2010
	Phase I	3	Jayasundara *et al.*, 2019
	Phase II	4	Jayasundara *et al.*, 2019
	Proportion of OMPs with phase III trials	51%	Odnoletkova *et al.*, 2019
	Phase III	4	Jayasundara *et al.*, 2019
	Phase III (accounting for products getting approval based on Phase II only)	2	Calculation
	Approval	1	Paul *et al.*, 2010
	HTA	1	EFPIA Patient W.A.I.T. Indicator 2018 survey
	Note that the duration of phase III inputted in the model is a weighted average between the average duration of phase III for the 51% of products which have a phase III (4 years) and the other 49% which rely on phase II data for marketing authorization (0 years).		
Probability of success	Preclinical	100%	Assumption
	Phase I	76%	Wong *et al.*, 2019
	Phase II	49%	Wong *et al.*, 2019
	Phase III	52%	Calculated using Wong *et al.*, 2019 and Thomas *et al.*, 2016
	Approval	89%	Thomas *et al.*, 2016
Treated patient population	Average prevalence per indication (per 10,000)	1.24	Medic *et al.*, 2017
	Patient diagnosed (% of prevalent population)	70%	Assumption
	Patient reimbursed (% of diagnosed population)	65%	Assumption
	Patient receiving and active treatment (% of patients getting access)	85%	Assumption
	Compliance rate	80%	Assumption
	Total population in EU5	323,975,817	Eurostat (2019 estimates)
	Prevalent population able to receive treatment	70%	Assumption
	Patients receiving a treatment	10,030	Calculation
	Annual population growth	0.2%	Eurostat (2016–2019 estimates)
	Peak market share (pre IP/OME loss)	57%	Calculation
	Market ramp time to peak market share (yrs)	6	Assumption
	Average number of indications per product	1.40	Assumption

Continued...

Table 5. Base case input parameters *continued...*

Category	Input	Value	Source
Impact of loss of marketing exclusivity	ATMPs (% of total OMPs)	12%	Technopolis Group Orphan Study
	Biologics (% of total OMPs)	24%	Technopolis Group Orphan Study
	Small molecules (% of total OMPs)	64%	Technopolis Group Orphan Study
	Drop in ATMPs market share after loss of IP/OME (%)	0%	Assumption
	Drop in biologics market share after loss of IP/OME (%)	0%	Assumption
	Drop in small molecules market share after loss of IP/OME (%)	50%	Assumption
	Average market share post IP/OME loss	38%	Calculation
	Drop in price after loss of IP/OME	5%	Assumption
	We theorized that generic/biosimilar entry may impact revenue in two main ways: either price is maintained at its original level and market share is eroded, or price drops close to the level of competitors to retain a significant portion of the market. Here, we assume that the former mechanism is most applicable to orphans (i.e. price is preserved at the expense of market share). Further, we assumed that biologics and ATMPs see no competitor entry, to reflect the significant hurdles to biosimilars development in the orphan space. On the other hand, we assume that all small molecules see generic entry and experience a significant reduction in their market shares (50%) when this happens. The 5% drop in price after loss of IP/OME aims at capturing country-specific mandatory discounts at the time of loss of protection (e.g. in France).		
Price	Average net price (EU5)	€76,709	Calculation based on Medic *et al.*, 2017
	Annual price erosion	2%	Assumption
	Revenue multiplication factor (EU5–EU28)	1.21	Detiček *et al.*, 2018
	Price is set as a function of prevalence, which allows to retain the correlation between patient population size and price observed in real-life. The equation for the function was obtained by fitting a logarithmic function to the price-prevalence curve reported by Medic et al. for German prices. German prices were chosen as the reference for EU prices because they are available at net level.		
Intellectual property	OMPs without patent/SPC at start of OME	30%	Technopolis Group Orphan Study
	OMPs with patent/SPC still in force at end of OME	49%	Technopolis Group Orphan Study
	OMPs with patent/SPC expired at end of OME	22%	Technopolis Group Orphan Study
	Average market protection (from approval, including IP, SPC and OME)	13	Calculation based on Technopolis Group Orphan Study, see previous section
	Average overall market protection was estimated by a weighted average between the share of products with IP/SPC protection in place at the start of the OME period and the average duration of IP/SPC and OME protections, respectively. The numbers thus obtained were then summed to estimate the average market protection from approval, including OME. The distribution of market protection is aligned with what is observed in practice, as overall protection period ranges from 10 to 19 years.		

Continued...

Table 5. Base case input parameters *continued...*

Category	Input	Value	Source
Development expenses	Total pre-clinical costs (global)	€5,234,563	Paul *et al.*, 2010
	Total phase I costs (global), unadjusted for risk or cost of capital	€29,041,878	Wouters *et al.*, 2020 *Based on analysis of supplementary materials*
	Total phase II costs (global), unadjusted for risk or cost of capital	€78,700,178	Wouters *et al.*, 2020 *Based on analysis of supplementary materials*
	Total phase III costs (global), unadjusted for risk or cost of capital	€155,388,568	Wouters *et al.*, 2020 *Based on analysis of supplementary materials*
	% of global costs attributable to Europe	34%	EFPIA, 2019
	Annual preclinical costs (Europe)	€1,779,163	Wouters *et al.*, 2020
	Annual phase I costs (Europe)	€3,007,434	Calculation
	Annual phase II costs (Europe)	€6,673,592	Calculation
	Annual phase III costs (Europe)	€12,800,365	Calculation
	Cost of approval phase (EMA)	€488,278	Calculation
	Cost of HTA	€–	Assumption
	The development costs highlighted above appear lower than costs of R&D routinely quoted. One of the main reasons is that published estimates of R&D costs per approved product reflect the costs of failure. That is, these estimates account for risk (i.e. probability of success) and cost of capital (i.e. discount rate). As our model also accounts for these estimates, we used figures for direct out-of-pocket expenses reported in the article. When capitalized, mean orphan-specific R&D costs are estimated at ~1bn USD, in line with published literature. Cost of approval is calculated as a weighted average of EMA fees (e.g. pharmacovigilance, marketing authorization, scientific advice) for SME and non-SME sponsor. HTA costs are assumed to be 0 to avoid double-counting, as they are already accounted for in the SG&A expenditure.		
Other costs	Annual ongoing R&D costs	€1,365,742	Berdud *et al.*, 2020
	Cost of goods (% of revenues)	32%	Assumption
	SG&A expenditure (% of revenues)	22%	Assumption
	Cost of capital	10.5%	Wouters *et al.*, 2020
	Annual ongoing R&D costs for OMPs are assumed to be ~1.3 million euros, in line with a recent similar model developed by the Office of Health Economics. The average cost of goods is calculated as a weighted average between the share of OMP types (i.e. ATMPs, biologics and small molecules) and their respective cost of goods, which is assumed to be higher for ATMPs and biologics versus small molecules. A fixed percentage of the revenues is assumed to cover SG&A costs, which include a wide range of expenses, such as rent, salaries and marketing.		

'No Regulation' scenario

Table 6. 'No Regulation' scenario input parameters

Category	Input	Value	Source
Duration of phases (yrs)	Approval	2	Assumption
Probability of success	Phase III	47%	Assumption
	Approval	80%	Assumption
	The probability of Phase III and regulatory approval success was assumed to be 10% lower for non-orphan products than orphan ones. This is in line with assumptions by the Office of Health Economics[48].		
Treated patient population	Average number of indications per product	1.2	Assumption
	All other parameters unchanged		
Impact of loss of marketing exclusivity	*All other parameters unchanged*		
Price	Price multiplier	67%	Assumption
	Average net price (EU5)	€51,328	Calculation
	The price multiplier allows to lower the price of non-OD products by 33%, while preserving the prevalence-price relationship.		
Intellectual property	Average market protection (from approval, including IP and SPC)	9.5	Calculation based on the Technopolis Group Orphan Study
	Products don't experience any additional protection provided by OME.		
Development expenses	Increase in preclinical costs w/o OD (no EU aid for research)	10%	Assumption
	Annual preclinical costs	€1,957,080	Calculation
	Cost of approval phase (no fee waiver)	€740,919	Calculation
	We assumed a 10% increase in preclinical costs, as OMP sponsors would not have benefitted from EU research aids or fee waivers, leading to an increase in preclinical costs.		
Other costs	*All parameters unchanged*		

Estimating effective market protection

To calculate the average duration of effective market protection, we first distinguished between products with and without patent/SPC protection at the time of marketing authorisation. We further differentiated between products with and without patent/SPC protection at the time of OME expiry. We used weighted average of market protection across these groups.

[48]Berdud *et al.*, 2020

Table 7. Estimation of average effective market protection

	Products with IP/SPC protection at MA		Products without IP/SPC at MA
	Products without IP/SPC at OME expiry	Products with IP/SPC at OME expiry	–
Number of OMPs (%)	23 products (21.9%)	51 products (48.6%)	31 products (29.5%)
Average IP/SPC duration from MA	13.5 years*	13.5 years*	0 years
Average IP/SPC duration across all OMPs	*9.5 years*		
Average additional protection provided by OME	2.3 years**	0 years	10 years**
Average OME duration across all OMPs	*3.5 years*		
Average duration of effective market protection	9.5 + 3.5 = 13 years		

*According to the Technopolis Group Orphan Study (2020) (page 143), IP/SPC extends on average 3.5 years beyond OME for products which lose OME before IP/SPC expire. We therefore assessed the duration of IP/SPC at 13.5 years for products with IP/SPC at OME expiry, and used the same figure for those without IP/SPC at the end of OME in the absence of further data. **Table 7, page 142 of the Technopolis Group Orphan Study (2020).

Accounting for uncertainty

Model inputs were varied simultaneously and randomly within their probability distribution. The parameters included in the model, their mean values, their standard errors (SEs), and the distributions used for random sampling are shown in **Table 4**.

Where SEs were not available from the source (most variables), they were calculated from the 95% interval with the formula:

$$SE = \frac{(\text{Upper confidence limit} - \text{lower confidence limit})}{(2*1.96)}$$

assuming that the confidence interval ranged ±20% from the parameter's mean.

Table 8. Probabilistic analysis inputs

Category	Parameter	SE	Distribution
Duration of phases (yrs)	Preclinical	0.102	Log-normal
	Phase I	0.335	Log-normal
	Phase II	0.409	Log-normal
	Phase III	0.215	Log-normal
	Approval	0.112	Log-normal
	HTA	0.104	Log-normal
Probability of success	Preclinical	No variation assumed around this parameter (all products are assumed to enter phase I of development)	
	Phase I	0.077	Beta
	Phase II	0.050	Beta
	Phase III	0.053	Beta
	Approval	0.091	Beta
Treated patient population	Patients receiving a treatment	4093.878	Log-normal
	Annual population growth (%)	0.000	Log-normal
	Peak market share (pre IP/ OME loss)	0.058	Beta
	Market ramp time to peak market share (yrs.)	0.612	Log-normal
	Market share post IP/OME loss	0.039	Beta
	Drop in price after loss of OME	0.005	Beta
	Average number of indications per OMP	0.143	Log-normal
			Continued...

Table 8. Probabilistic analysis inputs *continued...*

Category	Parameter	SE	Distribution
Price	Average net price (EU5)	9614.045	Gamma
	Annual price erosion	0.002	Beta
	Revenue multiplication factor (EU5/EU28)	0.123	Log-normal
	Average effective market protection (from approval)	1.324	Log-normal
Development expenses	Annual preclinical costs	181547.277	Gamma
	Annual phase I costs	306881.062	Gamma
	Annual phase II costs	680978.789	Gamma
	Annual phase III costs	1306159.732	Gamma
	Cost of approval phase	49824.279	Gamma
Other costs	Annual ongoing R&D costs	139361.432	Gamma
	Average COGS (% of revenues)	0.033	Gamma
	SG&A (% of revenues)	0.022	Gamma
	Cost of capital	0.011	Log-normal

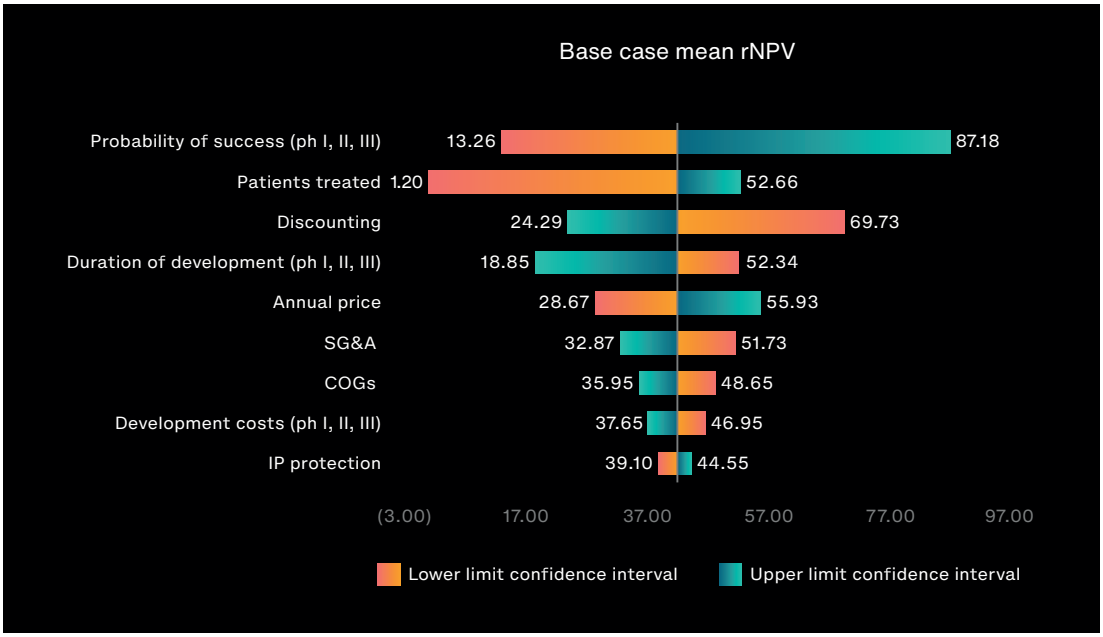
Full results

Table 9. Model outputs

	Base case (status quo)	'No Regulation' scenario (hypothetical scenario)
Proportion of products predicted to be developed (i.e. with rNPV > 0) (%)	95% [93%; 97%]	43% [42%; 44%]
rNPV (€ mln)		
Mean	37.58 [37.03; 38.12]	-0.22 [-0.44; 0.00]
Median	33.75 [33.21; 34.30]	-1.75 [-1.97; -1.54]
Revenue over lifecycle (€mln)		
Mean	5,720.03	3,022.05
Median	5,667.20	2,983.15
Costs over lifecycle (€mln)		
Mean	3,161.88	1,716.27
Median	3,119.00	1,688.22

Sensitivity analyses

Figure 3. Deterministic sensitivity analysis for the base case



Green bars represent the mean rNPV when the upper limit of the confidence interval is used instead of the mean for a selected input parameter. Orange bars represent the mean rNPV when the lower limit of the confidence interval is used instead of the mean for a selected input parameter. For example, consider the third row, reporting the model's sensitivity to the value of discounting. If the discounting parameter is set to the lower limit of the confidence interval (8.4%) instead of its mean (10.5%) – all other model parameters being unchanged – the mean rNPV jumps to almost €70 million. Conversely, if discounting is set to the higher limit instead (12.6), the mean rNPV drops to €24.29 million.

Figure 4. One way sensitivity analyses for interim parameters in the base case

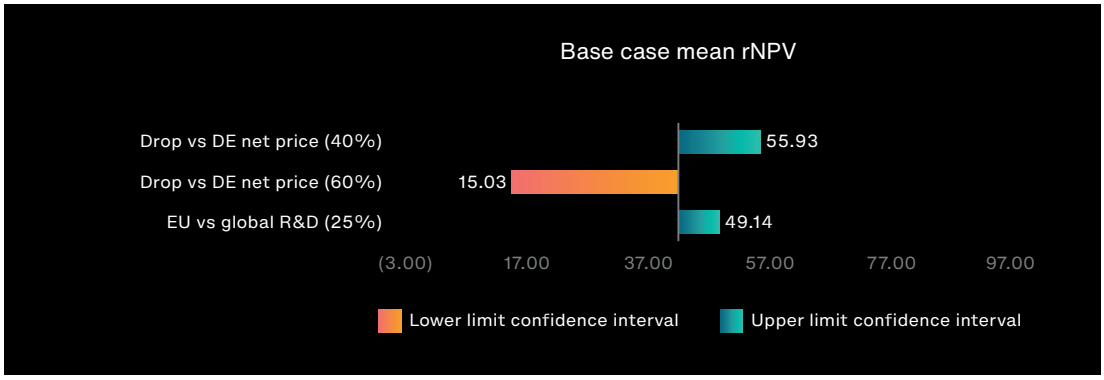


Figure 5. Deterministic sensitivity analysis for the 'No OMP Regulation' scenario

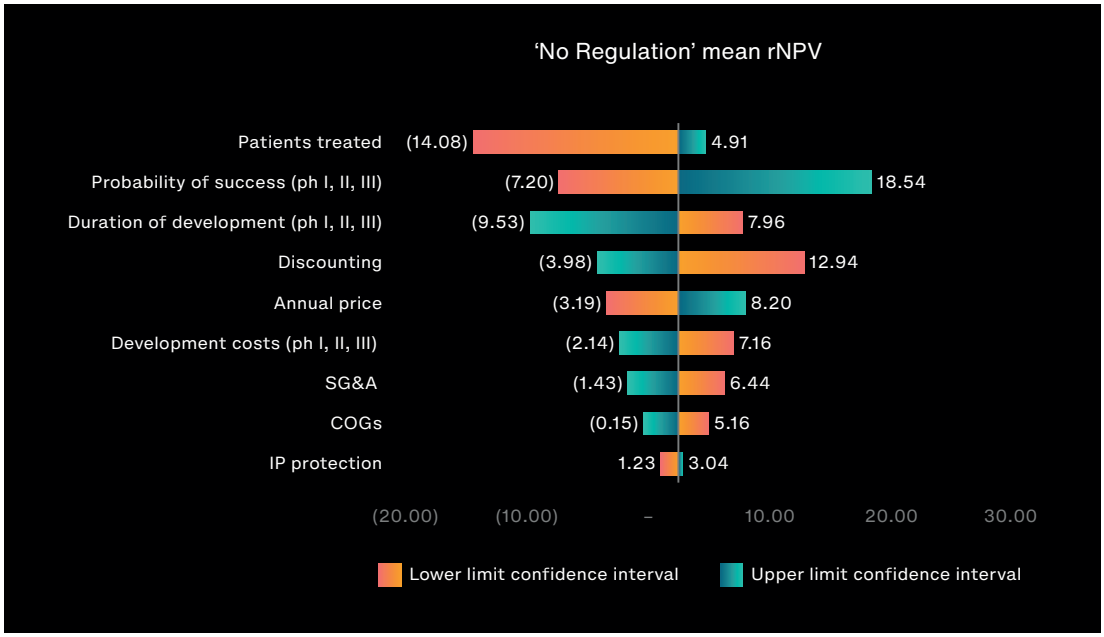
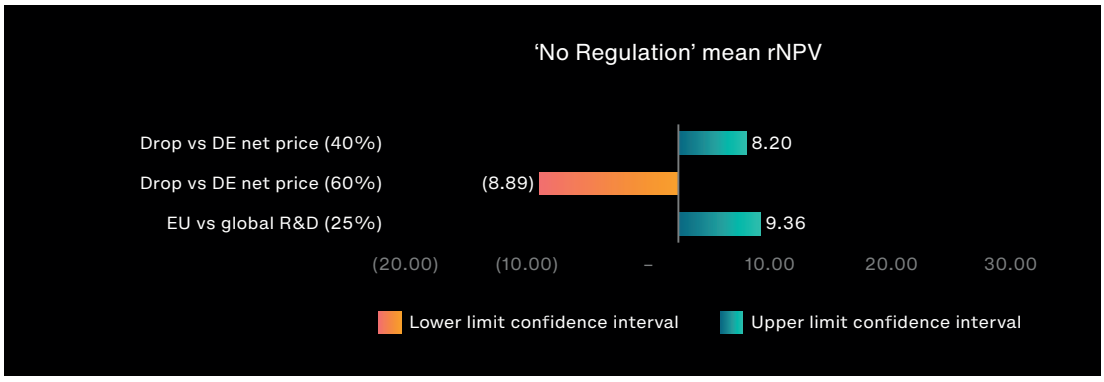


Figure 6. One way sensitivity analyses for interim parameters in the base case



Scenario analyses

Table 10. Scenario analyses regarding assumptions for the 'No Regulation' scenario

	'No Regulation' scenario		
	No impact on probability of success or preclinical costs	25% price differential vs. status quo	50% price differential vs. status quo
Proportion of products predicted to be developed (i.e. with rNPV > 0) (%)	62% [62%; 63%]	53% [52%; 53%]	18% [18%; 19%]
rNPV (€ mln)			
Mean	5.55 [4.69; 6.42]	2.60 [1.81; 3.38]	-6.60 [-7.10; -6.10]
Median	3.37 [2.51; 4.23]	1.21 [0.43; 2.00]	-7.67 [-8.17; -7.17]
Revenue over lifecycle (€mln)			
Mean	3,016.03	3,366.69	2,258.02
Median	2,993.10	3,324.03	2,247.87
Costs over lifecycle (€mln)			
Mean	1,711.83	1,897.83	1,302.72
Median	1,676.14	1,863.38	1,294.07

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