

A black and white photograph of a glowing lightbulb hanging from a cord, positioned centrally over a blurred background of people in a meeting. The lightbulb is the focal point, symbolizing an idea or a challenge.

Economic and Financial Challenges of Developing Orphan Medicinal Products

Does the European Regulation Tackle them?

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ohe.org



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Key messages

<p>Key message 1: The EU OMP Regulation has successfully incentivised companies to invest in the development of OMPs</p> <ul style="list-style-type: none"> • Marketing authorisations (MA) granted to orphan drugs between 2000 and 2018 grew at a compound annual growth rate of 15%. • More than a third (35%) of granted MAs are held by OMP-focused developers. • Nearly half (46%) are held by broader-portfolio companies.
<p>Key message 2: The EU OMP Regulation is crucial to manage the financial unpredictability of OMP development</p> <ul style="list-style-type: none"> • The financial performance of OMP-focused companies is characterised by financial instability. • OMPs generate lower and more volatile returns than medicinal products for common diseases. The incentives of the EU OMP Regulation are crucial to maintain a healthy R&D pipeline of and investment in new OMPs. • Changes to EU OMP Regulation would impact financial returns generated by OMP investment, could significantly decrease the number of OMPs developed, and in some cases could threaten the financial sustainability of OMP-focused companies (which hold 35% of the OMPs marketed between 2008 and 2018).
<p>Key message 3: EU OMP Regulation does not create monopolies. Rather, competition is increasing both during and after market exclusivity. However, it remains limited, <i>inter alia</i>, due to the short time period since the EU OMP Regulation was put in place and the small size of OMP markets</p> <ul style="list-style-type: none"> • Nearly a sixth of all OMP indications were treatable by more than one product still protected by market exclusivity (and two-thirds of them were in oncology). • More than one out of six OMPs with expired market exclusivity faced competition from at least one generic version. • Competition in the OMP space is expected to grow in some rare disease indications, as long as the EU OMP Regulation continues to provide incentives for investments.
<p>Key message 4: There are numerous areas of value OMPs bring unaccounted for by HTA metrics</p> <ul style="list-style-type: none"> • Patients may value treatments even when there is substantial uncertainty around effectiveness and the potential improvement in their condition. • Society may be willing to give priority to patients with severe conditions and conditions where no effective treatment is currently available (as is the case for many rare diseases) • OMPs can contribute to the quality of life and well-being of carers and family members, reducing physical and mental burdens. Reducing the burden of informal care can boost productivity and potentially offset OMP costs. • HTA and decision-making processes should account for all important sources of patient and societal value generated by OMPs.

Summary of the report

Rare diseases represent a priority area of unmet medical need in Europe. At present, there are between 6,000 and 8,000 distinct rare diseases – those with a prevalence of less than 5 in 10,000 – defined by the European Union (EU), affecting between 27 and 36 million EU citizens¹. Only 5% of these diseases are currently treatable². Recognising the importance of stimulating research and development into new therapeutic solutions for rare diseases, the EU in 2000 introduced the EU Regulation on Orphan Medical Products (OMPs)³.

This report assesses the extent to which this Regulation has successfully incentivised companies to invest in research and development of OMPs. Secondly, it analyses the financial challenges of developing OMPs, and within this context what the implications of changing the Regulation would be for firms' future investment decisions. Thirdly, it analyses the level of competition between OMPs in the market for rare diseases at present, and how this relates to the Regulation. Finally, the report explores key areas of benefits to patients, their carers, and society generated by OMPs.

To explore the effect of the Regulation on research and development (R&D) of OMPs, data from the European Medicines Agency (EMA) were used to analyse the number of marketing authorisations granted annually since 2000, and the type of sponsors of these authorisations⁴.

A first analysis of the data collected from the EMA indicates that the Regulation appears to have achieved its goal of incentivising companies to invest in the development of OMPs. The number of marketing authorisations granted by the EMA has grown steadily at a Compound Annual Growth Rate (CAGR)⁵ of 12% between 2001 and 2018. This is echoed by the number of designations granted by the European Commission (EC), which has grown at a CAGR of 15% between 2000 and 2018. Of the marketing authorisations granted between 2008 and 2018, 35% were to companies specialising in OMPs, and 46% were to companies which develop OMPs as part of a broader portfolio and pipeline including medicines for non-rare indications.

What are the main hurdles when developing OMPs?

It has been argued that the EU OMP Regulation is unnecessary and that the prices of OMPs and profits of the companies which invest in them are 'too large' (Hughes and Poletti-Hughes, 2016; Rollet et al., 2013). However, this criticism is typically based on analysis of the financial performance of companies which own the market authorisation for OMPs but also invest in other types of products. As such, the specific financial challenges posed by the development of OMPs are obscured. Moreover, while individual molecules may indeed be highly successful in terms of uptake and sales, this can be seen as a necessary financial return to offset the high failure rate associated with the development of OMPs, as well as other challenges that can be particularly acute for OMPs such as barriers to access for patients and the need to generate post-launch Real-World Evidence (RWE).

¹ EC report to the Conference "Medicines for rare diseases and children: learning from the past, looking to the future" in June 2019. Available at https://ec.europa.eu/health/human-use/events/ev_20190617_en

² EC report to the Conference "Medicines for rare diseases and children: learning from the past, looking to the future" in June 2019. Available at https://ec.europa.eu/health/human-use/events/ev_20190617_en

³ See: <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF>

⁴ The analysis covers a time period in which the UK was a member of the EU. At the time of publication, the UK is no longer a member of the EU.

⁵ CAGR provides a measure annual growth rate for temporal series as if the growth rate attributable to each year is constant.

We compared the financial indicators of companies specialising in OMPs (“OMP-focused”) and companies with broader product portfolios (“broader-portfolio”). Our findings suggest that the development of OMPs can be more challenging than medicines for more common conditions. Overall, Earnings Before Interest, Tax, Depreciation and Amortisation (EBITDA) are lower amongst OMP-focused than broader-portfolio companies. Most importantly, the EBITDA, and consequently returns to shareholders, are also more volatile amongst OMP-focused companies, which typically alternate between periods of losses and periods of profits. The gross margin generated by OMP-focused companies is slightly higher than that generated by broader-portfolio companies, but once indirect and fixed costs are taken into account their performance is significantly worse.

The Regulation has attempted to address the lower returns and higher risk (at least in the short term) of investing in OMPs through the following measures:

1. Protocol assistance, which can expedite the research and clinical development of OMPs, increase the success rates and, in principle, reduce R&D cost and bring revenue forward.
2. Market Exclusivity (ME), which ensures that once firms bring new products to market, the reward period will be long enough to compensate for losses during the investment phase.

Although the data did not allow us to analyse how the level and volatility of returns vary between OMPs and other products developed by broader-portfolio companies, the Regulation may play the same role in helping to direct internal investments towards OMPs.

The potential impact of changes to the Regulation was estimated using a Net Present Value (NPV) model, with four scenarios in addition to the current situation (or ‘baseline’). The effect of these scenarios on the expected NPV of investment was considered for the OMP-focused industry as a whole, as well as in two case studies based on data collected from the OMP-focused arm.

In the baseline scenario, for the industry as a whole and for both case studies, the expected NPV of the investment was positive. However, any changes from this baseline significantly decreased expected NPV. Reducing the ME by two years has a negative impact on the expected NPV in all cases (the two case studies and the industry as a whole) but overall the expected NPV remains positive. However, removing protocol assistance in combination with reducing the ME period by two years turns the expected NPV negative in both case studies. This suggests that any of the modelled changes to the Regulation could lead to a decrease in the number of OMPs developed. Some of the assessed changes to the Regulation could undermine the business model under which OMP-focused companies operate, and therefore effect their continuing activities in this area. Assuming the returns cycle of OMP projects within broader-portfolio companies mirrors the returns cycle of OMP-focused companies, it would also no longer be more rational for broader-portfolio companies to prioritise investments in (some) OMPs relative to other products.

What is the degree of competition in the market for rare diseases?

Our analysis suggests that competition in the market for rare diseases is relatively low, both during and after the ME period. Less than 15% of all OMP indications were treatable by more than one product still protected by ME (and two-thirds of these were in oncology). Less than 17% of OMPs for which the ME period had expired faced competition from one or more generic versions.

The fact that there is limited competition could be attributable to two factors: the scientific challenge of developing new medicines which demonstrate a significant benefit compared to the existing standard of care; and the small size of the market for OMPs. This combination makes it unlikely that subsequent entrants would be able to generate sufficient returns to justify investment. In addition, price pressure from reimbursement authorities in Europe often leads to delays in access and uptake

of OMPs and sends negative signals about follow-on investment. A policy aimed at stimulating competition in the OMP space within the current regulatory framework should address these barriers to access and uptake to incentivise competitor entry.

It should be noted that ME does not necessarily create monopolies, as ME is granted to prevent “similar” goods from entering the market during the exclusivity period. If a product demonstrates a significant benefit compared to the existing standard of care, it can be granted the OMP designation and, effectively, break the ME of an existing OMP in the same indication.

Finally, there are some indications where competition in the OMP space may be increasing. We found that 88 of the 552 indications for which there were medicines with orphan designations had two orphan designated medicines, and 131 had three or more. We note that these molecules are still in the early development stages and may not reach the market due to the inherent riskiness of the drug development process. However, between 2012 and 2018, new orphan designations were usually granted to products that treat a condition for which there are alternative treatments available.

What is the true value of OMPs?

There are several dimensions of value associated with OMPs which are either partially or entirely absent from most Health Technology Assessment (HTA) guidelines. Firstly, it has been argued that patients value treatments regardless of high uncertainty around response rates or other outcomes when these treatments could lead to a significant improvement in their condition (or a cure). Secondly, there is evidence to suggest that society prefers to allocate greater resources to patients with severe conditions and conditions where no effective treatment is currently available (as is the case for many rare conditions), rather than maximising overall health gains across all patients. Thirdly, there are potentially significant effects of OMPs on outcomes such as quality of life (and more generally, well-being) of carers and family members. Decreasing their physical and emotional burden could also increase their ability to go back to work or social activities. Greater labour force participation (and by extension, greater tax revenues) could offset some of the costs of OMPs.

Conclusion

The Regulation on OMPs introduced by the EU appears to have been successful in incentivising investment in companies specialising in OMPs, as well as in encouraging companies which develop OMPs as part of a broader portfolio to direct internal investment towards OMPs. There have been concerns that the Regulation provides disproportionately large incentives and enables unreasonably high profits. Our analysis shows that OMPs generate more volatile returns than other products for more common conditions. We argue the Regulation is necessary to overcome these challenges and that changes to it could lead to significantly lower numbers of OMPs being developed, and in some cases threaten the survival of companies which rely solely on developing OMPs.

There have also been concerns that the Regulation has stymied competition in the OMP market. Our analysis suggests that this lack of competition is a likely feature of the OMP space due to its characteristics, rather than the longer ME period. Moreover, there are rare disease indications where competition is increasing and will continue to do so into the medium term, as long as the Regulation continues to provide incentives for investment.

We conclude by noting that the full value provided by OMPs might not be captured by many current HTA processes. More research is needed to identify the full range of the value provided by OMPs and to generate relevant patient and societal preferences evidence to inform decision-making processes around OMPs.

1 Introduction

Rare diseases represent a priority area of unmet medical need in Europe. The European Commission (EC) estimates that there are between 6,000 and 8,000 distinct rare diseases (EC, 2019) – defined as diseases with a prevalence of less than 5 in 10,000 – in the European Union (EU). Individual rare conditions affect small populations, but as a whole they affect more than 30 million EU citizens (representing 6 - 8% of the population in the EU) (EC, 2019). Only 5% of these diseases are currently treatable. In the aggregate, these conditions have substantial health, economic, and social impacts.

Recognising the importance of stimulating research and development into new therapeutic solutions for rare diseases, the European Commission (EC) introduced the EU Regulation on Orphan Medicinal Products (OMPs)⁶ in 2000. The aim of the Regulation was to ensure that patients with rare conditions could benefit from the same quality of treatment as other patients. The Regulation was intended to address existing market failures, in recognition of the fact that the size of the market for any individual OMP is usually too small to attract optimal R&D investment. The Regulation introduced a pull incentive (the Market Exclusivity (ME) for 10 years) and push incentives including fee reductions and protocol assistance. Almost two decades from its introduction, it is important to assess the impact of the Regulation so far, and to consider possible effects of future changes. It is also important to understand if the unmet need recognised by the Regulation level is a consistent priority at the country level and within individual health systems. Given the constrained resources of most health systems, it is important to understand whether the benefits associated with OMPs, including their alignment with patient and societal preferences, are commensurate with their costs.

The small size of patient populations and the lack of effective treatments for most rare diseases make the development of OMPs a complex and financially risky process. In addition, there are challenges in the generation of evidence for HTA agencies (Annemans et al., 2017), including:

- patient recruitment for trials which are often multi-country;
- lack of epidemiological data and natural history data;
- lack of validated endpoints to predict long-term effects;
- lack of consensus on comparators.

There are also commercial challenges associated with the adoption of new treatments in individual EU countries, which frequently have limited experience and knowledge of rare conditions. These factors often apply in more common conditions, but they are particularly recurrent and acute with rarer conditions.

From a patient perspective, the diagnosis and management of rare conditions can be demanding and problematic. For example, many rare conditions affect multiple organs and have a variety of symptoms, and hence need to be managed by different parts of the healthcare system.

This report assesses the extent to which the Regulation has incentivised companies to invest in the R&D of OMPs. Secondly, it analyses the financial challenges associated with developing OMPs, and in this context, the implications of changing the Regulation with regard to firms' future investment decisions. Thirdly, it analyses the level of competition between OMPs in the market for rare diseases

⁶ [*Regulation \(EC\) No 141/2000 of the European Parliament and of the Council*](#)

at present, and how this may be affected by the Regulation. Finally, the report explores key benefits of OMPs to patients, their carers, and wider society.

2 Methods

Our approach combined different elements of evidence collection (i.e., European Medicines Agency (EMA) data, pharmaceutical companies' financial statements, secondary literature) and analyses of the financial challenges of developing OMPs and competition in markets for rare diseases. The evidence collected and results from our data analysis were combined to produce a general assessment of the EU OMP Regulation and a set of key messages to policymakers for refinement of the Regulation.

We started by creating a core dataset based on an extraction of all medicines with current orphan designation from the European Commission Community Register of OMPs as of April 2019⁷. Medicines for which the orphan designation had been withdrawn by the sponsor company were excluded. To this, we linked information on the characteristics of the medicines, including licence information, the indication, and the sponsor company.

We also created a supplementary dataset limited to molecules with orphan designation by generic name and with expired ME to analyse aspects of generic competition. The resulting list of molecules was refined by excluding those whose orphan designation (and ME) was withdrawn by the sponsor.

2.1 Financial challenges of developing OMPs

We took a two-part approach to analysing the financial challenges faced by OMP innovators: analysis of financial indicators and modelling of different NPV scenarios. This provided a characterisation of the business model of existing OMPs and a basis for assessing the financial challenges of developing new OMPs.

2.1.1 Companies database and financial indicators

From the core database, we selected two subsamples of companies: (i) a subsample of seven OMP-focused companies (the comparator arm) and (ii) an equal-size subsample of companies that represent the pharmaceutical industry in general (the control arm). To categorise companies as OMP-focused, we adopted a simplified version of an approach developed by Solà-Morales (2019) and Morel et al. (2016), described in more detail below. Companies in the control arm may have OMPs in the pipeline which are contributing to a fraction of their R&D cost, leading to some degree of bias.

The comparator arm included companies with a product portfolio and pipeline targeting only rare conditions. Analysing these OMP-focused companies provided evidence on the financial challenges specific to investing in the development of OMPs, without requiring full information on R&D costs at the molecule development level or operational costs and sales information.

The control arm allowed us to contrast the financial and economic challenges of developing OMPs with the challenges of developing medicines for more common conditions. For this arm we included broader-portfolio companies whose product portfolio and pipeline target a range of therapy areas and conditions, including but not limited to rare diseases.

⁷ http://ec.europa.eu/health/documents/community-register/html/reg_od_act.htm?sort=a (extracted April 2019)

For both arms, we selected our sample across a distribution of therapeutic areas, including cancer, metabolic and alimentary disorders and ‘other’, where all the other therapeutic areas were included.

To inform our analysis of the financial challenges faced by developers of OMPs, we extracted a set of financial indicators from publicly available sources, including companies’ financial statements and annual reports, as well as operating performance data from Morningstar⁸. We also reviewed relevant management and health economic literature (Solà-Morales, 2019; Hughes and Poletti-Hughes, 2016; Morel et al., 2013; Leahy, 2012; Cool and Dierickx, 1993)⁹.

2.1.2 Net present value (NPV) model

In order to characterise the business model for R&D into OMPs, and to provide estimates of the impact of potential changes to the EU OMP Regulation, we adapted an NPV model used by Baird L.G. and colleagues (Baird et al., 2013). NPV models estimate the value of future cash flows (positive or negative) associated with an investment – here, an R&D investment in a new medicine – discounted to the present. NPV analysis is a form of intrinsic valuation used extensively across finance and accounting for determining the value of a business, investment security or capital project (Hopkinson, 2017). The NPV of an investment also indicates the maximum price investors should be willing to pay in order to obtain a rate of return equal to the cost of capital. In other words, an NPV of zero rewards the investment at a rate equal to the cost of capital. Since the Regulation was put in place, the number of medicines with orphan designation and of marketing authorisations of these medicines has increased. This suggests that the regulation has had a positive impact on expected return, and supports the use of NPV as a key indicator of return on investment in OMP R&D.

We calibrated the model to estimate the average NPV of the investment in R&D required to fund the development of a new successful OMP, and the expected sales generated by such a product. In doing so, we considered rare disease populations; average revenues per product; and other cost and revenue inputs collected from the analysis of the financial indicators. To validate the analysis, we estimated the value of the average investment in a new OMP, using two companies in our control arm as case studies.

To estimate the R&D cost of a successful OMP, we followed the method established in the literature (Schuhmacher et al., 2016; DiMasi et al., 2016; Rollet et al., 2013; Mestre-Ferrandiz et al., 2012; Paul et al., 2010) which accounts for the risk of development failures (i.e., the likelihood a new molecule fails to proceed from one R&D phase to the next). Figure A.2.1 in Appendix 2 of this report illustrates the method used to estimate the cost of a new successful medicine (including OMPs). Our model incorporated the latest estimates of success rates specific to OMPs (Wong et al., 2019)¹⁰.

The NPV analyses were used to assess the (average) rate of return on investment in the OMP space and the potential impact of changes to industry-level incentives (the Regulation). To populate the model, the following inputs were required:

- an estimate of the R&D cost of a new successful OMP which considers the specific cost of each development phase (including the regulatory review and post-approval RWE collection) and adjusted by success rates, time of each development phase, average patient numbers per phase, cost of capital and the share of R&D cost attributable to Europe;

⁸ See <https://www.morningstar.com/>

⁹ A detailed comprehensive list of selected financial indicators and definitions is available in Appendix 1. To report results only a subset of the indicators selected will be discussed along the main text of this report.

¹⁰ It is important to note that Wong et al., (2019) do not break down phase III and regulatory review success rates. We use the same success rate for regulatory review of Thomas et al., (2016) and using both we calculate the corresponding success rate of phase III.

- patient prevalence estimates for rare and ultra-rare diseases¹¹ in the EU and, where relevant for the case studies, indication-specific prevalence in the EU;
- commercial factors including prices of OMPs¹² (alternatively, EU specific revenue per product for the case studies), uptake rates, uptake time trend until peak volumes and ME period based on regulatory approval and ME granted under the Regulation¹³;
- manufacturing, distribution, sales and administrative costs incorporated as percentages of drug revenues;
- corporate tax for pharmaceutical companies in the EU5¹⁴ countries;
- the discount rate for capitalisation and discounting of cost and revenues.

All model inputs were populated using publicly available data and assumptions¹⁵.

To assess the impact of potential changes to the Regulation on the economic incentives and financial performance of the pharmaceutical industry with regard to R&D in OMPs (as an OMP-focused or a broader-portfolio firm), we modelled the base case (current context) and scenarios involving the following policy changes:

- **Policy change 1:** a reduction of two years of the ME period with a 50% loss in value sales
- **Policy change 2:** a reduction of five years of the ME period with a 50% loss in value sales
- **Policy change 3:** removal of protocol assistance, modelled as a 10% reduction in the success rates of both phase III and regulatory review, and an increase of six months in the time for regulatory review and marketing authorisation.
- **Policy change 4:** policy changes 1 and 3 together

Estimates of NPV under each of the four scenarios modelled were compared to the base case to estimate the impact of changes to the Regulation. All estimates, including the base case, were assessed to illustrate the business model of current OMP programmes, including the expected rate of return, and to determine the possible impact of changes to the Regulation on investment decisions in the OMP space.

The results and figures generated by the models should be interpreted with some caution, as they are based on data from disparate sources and include assumptions around key market dynamics, including rate and speed of uptake. However, notwithstanding these unavoidable limitations, the results provide information about the expected effects of Regulation changes on incentives and the business model of OMPs.

¹¹ According to the European Medicines Agency's (EMA), rare diseases are defined as life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people in the EU (25 in 50,000 people). Orphan designations are granted by EMA to medicines that target to treat rare diseases. See: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac0580b18a41. SMC and NICE additionally define ultra-orphan drugs as medicines that have been granted by the EMA with the orphan status and target to treat conditions with a prevalence of 1 in 50,000 people in England and/or Scotland. See: <https://www.scottishmedicines.org.uk/media/2782/pace-overview-document.pdf>

¹² Price information was collected from published peer reviewed literature (Rollet et al., 2013)

¹³ See [Regulation \(EC\) No 141/2000 of the European Parliament and of the Council](#)

¹⁴ At the time of analysis, the EU5 countries were France, Germany, Italy, Spain and the UK.

¹⁵ Detailed explanation of the method and data sources for inputs is available in Appendix 2.

2.2 Competition in markets for rare diseases

To explore the extent to which a competitor product is likely to enter an OMP indication/class prior to patent expiry, we identified OMP indications where more than one on-patent product with a current orphan designation (and current ME) was available. This list was derived from the core database of OMPs. For each of these indications, we present the list of the on-patent products, the manufacturers of these products and the timing of entry of the competitors.

To measure competition and degree of market concentration, more sophisticated indicators, such as the Herfindahl-Hirschman Index (HHI) and indexes reflecting the degree of substitutability of the products, can be used. However, these indexes were not feasible here because we did not have access to market statistics and data about competitors' true market shares. It is important to note that, given the limited number of competitors observed, the use of HHI would not add relevant information beyond that indicated with our chosen method.

To analyse the entry of generic products, we selected products with a current orphan designation and expired ME. From the 47 products satisfying these criteria, we excluded products that were withdrawn from the Community Register of designated orphan medicinal products on request of the sponsor (N=5). For each of the 42 products remaining, we used the EMA license database (<https://www.ema.europa.eu>) to match their active substance with all biosimilars and generics with the same active substance and an active marketing authorisation for the same indication.

2.3 Value of OMPs

The aim of the final part of the analysis was to explore the benefits that OMPs can deliver (or have delivered) to patients and society when used in individual European countries.

We based this analysis on a set of core papers from the peer-reviewed and grey literature around the following topics: "value frameworks", "value frameworks for OMPs", "value of innovative interventions such as gene therapy", "value elements of OMPs". This was complemented by a targeted literature search for specific value elements relevant for OMPs, including severity of the disease, equity, family spill-overs and productivity gains, scientific spill-overs, the value of hope and value of cures, and insurance value.

3 Results

3.1 Key trends in OMP approvals

Since the implementation of the EU OMP Regulation in 2000, the number of marketing authorisations granted by the EMA has grown at a Compound Annual Growth Rate (CAGR) of 12% between 2001 and 2018. Although some variation in annual growth rates has been observed, a clear and increasing trend in the number of new authorisations can be seen. Several studies have suggested this increasing trend is an effect of the Regulation (Solà-Morales, 2019; Wilsdom et al., 2017; Mestre-Ferrandiz et al., 2010).

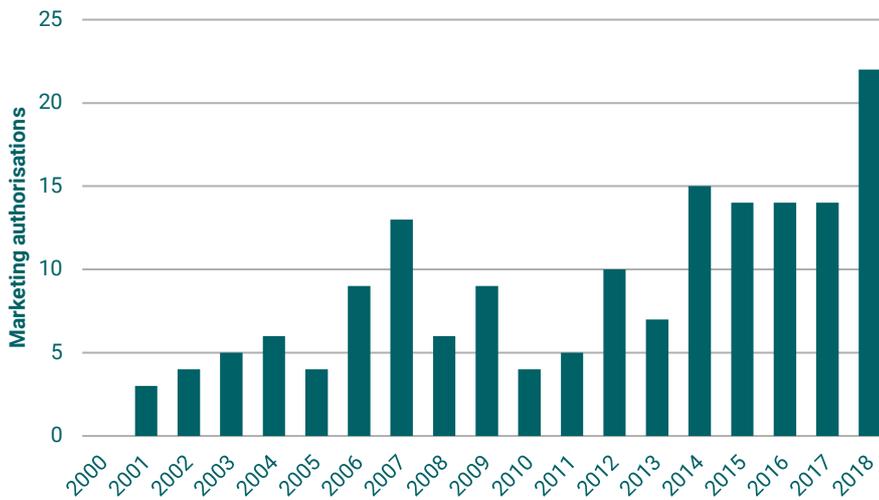


FIGURE 1: MARKETING AUTHORISATIONS OF OMPs PER YEAR 2000-2018

Source: EMA, https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf

The total number of orphan designations granted by the European Commission for the period 2000-2018 amounted to 2121, with 14 designations granted in 2000, increasing to 169 in 2018, as illustrated in figure 2. This equates to a CAGR of 15% for orphan designations between 2000 and 2018. The increasing trend in the number of new orphan designations was also ascribed to the Regulation by the same studies (Solà-Morales, 2019; Wilsdom et al., 2017; Mestre-Ferrandiz et al., 2010).

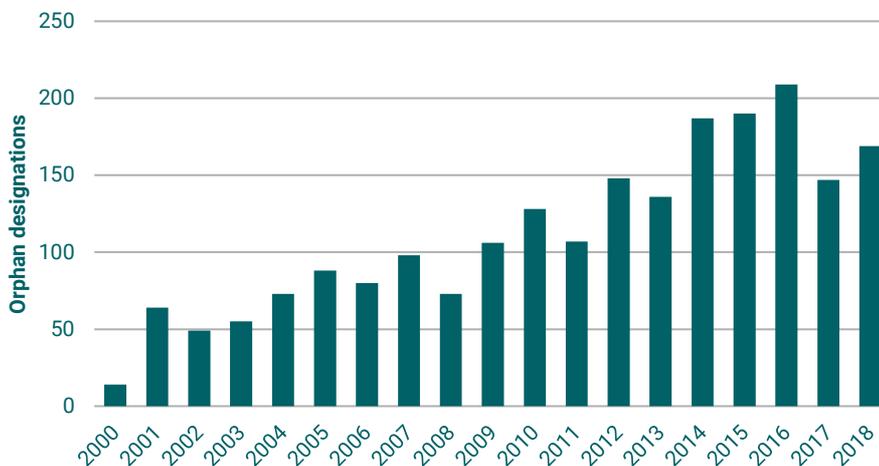


FIGURE 2: EUROPEAN COMMISSION ORPHAN DESIGNATIONS PER YEAR 2000-2018

Source: EMA, https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf

As both figures show, there has been a clear and positive response from the pharmaceutical industry since the Regulation was implemented, leading to an increased number of innovative products.

We also collected information about the sponsors that brought OMPs to the market. This dataset did not capture designated products that were marketed for an orphan indication but whose ME period had expired. The dataset contained information on the sponsors of a sample of 136 orphan medicines approved between 2008 and 2018 and which are included in the information presented in

Figure 1. Figure 3 represents the distribution of the marketing authorisations between OMP-focused, broader-portfolio and other (a category that includes companies highly specialised in a therapy area but not only in orphan indications).

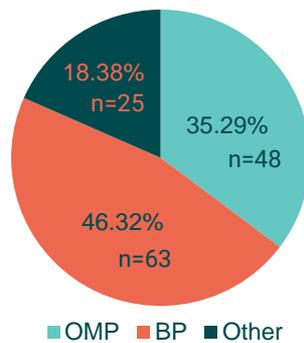


FIGURE 3: DISTRIBUTION OF MARKETING AUTHORISATIONS BY TYPE OF SPONSOR

Notes: OMP stands for OMP-focused companies, BP for broader-portfolio. The OMP, BP and other pie charts also include information on the number of new OMPs granted with marketing authorisation by the EMA
Source: The European Commission.

As shown in Figure 3, a significant share of the OMPs which were brought to market in the last decade is still protected by ME and was developed by OMP-focused companies.

As highlighted in the Regulation, one of its main objectives was to incentivise the investment in new medicinal products for rare diseases where there was a recognised market failure, i.e.

“[...] without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; [...]” (Regulation (EC) No 141/2000, article 3.1).

The success of this objective is reflected in the distribution of the source of the 136 new OMPs brought to market between 2008 and 2018. Forty-eight (35%) were brought to market by OMP-focused companies, 63 (46%) were by broader-portfolio companies and 25 (20%) by ‘other’ companies. The literature suggests that, because of the Regulation, companies have attracted funds for, and directed investment to, the development of new OMPs (Solà-Morales, 2019; Wilsdom et al., 2017; Morel et al., 2016; Rollet et al., 2013).

However, questions have been raised about whether the Regulation is needed to sustain investment in the OMP space. In particular, critics have highlighted the profitability of companies investing in OMPs and the high prices of many orphan drugs (Hughes and Poletti-Hughes, 2016; Rollet et al., 2013). Much of this criticism has focused on the financial performance of companies that hold OMP marketing authorisations in their product portfolios but are not necessarily focused on OMPs. Critics focus particularly on their high market capitalisation, calculated as the number of outstanding shares multiplied by the current share price. However, many companies with marketed OMP products do not invest exclusively in the OMP space, i.e. are not OMP-focused. This means that their financial performance, typically measured as their market value, is not exclusively due to the development and commercialisation of OMPs. Such criticisms, therefore, relate more to the performance of the overall pharmaceutical industry than to the specific performance of OMP-focused firms.

Accurate estimation of the economic returns of a specific OMP is difficult due to technical and informational barriers. It is also important to consider the cost of failures in the R&D process to understand net returns to R&D in OMPs. Other factors to consider are:

- barriers to access for patients leading to low and slow uptake, and delays in reimbursement and access decisions;
- economies of scale with the existing portfolios, and;
- the cost of generating post-launch RWE, which is particularly relevant for OMPs marketed under conditional approval.

These factors may vary considerably by condition and medicine, between companies, and across countries. For example, the degree of clinical success may vary considerably between therapy areas (Wong et al., 2019; Thomas et al., 2016; Hay et al., 2014), as will patient populations and the feasibility of randomised clinical trials. Additionally, in countries like Germany and France, all OMPs with marketing authorisation are widely accessible, while in England less than 50% of OMPs are (routinely) funded by the NHS (Zamora et al., 2019). However, England often provides access to oncology orphan drugs through the cancer drugs fund (CDF), sometimes following a negative, or no, decision by NICE. Therefore, it is necessary to consider the whole spectrum of OMPs to have a full understanding of the OMP business model.

3.2 Which are the main hurdles when developing OMPs?

3.2.1 Financial challenges

To provide a specific measure of financial challenges faced by OMP developers, we compared a sample of OMP-focused companies with a sample of broader-portfolio companies. The main indicators we analyse are Earnings Before Interest, Tax, Depreciation and Amortisation (EBITDA)¹⁶ and the Return on Equity (RoE)¹⁷. It is important to note that the analysis performed does not aim to compare the absolute value of the two indicators between arms. Rather, we analyse the variability of the indicators within each arm, exploring whether companies in the same arm show the same results, or whether results vary within arms.

Figures 4 and 5 show EBITDA for the OMP-focused and broader-portfolio samples, respectively. Comparison of absolute figures of EBITDA shows that the operational performance of companies in the broader-portfolio arm is higher than that of OMP-focused companies. Importantly, the comparison also shows that the performance of the OMP-focused arm is more volatile, as it alternates between periods of profits and losses.

Among the companies in the OMP-focused sample, there were three notable cases which we labelled as OMP1, OMP2 and OMP7:

- OMP1 was a well-established orphan developer, specialised in metabolic and alimentary disorders. It showed stable performance over the years considered in the study. OMP1 was something of an outlier as no other company showed such a pattern.
- OMP2 was an emerging company with only one product authorised by the EMA, in 2016, for a rare genetic disease. After several years of further investment, OMP2 marketed the new

¹⁶ Earnings Before Interest Tax Depreciation and Amortization is a measure of a company's overall financial performance or profitability that excludes all income generated through company's financial activity.

¹⁷ RoE is a measure of financial performance calculated by dividing net income by shareholders' equity

medicine in 2018. This is another outlier in the sample, as their EBITDA was consistently negative over the period under study.

- OMP7 was a well-established company specialised in the respiratory therapy area. It was performing well at the end of the study period but had a history of underperformance and high R&D investment.

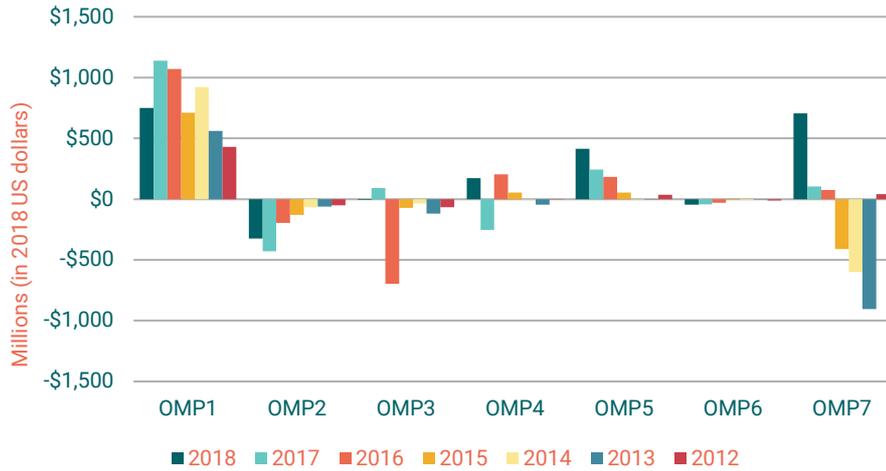


FIGURE 4: EBITDA OF OMP-FOCUSED COMPANIES 2012-2018

Sources: Morningstar® and companies published financial statements.

As shown in Figure 5, the EBITDA operating performance of companies in the broader-portfolio arm was stable over the period of the study, with no cases of alternating profits and losses.

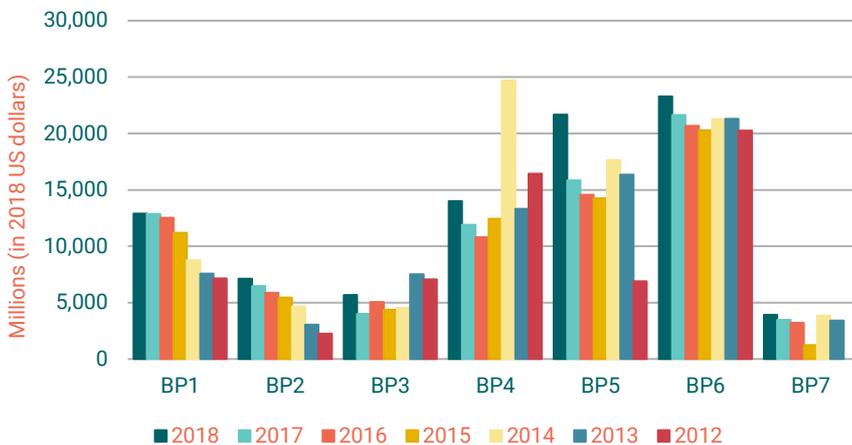


FIGURE 5: EBITDA OF BROADER-PORTFOLIO COMPANIES 2012-2018

Sources: Morningstar® and companies published financial statements.

Similar patterns were observed when analysing RoE. Figures 6 and 7 show financial performance from the point of view of shareholders. The OMP-focused arm shows a higher volatility in returns to shareholders. They also show that the OMP-focused arm alternates between periods of positive returns and negative returns, suggesting that shareholders need to have a long-term orientation to invest in those companies.

From Figure 6, it can be seen that OMP2 had only negative returns over the period. OMP7 experienced five years of negative return (2012-2016) until the company accrued positive returns in 2017, becoming highly profitable in 2018. OMP5, another well-established company, experienced three years of negative returns (2012-2014) and then four years of positive returns (2015-2018). This demonstrates the lengthy investment time needed to generate positive returns and to market what became, in 2015, the company's two top-selling drugs.



FIGURE 6. RETURN ON EQUITY OF OMP-FOCUSED COMPANIES 2012-2018

Sources: Morningstar® and companies published financial statements.

The case of OMP4 was especially notable. OMP4 was a company with more than 25 years of history and one product in the market. The company shows positive returns in early years of the analysis, but these are in fact a consequence of "negative equity" reported in its consolidated financial statements, driven by a shareholder deficit¹⁸.

In contrast, Figure 7 again demonstrates the stable performance of all broader-portfolio companies, with two exceptions: BP2 and BP7. Both showed periods with negative returns that were not reflected in EBITDA analysis of Figure 4. Upon investigation, it was concluded that the negative performance on this indicator reflected specific financial adjustments rather than poor operating performance.

¹⁸ A shareholder deficit is also known as "negative equity". It happens when a company has more liabilities than assets.

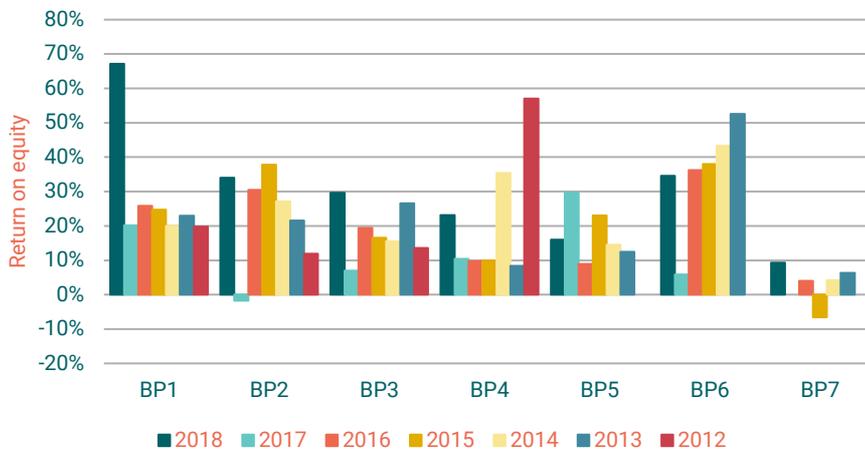


FIGURE 7: RETURN ON EQUITY OF BROADER-PORTFOLIO COMPANIES 2012-2018

Sources: Morningstar® and companies published financial statements.

The analysis of the operating performance of OMP-focused companies consistently shows a weak and volatile operating performance. A consequence of such volatility is a constant need to signal to current investors that returns can be expected in the long run, in order to attract and maintain enough funding to progress OMP R&D pipelines. Attracting funding during the investment phase, when operating performance is low, will be difficult or impossible if companies cannot signal potential positive returns in the long run.

Although the data are most conclusive for the OMP-focused companies, broader-portfolio companies face similar issues when making decisions about whether to invest in rare or more common diseases. Given their broad product portfolio and R&D pipelines, the impact of individual investment decisions on overall financial performance indicators is smaller. However, decisions of broader-portfolio companies still rely on expected relative returns between investments in OMPs and more common diseases which are characterised by larger markets (larger patient populations) and wider market access. Initiating and maintaining projects in the OMP space requires a sufficient return in the long term, a challenge that the EU OMP Regulation was intended to solve and appears to have accomplished based on this evidence.

Arguably, the EU OMP Regulation successfully signals that investment in OMP R&D will provide returns comparable to investments in more common conditions. In addition, protocol assistance¹⁹ provides support to expedite the research and clinical development of OMPs, reducing the costs and development horizon of OMP R&D programmes. Success rates, particularly in terms of marketing authorisation approvals, can also be increased, and revenue brought forward. At the same time, ME²⁰ ensures that once firms succeed in bringing new products to the market, the reward period will be long enough to compensate for costs and foregone revenue during the development phase. Therefore, it can be argued that the Regulation has contributed to the business case for OMP investment, ensuring the survival of OMP-focused companies during periods of negative revenue, and encouraging broader-portfolio companies to invest in OMPs alongside medicines for more common conditions.

Further analyses with other financial indicators also help to illuminate the OMP business model. Table 1 shows a summary of indicators for the OMP-focused and broader-portfolio arms.

¹⁹ See article 6 of [Regulation \(EC\) No 141/2000 of the European Parliament and of the Council](#)

²⁰ See article 8 of [Regulation \(EC\) No 141/2000 of the European Parliament and of the Council](#)

TABLE 1: SUMMARY OF FINANCIAL INDICATORS

	OMP-focused	Broader-portfolio
	Mean	Mean
Debt/Equity ^a	0.80	1.30
R&D/Revenue ^b	0.48	0.15
Gross margin	0.83	0.73
SGA expenses/Sales	0.43	0.26
Sales/SGA expenses	2.30	3.88

Notes: definitions of all financial indicators are provided in Appendix 1. The mean in each case has been calculated as the arithmetic average of all years' arithmetic averages of all sample observations' values of the indicator in the row; ^aOMP4 has been excluded from the calculation to avoid counterintuitive values; ^bOMP2 and OMP6 have been dropped from calculation as they present outlier data that magnifies the result in several years.

Sources: Morningstar® and companies published financial statements.

Table 1 highlights three important observations. First, the debt to equity ratio in the first row shows that OMP-focused companies are more likely to finance their assets through equity, whilst broader-portfolio companies are more likely to finance through debt. In part, this likely reflects differences in the cost of capital to the different companies. As shown above, returns to OMP R&D are more volatile and therefore of higher risk; as a consequence, investors demand a greater expected rate of return to compensate for this risk. This is reflected in estimates of the cost of capital to the two groups. 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). As the cost of debt is relatively greater for OMP-focused companies, they have relatively less access to debt finance. The EU OMP Regulation has encouraged investment in OMP-focused companies by reducing the risk associated with investment in OMPs and by improving returns over the OMP life cycle through protocol assistance and ME. These incentives reduce risk and volatility and signal to investors that positive returns on investment can be expected over the long run, helping OMP-focused companies to attract funding to finance their R&D activities.

Second, R&D costs among OMP-focused companies represented a considerably larger share of total revenue than for broader-portfolio companies. This suggests that companies investing strictly in developing OMPs need to reinvest a larger share of the revenue back into R&D as compared to companies in the broader-portfolio category, which implies lower dividends and more difficulty in attracting funding. Although clinical trials required for OMP R&D are smaller than those for more common diseases, that does not necessarily mean that the overall R&D cost of developing a new OMP is low. In particular, the high failure rates at each stage of development (Wong et al., 2019) mean that R&D in OMPs can represent a large share of expected, risk-adjusted returns, making R&D in OMPs expensive. Additionally, sales volumes are considerably lower because of the small patient populations, constraining potential revenue and again increasing the share of R&D as a proportion of expected returns.

Market exclusivity mitigates this pressure in some respects. Where a newly approved medicine provides a significant benefit, ME secures a longer time under protection to provide reasonable returns, increasing maximum revenue. In the absence of an exclusivity period, there would be pressure to maximise the initial price to generate returns as quickly as possible, before the entry of a potential competitor. By offering the right incentives to the industry, the Regulation appears to have been effective in sustaining investment in OMP R&D.

To confirm that sales volumes are lower for OMPs due to smaller patient populations, we estimated the aggregate prevalence of rare conditions and, by extension, the total market for orphan medicines. We confirmed the average treatment population for the indications covered by OMP-focused companies. We used prevalence and incidence data of rare diseases from Orphanet²¹ and combined it with information about all labelled indications²² for each product generating revenue for companies in the OMP-focused arm. For our sample, the mean target treatment population in Europe was 33,300 patients, with the largest population being 76,200 patients and the smallest being only 14 cases worldwide. This is well below the absolute number of patients used to define a rare disease for the purpose of assigning an orphan designation in the EU28 (less than 256,200 patients)²³. It is important to stress that 33,300 patients are the potential mean target population estimated when all patients are diagnosed and provided treatment, but the actually-treated population is smaller, as not all countries provide access to innovative OMPs and not all patients access the medicine in countries where it is available. For example, Zamora et al. (2019) showed that Germany and France reimbursed 93% and 81%, respectively, of all OMPs authorised from 2001 until June 2016. The equivalent figure in Italy was 58.7%; 52.4% in Spain; 46.9% in England; 38.5% in Scotland; and 32.9% in Wales.

It should also be noted that the gross margin for the OMP-focused arm is slightly higher than for the broader-portfolio arm. However, in examining the relationship between Selling and General Administrative (SGA) expenses, OMP-focused companies require a higher percentage of their revenue (43%) to cover these expenses than broader-portfolio companies (26%). This suggests that developing OMPs, i.e., products with smaller target populations and constrained potential to generate revenues, still involves indirect and fixed costs similar to those for broader-portfolio companies. The inverse ratio in Table 1 (sales to SGA ratio) can be interpreted as showing that broader-portfolio companies generate 3.88 euro per unit spent on SGA while OMP-focused companies only generate 2.30 euro, around 40% less. In this sense, ME for OMPs helps to generate a rate of return closer to that of medicines for more common diseases.

3.2.2 The economics of developing OMPs. What is the potential impact of changing the EU OMP Regulation?

To test the impact of potential changes to the EU OMP Regulation, a model of NPV previously developed by the OHE and based on Baird et al. (2013) was calibrated to reflect the average NPV, from a commercial developer' perspective, of investing in a new product targeting a rare condition in the EU. The model was also calibrated to estimate the expected NPV of investing in OMPs for two case studies based on data collected for the OMP-focused arm of the financial analysis.

The expected NPV was estimated for the base case (representing the current policy situation) and for four scenarios based on potential legislative changes: 1) a reduction of the ME by 2 years; 2) a reduction of the ME by 5 years; 3) the removal of protocol assistance; and 4) a combination of 1 and 3.

Our working assumptions were as follows:

- When ME expires, generic/biosimilar versions of OMPs will be manufactured and marketed. Branded OMPs, no longer protected by ME, will then face a decrease in prices and market share equivalent to a 50% loss in sales value.
- The removal of protocol assistance will result in reduced dialogue between the sponsor and the EMA. The advice that EMA gives on procedures for evidence collection (e.g. tests and

²¹ See: Data available at

https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf

²² We used the Summary of Product Characteristics published at EMA

²³ Article 3.1.(a) of Regulation (EC) No 141/2000 of the European Parliament and of the Council establishes the definition of rare disease at "10 thousand persons in the Community [...]" which combined with the current population of the EU28 of 512.3 million (see: <https://ec.europa.eu/eurostat/web/population-demography-migration-projections/data>) produces a potential patient population at threshold of 256.2 thousand.

trials) needed to meet the quality standards of the agency will no longer be available and consequently there will be a decrease of 10% of development success rates (i.e., phase III, regulatory review) and an increase of half a year in regulatory review time.

Details of all our assumptions and literature sources are provided in Appendix 2.

The expected NPV of developing OMPs under the scenarios modelled is shown in Table 2.

TABLE 2: NPV MODELLING RESULTS PER NEW SUCCESSFUL MEDICINE (IN €2018 MILLIONS)

	BASELINE	SCENARIO 1 (reduction of the ME by 2 years)	SCENARIO 2 (reduction of the ME by 5 years)	SCENARIO 3 (removal of protocol assistance)	SCENARIO 4 (combination of 1 and 3)
Industry: OMP-focused	55.5 / 34.6	45.6 / 26.5	24.7 / 9.4	27.7 / 8.5	18.4 / 0.9
Case study 1	29.2 / 13.1	21.6 / 6.8	5.4 / (6.4)	3.5 / (11.3)	(3.6) / (17.2)
Case study 2	30.9 / 14.4	23.1 / 8.0	6.6 / (5.4)	5.0 / (10.1)	(2.2) / (16.0)

Note: ME = market exclusivity period. Industry: OMP-focused models the expected NPV of a new successful OMP for OMP-focused companies. Case studies are representations of two companies in the OMP-focused arm based on available data and authors' assumptions. Results are given with ranges of +/- 5% of the price assumption and treatment populations estimates. Results displayed within brackets mean negative numbers.

There are several key learnings from the NPV modelling exercise. Firstly, on average and adjusted for the risk of failures, the expected NPV of investing in a new OMP is positive in the base case. Although the value of the investment is positive for the base case, the margin over a zero rate of return is relatively narrow. Secondly, a reduction of 2 years in the ME period (Scenario 1 in column three) does not turn the expected NPV of an investment in a new (average) OMP in the OMP-focused model (row two) negative but diminishes it between 17.8% and 23.4%. For case study 1, Scenario 1 reduces the expected NPV between 26.1% and 47.8% with both bounds, lower and upper, remaining positive. Scenario 1 for case study 2 also reduces the expected NPV between 25.2% and 44%. For all cases, Scenario 1 had a negative impact of significant magnitude. A reduction of the ME period by five years (scenario 2) would further extend the negative lower bound of the expected NPV estimate for both case studies, along with decreases in the upper bound of around 80%. The effect would be that, for the industry average, the value of the investment would decrease between 55.5% and 72.9%. Thirdly, removal of the protocol assistance (scenario 3) also turns the estimated lower bound of expected NPV in the two case studies negative and has an impact on the industry average similar to the Scenario 2. Scenario 4 turns the expected NPV of the two case studies negative for both, lower- and upper-bound of the estimated range. The OMP-focused industry's expected NPV still remains positive but with the lower-bound of the estimate close to zero. Scenarios 2, 3 and 4 would have a high impact in the three cases modelled. In particular, scenario 4 would leave the two case studies modelled in a weak position to attract investment in the short and long term and therefore their survival might be at risk. It is important to note that estimated figures of expected NPV take into account the cost of all failed projects by adjusting the R&D cost by development phases' clinical success rates²⁴. It is different from a product-by-product NPV assessment as it intends to assess the expected NPV of an average new OMP project.

Focusing only on variations from the base case to each scenario, the model predicts that changes to the Regulation would have a significant impact on the expected NPV – on average and from the perspective of individual companies. We therefore conclude that companies are very sensitive to changes in legislation and incentives. If incentives are reduced, R&D projects for OMPs would

²⁴ For an explanation of the R&D cost estimation see Appendix 2.

experience reduced rates of return in response. Combining this with the financial challenges shown previously, it could be expected that legislative changes that reduce the incentives for OMP-focused companies would challenge their survival. The investment could leave the development of OMPs and be redirected to other areas. It is important to note that the business model for developing an OMP is the same for broader-portfolio companies. Hence, at the project level, changes in the policy will affect all OMP-specific investment. For OMP-focused companies, this means their entire business is put at risk; other companies that are not highly specialised in OMPs will adapt their investment by redirecting it to maximise expected returns.

The NPV scenario analysis is in line with the financial challenges previously identified through the analysis of the financial indicators (i.e., EBITDA, RoE, Debt to Equity, gross margin, sales to SGA). Companies focused only on developing OMPs face higher economic risks and their economic survival is dependent on a highly encouraging framework, as provided by the Regulation. Therefore, maintaining healthy investment in OMPs is also one of the primary effects of the current Regulation. As results from all scenarios confirm, the expected value of investing and direct resources to OMP R&D programmes would be negatively affected by changes in the Regulation. As noted above, this is the case regardless of the size or portfolio scope of the company. However, OMP-focused companies – those with a portfolio targeting exclusively, or mainly, rare conditions – might be more severely affected. The threat to their survival in a less regulated (or unregulated) environment would, therefore, be higher. In general, innovation in the OMP space would be damaged regardless of whether such innovation comes from OMP-focused, broader-portfolio or other types of companies.

The data collected from the EC for this work showed that OMP-focused companies accounted for 35% of all OMPs approved in years between 2008-2018, and that there was an increasing trend in the number of marketing authorisations granted over recent years (see Figure 1 of this report). As analyses presented in this report show, changes in the Regulation could damage the industry's expected future achievements in developing new OMPs. For instance, we have shown that the debt to equity ratio of these companies is lower, which means that their capacity to respond to shocks or periods of company downturn is weaker as they rely comparatively more on their equity. Combined with the volatility seen in the EBITDA, changes in the Regulation could put their survival at risk.

Although a change in the Regulation would not threaten the survival of broader-portfolio companies, it would certainly affect the relative return of their R&D programmes and thus investment in OMP programmes could be switched to other areas. In the medium or long term that would mean that the amount of innovation produced in the OMP space would diminish, reversing the recent trend towards patients suffering from rare diseases being provided with an increasing number of treatment options.

3.3 What is the degree of competition in markets for rare diseases?

3.3.1 Competition to date

According to our analysis, less than 15% (15 out of 110) of all OMP indications had more than one product still protected by ME. Of these 15 indications, 9 were in the oncology area. For 4 of 15 indications, the first OMP in a given indication was covered by the ME period for less than a year (i.e. the second OMP accessed the market less than a year after the entrance of the incumbent). For 14 out of 15 indications, the second OMP entered the market less than 6 years after the market authorisation of the first OMP in a given indication. Further details about the time of entry of competitors, therapeutic areas and the number of competitors per orphan indication are provided in Appendix 3.

This demonstrates that OMP developers are likely to face competition in a given therapeutic area during the ME period of their compound. Competition analysis of ME-protected products showed that there are several indications where multiple approved OMPs are competing. Our observations of

indications with one or more competing products showed that the EU OMP Regulation prevents the entry of similar products but allows the approval of products that “[...] will be of significant benefit to those affected by that condition”²⁵ compared to the available treatment option/s, even when these options are still protected by the ME²⁶. However, this is not the predominant pattern, as the vast majority of OMP indications do not have multiple entrants.

Our analysis of generic competition identified seven products out of 42 medicines (around 17%) with an orphan designation and expired ME (excluding those which were withdrawn by the sponsor), that have generic versions competing for the same orphan indication. The number of generic entrants for the seven cases varied from one to four. More details are shown in Table A.3.1 in Appendix 3.

The possibility that the 10 years of ME provided by the Regulation has, in effect, created long-term monopolies has become a key concern for the EC. However, ME does not necessarily create monopolies for the full length of the protected period:

- ME is granted to prevent “similar” goods from entering the market during the exclusivity period and “Therefore, exclusivity does not prevent a “non-similar” product – for example, a small molecule versus a biologic – from receiving the orphan drug designation for the same therapeutic indication” (Tambuyzer, 2010; pp 4);
- if a product demonstrates a significant benefit²⁷ compared to the existing standard of care, it can be granted with the designation and break the ME of an existing OMP in the same indication.

The limited competition observed within OMP indications might be due to the small size of the markets for OMPs, which do not attract subsequent entrants. As shown before in this report, OMP markets are characterised by small volumes and narrow operational margins for investors which might not attract competitors. Additionally, there are downward price pressures from HTAs and pricing authorities leading to delays in access and uptake that may further exacerbate the situation and send a negative signal for follow-on investment. More than half of the centrally authorised OMPs were available in the five big EU markets (i.e., France, Germany, Italy, the UK, Spain), but that reimbursement can be further restricted and delays between authorisation and decisions on reimbursement time are recurrent. The shortest time from authorisation to a reimbursement decision is observed in Italy and France where it takes 18.6 and 19.5 months respectively on average (Zamora et al, 2019). Factors behind these delays are multiple and can include not only lengthy reimbursement or HTA processes but also companies’ launching strategies. A policy to stimulate competition and innovation in the OMP space within the current regulatory framework should also aim to address these factors and reduce delays in access.

Based on the results observed in both analyses, it could be speculated that the reason for the limited competition for authorised OMPs, while their ME is still active, is the financial challenges we described above. However, it could also be that the period since the Regulation was implemented is relatively short (considering the period of clinical development programmes) and that competition between ME protected products is a new process still in development. The same can be argued for generic competition; there are only a few indications in which the ME period has expired and therefore generic competition in the OMP space is also a relatively new phenomenon. In the medium term, this competition is likely to increase as the ME of products that were approved between the late 2000s and 2010s expires in the next 3-5 years²⁸.

²⁵ Article 3.1.(b) of Regulation (EC) No 141/2000 of the European Parliament and of the Council

²⁶ Article 8.3 of Regulation (EC) No 141/2000 of the European Parliament and of the Council

²⁷ Article 3.1.(b) of Regulation (EC) No 141/2000 of the European Parliament and of the Council

²⁸ In the US where the Orphan Drug Act was implemented in 1983 and there is a 35-year experience of regulation, more than 50% of the orphan drugs that have lost ME face generic competition. For those not facing competition, the reason is

It is important to note that the absence of a fierce generic competition does not imply that the originator continues charging high prices and making high profits. The possibility of new market competitors' entry often pushes the originator to reduce prices in advance of the ME expiry date to prevent entry or minimise the number of entrants. This could be an optimal strategy for those companies which benefited from an ME period sufficiently long to recoup their investment. In other words, once the sunk costs of R&D investment are recovered, reducing prices can be an optimal decision. When the threat of competition is real, then cutting the price can signal that margins in that market are narrow and thus deter potential entrants.

The theory of contestable markets states that the threat of entry of the competitor is enough to discipline the incumbents. *"Opening up a market to potential entrants may be sufficient to encourage efficiency, and deter anti-competitive behaviour"* (Economics Online, 2019). Even if generics do not ultimately enter the market, a real and credible threat of their entry just before the expiration of ME disciplines the incumbent to behave as if the market is subject to competition (Baumol, 1986).

As highlighted in the section on financial challenges, a period of ME can be optimal. If the ME period expires too early and the developer has not yet recovered their investment, the developer will not be able to reduce prices as much as needed to prevent generic entry. From a payers' perspective, this could be efficient in the short run as it would reduce the prices of medicines for orphan drugs, and total expenditure, earlier. By the same token, however, this would damage the incentives for investing in the OMP space. In the long run, the risk would be that a sub-optimal amount of innovation would be produced. The market failure of the pre-Regulation era would produce the same dynamical inefficiency observed before 2000, at least in some therapeutic areas, indications and conditions.

3.3.2 Competition going forward

The core dataset allowed us to explore potential future competition. Orphan designations are assigned early in the development of a medicine. As a consequence, there are a number of medicines with a current orphan designation and without marketing authorisation, that might potentially reach the market. The results suggest that the pipeline will continue to maintain a level of competition in a number of markets (such as oncology) and there could be an increasing level of competition in others.

In the entire core dataset, which comprised 1,500 medicines in 552 indications, 333 indications had a single medicine with an orphan designation, 88 had two orphan designated medicines and 131 had three or more. This is illustrated in figure 8.

the low median spending they achieve in the US market (\$8.6 million per year). Those facing generic / biosimilar competition present similar revenue impact found in indications for common diseases with generic competition (IQVIA, 2018a).

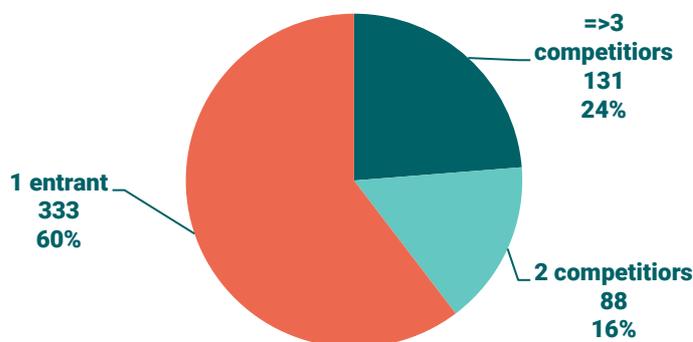


FIGURE 8: LEVEL OF COMPETITION IN INDICATIONS BY ORPHAN DESIGNATED MEDICINES STILL UNDER DEVELOPMENT

Source: EMA, https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf

Of the 113 indications where there was at least one medicine with both orphan designation and marketing authorisation, 45 indications had no other medicines in the pipeline for the same indication, 26 had one and 42 had two or more medicines potentially entering the market. We note that these molecules are still in early development stages, and may still fail and not necessarily reach the market.

An analysis of the last six years (2012-2018) shows that the orphan designation is usually granted to a compound in a given indication for which there is at least one other compound available on the market. Figure 9 below shows the number of OMP designations by year since 2012. The line plots the share of designations for which there are at least 2 or more medicines; this share increased from 21% in 2012 to 70% in 2018.

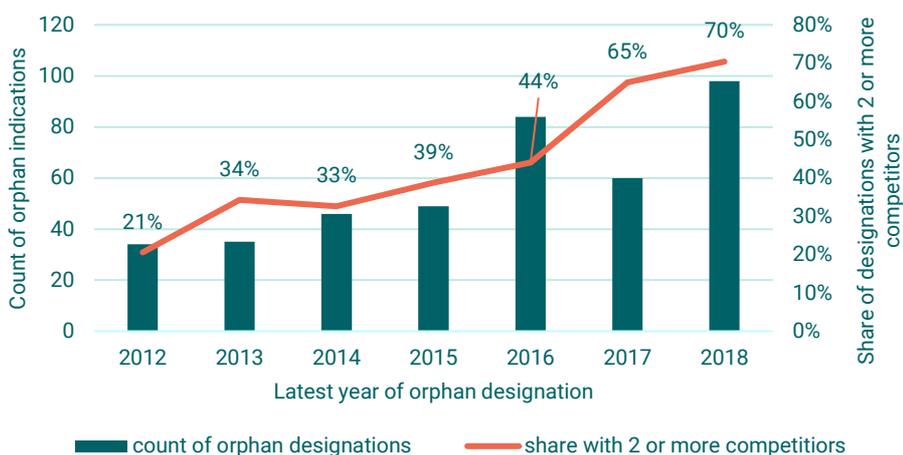


FIGURE 9: CURRENT PIPELINE OF ORPHAN DESIGNATED MEDICINES

Source: EMA, https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf

These statistics suggest that the pipeline of medicines has the potential to establish or maintain therapeutic competition for a number of orphan indications. This confirms that competition is a relatively new phenomenon that will grow significantly within the medium term and will be

established in the long term if the orphan designations that are currently in the pipeline reach the market.

3.4 The value of OMPs for patients, carers and families, and society

3.4.1 Approaches to valuing medical technologies and OMPs

There are elements that warrant consideration in value assessments of medical technologies, some of which are not considered in current HTA systems, but which are particularly relevant to OMPs. There has been increasing support for developing and implementing the so-called Value Frameworks (VFs), which capture benefits beyond health gains traditionally measured in HTA (such as the quality-adjusted life year, or QALY)

A key contribution in this direction is the ISPOR task force on VFs, and particularly Lakdawalla et al. (2018). The author's aim was to broaden the view of what constitutes value in health care and to spur new research on incorporating additional elements of value into cost-effectiveness analysis (CEA). Twelve potential elements of value are considered. Four of them – QALYs, net costs, productivity, and adherence-improving factors – are conventionally included in value assessments (although we note that the consideration of productivity gains varies substantially). Eight others, which are more novel in economic assessments, are defined and discussed: reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spill-overs. Some of them are theoretically well-grounded and have accepted methods for measurement and incorporation in HTA (most notably severity). Others, such as the value of hope and insurance value, require more methodological developments and endorsement in the policy arena.

In this section, we use economic theory and practical examples to describe how many of these considerations are particularly pertinent when considering the value of OMPs. To structure this discussion, we use the value 'flower' proposed by Lakdawalla et al. (2018 p.131) as a means to summarise the elements that warrant consideration in value assessments of medical technologies.

Elements of Value

Challenge: Map each element into an underlying economic framework for value assessment.

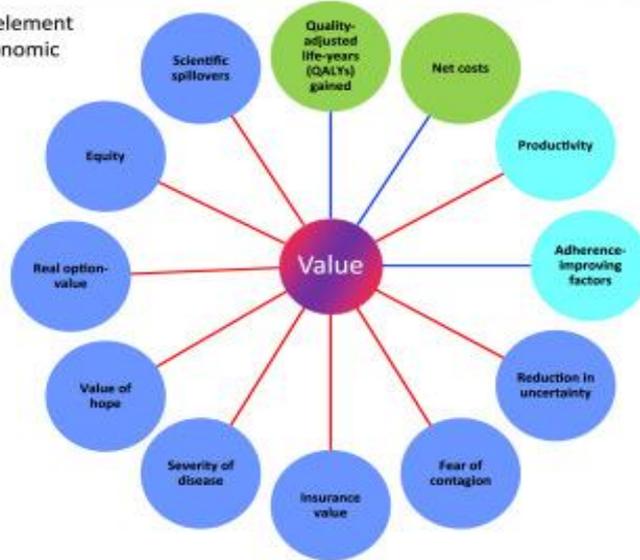


FIGURE 10: ELEMENTS OF VALUE, OR VALUE ‘FLOWER’

Note: Green circles: core elements of value; light blue circles: common but inconsistently used elements of value; dark blue circles: potential novel elements of value; blue line: value element included in traditional payer or health plan perspective; and red line: value element also included in a societal perspective.

Source: Lakdawalla et al. (2018 p.131).

Jena and Lakdawalla (2017) recommend that a VF for OMPs should recognise the unique issues associated with rare diseases. This includes adopting a societal perspective, which involves taking into account the treatment impact on all the elements presented, not only from the perspective of the patients but also of other parties concerned, particularly families and carers who can experience dramatic changes in their quality of life and in their ability to actively participate in society as a result of a rare condition affecting a close person. Assessing and considering the effect that a new treatment can have on those dimensions (such as the ability to return to work – the so-called productivity gain) is particularly relevant in the case for rare conditions, many of which affect young children.

In the next sections, we discuss briefly the key-value elements (beyond clinical improvements) which have specific relevance to OMPs.

3.4.2 Severity of disease

OMPs, by definition²⁹, treat diseases which are severe, and likely to lead to (rapid) death or chronic debilitation. QALYs and other measures of health gains treat two health gains of equal size as equal in value, regardless of the patient baseline from which these gains were realised. However, research across countries has consistently shown that societies tend to place more value on health gains accrued by patient populations with poorer baseline health, including those at the end of life – based on equitable or humanitarian principles.

3.4.3 Equity

Egalitarian principles hold that all persons should be treated equally and should be entitled to equality in access to healthcare and equality of outcomes (which is linked to the concept of severity as

²⁹ Article 3.1.(a) of Regulation (EC) No 141/2000. See: <https://eur-lex.europa.eu/eli/reg/2000/141/oj>

explained above). Compared to more common conditions, rare diseases are more likely to lack effective treatment and knowledge across the health systems to tackle the conditions appropriately (diagnosis can take a long time for example). This can put patients with rare diseases at a disadvantage in terms of equality of access to effective medications and equality of health outcomes.

Depending on the specific definition of equity and the type of intervention, there might be a trade-off between achieving efficient outcomes (for example, maximising total health gains at the population level) versus equitable outcomes (for example, a more homogenous distribution of these outcomes across different population groups).

3.4.4 Family spill-overs and productivity gains

There is growing evidence that carrying out caring duties, or being the family member of an ill relative, has a significant negative impact on quality of life (Wittenberg et al. 2019). As such, arguments have been made for incorporating the spill-over effects of serious illnesses on carers' and family members' health into standard HTAs (Prosser et al. 2007). These arguments are particularly relevant to rare diseases for three reasons: the severity of rare diseases, the frequency with which they occur in children, and the complexity of some of these conditions (which can affect multiple organs and are therefore difficult to manage). For example, a study in Italy carried out by Neri et al. (2015) found that 34% of the parents of children with cystic fibrosis reported short depression–happiness scale scores, suggestive of clinical depression. A study in Spain reported that the estimated average EQ-5D score (a well-known and used generic measure of quality of life) for Spinal Muscular Atrophy caregivers was 0.49 while that of the general population of the same age was 0.959 (Bastida et al, 2017).

Another relevant spill-over effect which is particularly relevant to OMPs is the effect of illness on labour productivity. The health spill-overs associated with rare diseases are particularly severe, and so too are the impacts on carers' and family-members' labour productivity. Many caregivers reported leaving work entirely to provide adequate support to the patient (Landfeldt et al., 2014). For example, an international study found that the annual cost of supporting a patient with Duchenne muscular dystrophy exceeded \$120,000. Less than half were direct medical costs (Landfeldt et al., 2014). A Spanish study reports that a patient with Spinal Muscular Atrophy presents an annual cost of over €30,000, of which almost 70% was due to informal care. The latter represents the tasks performed by patients' relatives to assist them in daily activities (Batista et al, 2017).

OMPs have the potential to alleviate these burdens by, for example, increasing the patients' autonomy (hence reducing the care required), simplifying the treatment pathways or reducing the number of hospital visits required, and ultimately they can, in some cases, allow carers to return to work or to other economic or social activities. While evidence on the economic burden of rare conditions is available, less data specific to the effect of new interventions on these aspects (for example how treatment can alleviate caregiving tasks) are produced. This might be due to the limited and often unsystematic way these broader societal impacts are considered by HTA decision makers (Garau et al., 2015).

3.4.5 Scientific spill-overs

Scientific spill-overs may arise when a treatment tackling a disease in a novel way is introduced, as it can pave the way for future scientific advances. Lakdawalla et al. (2018) provide the example of a new mechanism of action which is not valuable per se from an HTA or payer perspective (unless it generates proven health gains). This is applicable to OMPs because in many cases the first treatment developed might not yield substantial patient's health benefits, but could open up new scientific avenues, increase the knowledge of the disease among clinicians, and develop research networks. This might contribute to accelerating innovation in key areas of unmet need (Mestre-Ferrandiz et al., 2010). As pointed out by Sola-Morales (2019), (direct) health gains of new treatments are only one output of R&D investments. Other consequences of hindering or deteriorating the innovation ecosystem (potentially leading to the "collapse of the biotech industry") should be considered, most notably the negative impact on future generations. More generally, considerations

around the dynamic nature of innovation raise the issue for health care systems of rewarding long-term scientific benefits which are highly uncertain at the time of treatment launch, versus continuing to fund more established and proven treatments (with the risk of stifling or delaying medical advances).

3.4.6 Value of hope and value of cures

A value element rarely considered is around the attitude to risk of patients and their chance to respond to a new treatment. It has been shown that patients might have a preference for treatments with a high variance in their outcomes (mainly survival gain) in the *hope* of being the ones who obtain the highest benefits (such as a longer life extension or cure). Traditionally HTA frameworks focus on average estimates of these benefits, while patients might also be interested in the distribution of the key outcomes and willing to accept a high uncertainty around the average.

This is relevant for curative interventions, such as gene therapy. Patients may value curative OMPs with greater risk of negative side-effects or treatment failure more highly than alternative treatments with the same expected health gains (on average), but less variation in outcomes.

Rare diseases are more likely, compared to other conditions, to be targeted by curative medical products such as gene therapy. This is because rare diseases often result from genetic abnormalities rather than a combination of genetic, environmental and other factors.

3.4.7 Insurance value

Another novel element of value that has been identified as pertinent to OMPs is the benefits they provide to healthy individuals, by protecting them against the risk of future or possible ill-health. In simple terms, healthy individuals may value the availability of treatment for a disease which they do not have, in the same way as they value health insurance (Jena and Lakdawalla, 2017). Since healthcare is funded by all individuals in a population, the value of health technology to the healthy should arguably be considered alongside its value to individuals with the relevant disease.

Under this approach, the value of OMPs would increase substantially compared to other treatments for two reasons. Firstly, the value of insurance increases with the severity of the disease it protects against (because of the potentially catastrophic consequences), and rare diseases tend to be more severe than common conditions. Secondly, the value of insurance is relevant to the whole population, both the sick and the healthy. However, in the case of a rare condition, the proportion of the healthy will be higher, hence consequently the value of protecting against the disease.

In conclusion, there are several dimensions of value generated by OMPs which are either partially or entirely absent from current HTA. By failing to incorporate the value of cures, assessments undervalue the type of benefits that are important to patients. They also may not reflect societal preferences to prioritise patients according to the severity of their diseases. Finally, HTA might not capture the significant effect of OMPs on outcomes, such as quality of life (or more general well-being) of carers and family members, as well as the productivity gains, which could, in fact, offset some of the costs of OMPs.

4 Limitations

Our study includes a number of limitations, most notably:

- The financial volatility presented and discussed could have been caused by multiple factors, including companies' portfolio composition and performance and the size of the companies in question. More research would be needed to disentangle all possible factors.
- Given the lack of data, scenarios of changes in the EU OMP Regulation explored in the NPV analysis were largely based on authors' assumptions and the use of scarce evidence from the literature. More research is needed to test these assumptions and increase the robustness of the results.
- The analysis of the level and impact of competition going forward uses the number of active orphan designations for the same indication as a predictor of the future competition. Our core database supports this simple approach, but we acknowledge that some share of these designations will not make it to the market given historic failure rates. A more accurate estimator of future competition in the rare diseases space will require further research using more accurate pipeline data.
- Finally, we note that the impact of a removal of protocol assistance (the push element of the EU OMP Regulation incentives) might have a lesser impact than predicted by our model. A number of EMA regulatory pathways intended to accelerate the development of treatments for unmet need (i.e. conditional marketing, approval under exceptional circumstances, accelerated assessment, the Priority Medicines (PRIME) scheme) have recently been introduced. Although these are not exclusive to OMPs, it has been shown that these mechanisms have been used for treatments of rare diseases in the majority of cases (Tambuyzer et al., 2019).

5 Conclusion

This study assessed different aspects of the current EU OMP Regulation, in force since 2000, related to OMPs, from clinical development to market and patient access. The overall conclusion is that the OMP space is a growing area of R&D and is producing an increasing amount of medical innovation for patients suffering from rare conditions.

The current increasing trend in R&D that the OMP space is experiencing started soon after the implementation of the Regulation (Solà-Morales, 2019; EMA, 2018; Wilsdom et al., 2017) and appears to be continuing. **Since the adoption of the EU OMP Regulation, the number of marketing authorisations granted for OMPS has grown steadily, producing a total of 164 new OMPs.**

The study findings highlight the importance of maintaining the current regulatory framework in order to ensure the long-term survival of companies focused on the development of OMPs (OMP-focused) and maintain the investment of broader-portfolio companies in R&D for OMPs within the EU. **OMP-**

focused companies have marketed around 35% of all 136 marketing authorisations granted between 2008-2018³⁰.

The financial analysis demonstrated that, compared to broader-portfolio companies, OMP-focused companies are characterised by:

- a constrained capacity to generate revenues per unit of cost (i.e. R&D; SGA expenses) mainly attributable to low volumes of selling and targeted populations;
- alternating periods of positive and negative operating performance (i.e. EBITDA, RoE) which reflect periods of investment in new projects and periods of positive returns on such investments;
- alternating periods of positive and negative returns for shareholders, who finance a greater share of activity within OMP-focused companies than broader-portfolio companies.

All these characteristics indicate that **models of return on investment should focus on the entire industry R&D investment and activity. They should aim at reflecting the R&D cost of both successes and failures as well as the cost of capital in the particular space of OMPs.**

The ME provided by the Regulation plays a key role in ensuring the financial stability and long-term success of OMP-focused companies because it guarantees a sufficient period of rewards for new medicines that keep investors investing in the long run³¹ and during periods of low (or no) revenue and absence of positive return. In addition, **the ME also incentivises broader-portfolio companies to direct funds towards OMP programmes instead of investing them in other more common diseases** (assuming that returns of any OMP-specific programme are the same for OMP-focused or broader-portfolio).

Results from the NPV analysis showed that changes to the Regulation would likely have a significant negative impact on the value of the R&D investment and the business model for developing OMPs. **A reduction of the ME period of two and five years would reduce the expected NPV of a new successful OMP between 17% and 72% from an industry perspective, and between 25% and 148% (turning NPV negative) in the two case studies modelled. The scenario combining a reduction of ME by 2 years and the removal of protocol assistance produced negative results for the two case studies and results close to zero expected NPV for the general OMP-focused pharmaceutical industry.** These estimates are based on a set of assumptions and include the R&D cost incurred in failed projects. Figures presented in the analysis are not molecule or R&D project specific estimates. The model aims to represent the general business case for investing in OMPs and the scenario analysis showed how all policy changes proposed would impact the expected economic and commercial value of investing in developing OMPs.

Another general conclusion from the NPV analysis was that even after accounting for the cost of failed projects, **the current present value of investing in OMPs is positive (on average) but the margin above the breakeven point (NPV=0) is relatively low. Therefore, reductions in the ME period would make investments in OMP programmes less attractive (both from the perspective of OMP-focused and broader-portfolio companies).**

The Regulation provides a solid framework that sustains a healthy industry for OMPs. **Any attempt to weaken the IP protection and support provided to OMP manufacturers would most likely result in a decrease of investments in the OMP space or a shift towards other diseases or therapy areas.** The removal of a share of OMP-focused companies – responsible for 35% of new marketed OMPs

³⁰ Sponsor information of OMPs whose ME have expired is not captured in the dataset. We have sponsor information of a sample of 136 OMPs licensed between 2008 and 2018.

³¹ Compared to patents whose length may be variable depending on the development time till marketing authorisation, ME ensures a constant period of 10 years of exclusivity (article 8.1 of [Regulation \(EC\) No 141/2000 of the European Parliament and of the Council](#)), only revisable if conditions for designation are no longer met or enough profitability of the product is proven at the end of the fifth year (article 8.2.).

since 2008 – may be a future consequence of this policy change. Similarly, the business case for investing in OMPs within broader-portfolio companies – responsible for the 46% of new OMPs marketed since 2008 – would no longer be compelling and could lead to companies deciding to redirect internal resources to other areas, thus reducing the number of OMPs developed in the long run.

Most of the orphan indications do not show multiple entrants, although we observed some level of competition (in 15% of all OMP indications). Less than 17% of OMP with expired ME have one or more generic versions.

One potential explanation for **the low degree of competition is related to small populations and scientific challenges**. Rather than an unintended consequence of ME, the limited entry might be due to the small size of OMP markets, which does not attract subsequent entrants. In addition, the development of a much better product (required to gain the orphan status) entails a scientific challenge which can be difficult and have a low probability of success. Further, long HTA and price and reimbursement processes in individual countries leading to delays in access to OMPs send negative signals to follow-on investments. **Innovative and generic developers may dismiss the idea of entering because of (i) the scientific challenge of developing a significantly better product to compete for indications still covered by ME, (ii) low rewards expected due to small patient populations, and (iii) reasons associated with delays in accessing markets and gaining market share.**

An alternative explanation for the low degree of competition is that the period the EU OMP Regulation has been in force is relatively short compared to the timeframe required to successfully develop and bring an OMP to market plus the ME period granted to new OMPs. This means that **competition in OMP space is a new phenomenon that we expect to grow in the future**. Our analysis shows that competition is likely to materialise in the medium or long run. There is a pipeline of medicines with the potential to establish or maintain therapeutic competition for a number of orphan indications. In 2018, 70% of OMPs approved had two or more molecules under development with an orphan designation for the same indication which could potentially enter the market. **If there is a value to society derived from competition, it can be also attributed (to a significant extent) to the Regulation, as it has created the incentives to invest in the OMP space and generate a promising pipeline of new medicines in development with orphan designations.** Some may argue that a change to the current Regulation would not affect the current pipeline. However, the shift in the investment decisions from OMP to other areas is likely to reduce the number of new treatment options in the long term.

When analysing approaches to valuing medical technologies and OMPs, we highlighted that there are several dimensions of value generated by OMPs which are either partially or entirely absent from current HTA. These include the severity of the condition, family spill-overs and productivity gains, and the value of cures. By failing to incorporate them, assessments might undervalue the type of benefits that are important to patients. They also may not reflect preferences to prioritise patients, due to the severity of their diseases. Finally, HTA might not capture the significant effect of OMPs on outcomes, such as quality of life (or more general well-being) of carers and family members, as well as the productivity gains, which could, in fact, offset some of the costs of OMPs.

Going forward, more research is needed to identify the full range of value provided by OMPs and to generate relevant patient and societal preferences evidence to inform decision-making processes around OMPs.

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A.1 Appendix 1

A sample of pharmaceutical companies was selected for the financial challenges section of this study. The sample was split into two arms of seven companies each: orphan medicinal products developers (OMP) – or OMP-focused – and broader-portfolio (BP) companies. Companies in both arms were selected because they hold products with an orphan designation, although for companies in the broader-portfolio arm, products with orphan designation do not represent the majority of their portfolio. Table A.1.1 contains company information for each company included in the analysis.

TABLE A.1.1 COMPANY INFORMATION FOR FINANCIAL CHALLENGE ANALYSIS

COMPANY	SHORT NAME	ARM	PORTFOLIO
Alexion Europe SAS	Alexion	OMP-1	Metabolic
Amicus Therapeutics UK Ltd	Amicus	OMP-2	Metabolic
BioMarin International Ltd.	BioMarin	OMP-3	Other
Incyte Biosciences Distribution B.V.	Incyte	OMP-4	Cancer
Santhera Pharmaceuticals GmbH	Santhera	OMP-5	Other
Swedish Orphan Biovitrum AB	Sobi	OMP-6	Other
Vertex Pharmaceuticals Ltd.	Vertex	OMP-7	Other
Amgen Europe B.V.	Amgen	BP-1	Cancer
Biogen Inc.	Biogen	BP-2	Other
Eli Lilly Nederland B.V.	Eli Lilly	BP-3	Cancer
Merck & Co	MSD	BP-4	Other
Novartis Europharm Ltd.	Novartis	BP-5	Cancer
Roche Registration GmbH	Roche	BP-6	Cancer
Takeda Pharma A/S	Takeda	BP-7	Other

Note: portfolio category is based on the therapeutic indication of the company's orphan designated products.

We have selected a set of financial indicators and collected historic data for these indicators from publicly available sources – published financial statements and Morningstar®. The period covered was 2012-2018. Table A.1.2 show all financial indicators included in our analysis and definitions.

TABLE A.1.2 FINANCIAL INDICATORS AND DEFINITIONS

INDICATORS	DEFINITION
Revenue	All revenue generated by the firm in a year
Revenue product	All revenue generated by the firm in a year excluding revenue generated by financial investments and activity
Average gross margin %	Total revenue product minus direct costs (costs of sales), all divided by total revenue product
Cost sales/revenue product	Direct costs divided by revenue product (the inverse of average gross margin %)
Operating income	Operating revenue minus costs of goods sold minus operating expenses minus depreciation minus amortization
Net income attributable to shareholders	Revenue less all expenses less the non-controlling interests
R&D expenditure	Total R&D investment of the firm in a year
R&D to revenue ratio	Total R&D investment of the firm in a year divided by revenue product
Selling General & Administrative (SGA) expenses	All non-production expenses incurred by a company in a year. This includes expenses such as rent, advertising, marketing, accounting, litigation, travel, meals, management salaries, bonuses, and more.
Sales to SGA ratio	Revenue product divided by SGA expenses
SGA / revenue	SGA expenses divided by total revenue
Equity	The difference between the value of assets and the value of the liabilities (or debt)
Debt	The value of assets financed with liabilities
Debt to equity ratio	Debt divided by equity
Return on equity	Net income of the firm – revenue less all expenses – divided by equity
Total assets	The total value of all assets owned by the firm
Total debt to total assets ratio	Debt divided by assets – the share of the assets that is financed by liabilities
Return on assets	Net income of the firm – revenue less all expenses – divided by total assets
EBITDA	Earnings before interest, tax, depreciation and amortisation (EBITDA) is a measure of a company's operating performance.
EBITDA margin	EBITDA divided by Revenue

A.2 Appendix 2

A Net Present Value (NPV) model of a successful new medicine was developed which incorporates the R&D cost of a new successful medicine following the method of Mestre-Ferrandiz et al. (2012). Figure A.2.1 shows a diagram of the model used to estimate the R&D cost of a new successful orphan medicine where all inputs the model requires are shown. We have introduced the hypothetical cost per phase of the model in Figure A.2.1 into the NPV model according to the time when they were exactly incurred. The capitalisation of all them is then completed by NPV value calculation.

Development phase	Mean cost per stage	Probability of success	# of compounds per stage per one successful medicine	Hypothetical cost per phase	Stage duration (years)	Cost of capital	Capitalised cost per successful medicine
Pre-Clinical (PC)	MPCP: Mean cost of pre-clinical phase	P1: probability of success pre-clinical	$\#PC=1/PT$	Cost of PC= $\#PC*MPCP$	Time duration of each development phase in years	Cost of capital applied to estimate the capitalised cost per stage	Capitalised cost of PC
Phase I (PI)	MCP1: Mean cost of phase I	P2: probability of success of phase I	$\#PI=\#PC*P1$	Cost of PI= $\#PI*MCP1$			Capitalised cost of PI
Phase II (PII)	MCP1I: mean cost of phase II	P3: probability of success of phase II	$\#PII=\#PC*P2$	Cost of PII= $\#PII*MCP1I$			Capitalised cost of PII
Phase III (PIII)	MCP1II: mean cost of phase III	P4: probability of success of phase III	$\#PIII=\#PC*P3$	Cost of PIII= $\#PIII*MCP1II$			Capitalised cost of PIII
Regulatory review & Marketing Authorisation (MA)	MCMA: mean cost of regulatory review and marketing authorisation	P5: probability of success of regulatory review and marketing authorisation	$\#MA=\#PC*P4$	Cost of MA= $\#MA*MCMA$			Capitalised cost of MA
Post-launch Real-World Evidence (RWE)	MCRWE: mean cost of real-world evidence	P6: probability of success of post-launch real-world evidence	$\#RWE=\#MA*P5$	Cost of RWE= $\#RWE*MCRWE$			Capitalised cost of RWE
Overall probability of success: $PT=P1*P2*P3*P4*P5*P6$			Result= $\#RWE*P6=$ 1 successful medicine			=	
							Total capitalised R&D cost of a new successful medicine

FIGURE A.2.1: MODELLING THE R&D COST OF A NEW SUCCESSFUL OMP

All other inputs of the model were populated by using estimates from the literature or authors assumptions. Table A.2.1 lists all model inputs, estimates and assumptions.

TABLE A.2.1 NPV MODEL INPUTS AND ASSUMPTIONS

INPUT	SOURCE	VALUE
Clinical trial costs: phase I-II-III (US\$/patient/study)	Batelle and PhRMA report (2015). Available at: http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf	\$38,500/patient (phase I) \$40,000/patient (phase II) \$42,000/patient (phase III)
Size of clinical trials by phase in number of patients	Berdud et al. (2018). Available at: https://www.ohe.org/publications/establishing-reasonable-price-orphan-drug	211 patients (phase I) 361 patients (phase II) 929 patients (phase III)
Times of development per phase	Pharma Intelligence, 2019. Pharmaprojects. Available at: http://pharmaintelligence.informa.com/products-and-services/data-and-analysis/pharmaprojects	Phase I: 2 years (all indications) Phase II: 3.5 years (all indications) Phase III: 3 years (all indications) Regulatory review (non-orphan): 1.5 years Regulatory review (orphan): 1 year
Development phase success rates	Wong et al. (2019); Thomas et al., (2016)	Phase I: 0.759 Phase II: 0.488 Phase III: 0.5247 Regulatory review: 0.89
Cost of capital	Rollet et al. (2013)	14%
Operating cost (% of revenue)	Authors assumption based on data from financial indicators analysis section of this report	60%
Tax rate	KMPG. Average of EU5. Year 2018. Available at: https://home.kpmg/xx/en/home/services/tax/tax-tools-and-resources/tax-rates-online/corporate-tax-rates-table.html	26%
Market Exclusivity length for baseline	<i>Regulation (EC) No 141/2000 of the European Parliament and of the Council</i>	10 years since marketing authorisation approval
Uptake rate of medicine by target population	Authors assumption	50%
Number of patients treated per year and condition	Estimated using product label information of the OMP-focused companies and incidence/prevalence data available at Orphanet. Data available at https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf	Industry average in EU28: 26,400 Case study 1 average in EU28: 21,979 Case study 2 average in EU28: 39,166
Cost per patient per year of orphan drugs	All orphans average: Rollet et al (2013) Case studies: estimated by using product specific sales and patient populations	Industry average: US\$31,945 Case study 1: US\$26,629 Case study 2: US\$16,930
Peak sales year	Authors assumption	5 years after marketing authorisation
Sales function	Authors assumption	Linear increase since market launch until peak sales
Sales after generic entry (post ME)	Authors assumption based on IQVIA (2018a)	50% reduction of value sales
R&D cost share attributable to EU28	Assumption based on the EU28 global pharmaceutical value sales market share. Source: World Review Analyst 2018 (IQVIA, 2018b)	30%
Protocol assistance removal effect for scenario 3	Authors assumption based on the regulation text: <i>Regulation (EC) No 141/2000 of the European Parliament and of the Council</i>	10% decrease of the phase III success rate and regulatory review success rates An increase of half a year in regulatory review time (based on the data of times of development)
Post-launch real world evidence costs and time	Berdud et al. (2020)	US\$4.5 million globally
Regulatory review cost	Berdud et al. (2020)	US\$29.4 million globally

A.3 Appendix 3

Table A.3.1. shows by indication (column 1), all medicines approved to treat patients with the same rare condition (column 2), and full years until first (column 3), second (column 4) and third (column 5) competitor entry.

TABLE A.3.1: COMPETITION UNDER MARKET EXCLUSIVITY AND TIME OF COMPETITOR ENTRY

INDICATION	PRODUCTS	1 ST COMP.	2 ND COMP.	3 RD COMP.
Acute myeloid leukaemia	Dacogen (2012), Rydapt (2017), Mylotarg (2018), Vyxeos (2018)	5	6	6
Multiple myeloma	Imnovid (2013), Farydak (2015), Kyprolis (2015), Ninlaro (2016)	2	2	3
Tuberculosis	Delyba (2014), Granupas (2014), Sirturo (2014)	0	0	
Inborn errors in primary bile acid synthesis	Orphacol (2013), Kolbam (2015), Chenodeoxycholic acid leadiant (2017)	2	4	
Mantle cell lymphoma	Torisel (2009), Imbruvica (2014), Revlimid (2016)	5	7	
Acute lymphoblastic leukaemia	Xaluprine (2012), Iclusig (2013), Blyncito (2015)	1	3	
Chronic lymphocytic leukaemia	Arzerra (2010), Gazyvaro (2014), Imbruvica (2014)	4	4	
Cutaneous T-cell lymphoma	Adcetris (2017), Ledaga (2017), Poteligeo (2018)	0	1	
Cystic fibrosis	Bronchitol (2012), Kalydeco (2012), Symkevi (2018)	0	6	
Cystinosis	Procysbi (2013), Cystadrops (2017)	4		
Diffuse large B cell lymphoma	Yescarta (2018), Kymriah (2018)	0		
Gaucher disease	Vpriv (2012), Cerdelga (2015)	3		
Idiopathic pulmonary fibrosis	Esbriet (2011), Ofev (2015)	4		
Ovarian cancer	Yondelis (2009), Zejula (2017)	8		
Pulmonary arterial hypertension	Opsumit (2013), Adempas (2014)	1		

Note: products in column 2 were approved when all were under ME. Columns 3-5 show how many full years passed until the 1st, 2nd and 3rd competitors entered the market respectively. Nine out of fifteen indications with competition have at least two competitors (additional to the first in market) still protected by ME. In four indications out of the fifteen the first competitor entered the market within the first year after the approval of the first in the market. For fourteen out of the fifteen indications with competitor under ME period, the second in the market (first competitor), was approved within six years of the approval of the first in the market.

In table A.3.2 the seven indications in which we have observed generic competition are shown. In addition to the indication, Table A.3.2 also shows the active substance in column 2 (generic name), tradename of the molecule in column 3, the date of the market authorisation of the first in the market in column 4, the number of generics approved for the indication in column 5 and the dates of entry of the first, second, third and fourth generic in columns 7 to 10 respectively.

TABLE A.3.2: COMPETITION UNDER MARKET EXCLUSIVITY AND TIME OF COMPETITOR ENTRY

INDICATION	ACTIVE SUBSTANCE	TRADENAME	DATE OF MARKETING AUTHORISATION	NUMBER OF GENERICS / BIOSIMILARS	DATE 1 ST GEN.	DATE 2 ND GEN.	DATE 3 RD GEN.	DATE 4 TH GEN.
N -acetylglutamate synthetase (NAGS) deficiency	N-carbamyl-L-glutamic acid/Carglumic acid	Carbaglu	24/01/2003	1	23/06/2017			
Conditioning treatment prior to haematopoietic-progenitor-cell transplantation	Busulfan	Busilvex	09/07/2003	1	22/09/2014			
Essential thrombocythaemia	Anagrelide hydrochloride	Xagrid	16/11/2004	1	15/02/2018			
Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	Sildenafil citrate	Revatio	28/10/2005	2	15/09/2016	14/11/2016		
Tyrosinaemia type 1	Nitisonide	Orfadin	21/02/2005	2	24/08/2017	26/07/2018		
Gaucher disease	1,5-(Butylimino)-1,5-dideoxy, D-glucitol/Miglustat	Zavesca	20/11/2002	3	22/03/2017	09/11/2017	18/02/2019	
Chronic myeloid leukaemia	Imatinib	Glivec	07/11/2001	4	07/01/2013	17/04/2013	30/06/2013	25/09/2013



A total number of 47 indications have lost the exclusivity since 2000, with 5 of these being withdrawn from the Community Register of designated orphan medical products on request of the sponsor. This means that for 42 out of the 47 their orphan designation specific ME period expired. We observed, as per Table A.2. that for 7 of the 42 products (indications) where ME expired, generics were launched in those markets.



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