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An evaluation of the economic and societal impact of the orphan medicine regulation

Final report

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Abbreviations

COMP	Committee for Orphan Medicinal Products
CPGs	Clinical Practice Guidelines
DMD	Duchenne Muscular Dystrophy
EMA	European Medicines Agency
ERN	European Reference Networks
EC	European Commission
EU	European Union
HCP	Healthcare Professional
MA	Marketing Authorisation
MS	Member States
NRDP	National Rare Disease Plan
OECD	Organisation for Economic Co-operation and Development
OHE	Office of Health Economics
OMP	Orphan Medicinal Product
R&D	Research and development
SMEs	Small and medium-sized enterprises

Executive summary

Charles River Associates ("CRA") was asked by EFPIA and EuropaBio to conduct an evaluation of the societal and economic impact of the European Union (EU) Regulation on Orphan Medicinal Products (OMP), 17 years after its entry into force. The Regulation (EC) No 141/2000 (which we refer to as the Regulation) was introduced to ensure that patients suffering from rare conditions have the same quality of treatment as any other patient in the EU.

Prior to the Regulation, there were very few treatments for the 6000-8000 rare diseases that have been identified. Indeed only 8 products had been authorised for treating such diseases in Europe. There was a recognition that rare diseases are serious conditions that are usually genetic in origin with the majority (75%) emerging in childhood and resulting in a severe burden of illness with 1 in 3 children with a rare disease dying before their 5th birthday and many more living with debilitating conditions. The EC and Member States recognised that whilst only a small number of patients suffer from each of the orphan diseases that had been identified, rare diseases affected around 1 in 17 people, some 30 million people across the EU Member States. Given the small patient population associated to each condition and the corresponding limited commercial opportunity, there was concern that without incentives to encourage innovation in rare diseases, few new treatments for rare diseases would be developed.

To address this, the Regulation introduced a series of incentives for OMP manufacturers, including: protocol assistance; access to a centralised procedure allowing immediate marketing authorisation in all Member States; a system of reduced fees for regulatory procedures; and 10 years of market exclusivity. The impact of the Regulation and the extent to which it has achieved its objectives have been assessed before – in 2006 by the EC[i] and in 2010 by the Office of Health Economics (OHE).[ii] Both these reviews reported impressive progress in the number of OMPs but also noted that it was too early to assess the full impact of the Regulation, for example, the Commission reported that *"the true impact of the EU orphan initiative on public health will only be revealed progressively as longer-term experience is accumulated"*.

As additional data have now become available, this report provides an update on the number of clinical trials, orphan designations and market authorisations but, more importantly, focuses on assessing the impact on the health of patients and their families, the impact on the healthcare system and the economy (which have not been fully explored in the previous reports).

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i We will refer to this document as to the "2006 Commission report". Source: *Commission staff working document on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained.* Document on the basis of Article 10 of Regulation (EC) No 141/2000.

ii We will refer to this document as to the "2010 OHE report". Source: "Assessment of the Impact of Orphan Medicinal Products (OMPs) on the European Economy and Society", November 2010, A report was commissioned from OHE Consulting by the Joint EBE-EuropaBio Task Force on Rare Diseases and Orphan Medicinal Products.

Approach

Using the original objectives of the Regulation as well as the 2006 study from the Commission and the 2010 report from OHE, we have developed a set of indicators that can be used to assess the impact of the Regulation. CRA has assembled evidence from the academic peer-reviewed articles, discussion papers, white papers and grey literature and conducted 14 interviews with different stakeholder groups (patient groups, healthcare professionals, academic research network/clinical centres of excellence, and industry).

Drawing on the published literature, an analysis of trends and the interviews, we have sought to draw conclusions on the extent to which the Regulation is responsible for changes in these indicators. However, it is important to recognise that associating changed directly to the Regulation is challenging. The development of medicines depends on advances in scientific understanding (and there has been fundamental change in our understanding of genetic diseases over the last twenty years) and the development of medicines is undertaken globally and hence the changes we can observe are the result of the combined impact of the legislation in the US, Japan and EU and the scientific advances in the last two decades.

The findings from this study are organised in terms of: (1) the direct impact of the Regulation; (2) the societal impact; and (3) the economic impact.

Direct impact

The direct impact of the Regulation was assessed by looking at a set of indicators that measure the development and authorisation of OMPs. The objective was to compare data before and after the Regulation, however, the approach varies depending on the availability of comparative data. We found the following:

- **There has been a large increase in the number of medicines for rare diseases**. By May 2017, the EC had granted 1,868 orphan designations, and 133 OMPs had obtained marketing authorisation across the EU (compared to the 850 orphan designations and 63 OMPs authorisations as of December 2010 and only 8 medicines prior to the Regulation).
- **The OMPs developed address areas of significant unmet need**. Between 2002 and 2012, 304 orphan designations (44% of the total) were granted to medicines for conditions where there were no satisfactory method of diagnosis, prevention or treatment (and therefore no comparison with existing treatments was possible). In the other cases (406 orphan designations, 56% of the sample), the medicines provided 'a clinically relevant advantage or a major contribution to patient care'. The high number of OMPs being granted a conditional approval is also consistent with them addressing the areas of greatest unmet need. A wide number of diseases have been targeted, with cancer being the most targeted area (but only 37% of designations and authorisations are for cancer), and an increase in designations for diseases with lower levels of prevalence and hence fewer patients (the proportion of designations for conditions affecting fewer than 1 in 10,000 patients increased from 43% in 2006 to 60% today).
- **There has been a substantial increase in clinical trials.** We find there has been an increase (of 19%) in clinical trials for rare diseases including European patients over the past eight years (from 2,553 EU-based clinical trials in 2009 to 3,010 in 2017). Although it is not possible to make a direct comparison, this

represents a significant increase in the number of trials compared to the period prior to the Regulation. In comparison, the total number of clinical trials in Europe has declined over the same period (2009 to 2017) by almost 24%.

- **The use of protocol assistance has increased significantly.** The OMP manufacturers using the services provided under the Regulation by the EMA to facilitate marketing authorisation has increased dramatically. In particular, requests for protocol assistance increased from 4 in 2001 to 126 in 2016 (in total, there have been 1,092 requests between 2001 and 2016).

In summary, the evidence shows that the OMP Regulation has been successful in contributing to the development of medicines for rare diseases that were previously without licensed treatments, and that consequently there are many more treatments available for more patients with chronically debilitating and life-limiting conditions.

Societal impact

New evidence is available to show the longer-term benefits that the Regulation has delivered to the health of patients. In 2006, the Commission estimated that more than 1 million patients suffering from rare diseases in the EU might potentially benefit from the availability of these new treatments authorised since the Regulation came into force. We estimate that, by 2017, 7 times as many rare disease patients could benefit from access to OMPs.

***Impact on health and quality of life*: *Patient organisations reported that OMPs, developed thanks to the Regulation, have significantly improved patients' health and quality of life, and decreased their reliance on supportive care*.** To document this we have reviewed all of the 33 OMPs authorised in the last three years and collected evidence from the regulatory and health technology assessment processes that they went through (as reported in over 100 reports). By analysing OMPs approved since 2015:

- We highlight case studies covering both rare cancers and long-term or life-long genetic conditions (paediatric neuroblastoma, Multiple myeloma, Chronic lymphocytic leukaemia (CLL), Advanced Soft Tissue Sarcoma (STS), Adenosine deaminase deficiency, Hypophosphatasia and Lysosomal acid lipase deficiency (LAL)) where the treatments give patients the opportunity to enjoy a normal life expectancy, or they provide a significant improvement in survival, even though life expectancy remains short.
- We highlight case studies (for Multiple myeloma, Hereditary factor X deficiency, Narcolepsy, Haemophilia B, Non-24-hour sleep-wake disorders in blind people with no light perception) where OMPs reduce health-related issues that limit normal activities, thus improving patients' quality of life. Specifically OMPs help to reduce the pain, discomfort and anxiety associated with rare diseases and allow patients and their families to enjoy normal lives, such as planning family activities or holidays.

Where patients have access to OMP this has had a significant impact on patient health and quality of life. However, it is important to note that not all patients have access to these treatments – and this varies significantly from country to country - and that there are many patients with debilitating or life-limiting who could benefit from a new licensed

treatment who do not have access to it. For example, out of the 133 authorised OMPs, only 68 are reimbursed in the UK and only 84 in Spain.

***Impact on patients' role*: <u>The Regulation has empowered patients with rare diseases.</u>** According to the interviews with patient organisations, the Regulation and the associated policy programmes that followed (for example, the development of National Rare Disease Plans (NRDPs)) have increased awareness about rare diseases helping patient organisations in the EU to expand their activities. For instance, the Committee for Orphan Medicinal Products (COMP) within the EMA is the first scientific committee in the EU to include representatives of patients' organisations as full members. In parallel, patients have been included in other decision making processes. For instance, patient organisations have become more active in the assessment of medicines for rare diseases, through their involvement in health technology assessment processes and by working with other stakeholders to develop innovative solutions to market access challenges (for example, managed entry agreements).

***Impact on treatment provided by healthcare professionals:* <u>The level of awareness and specialist knowledge of HCPs has increased.</u>** The interviews with patient organisations and clinician groups also highlighted the role the Regulation has played in improving diagnosis and treatment protocols. A fundamental problem for patients with rare diseases is the struggle to be diagnosed. Survey data shows the length of time from symptom onset to an accurate diagnosis is around 4.8 years for a rare disease (with some patients waiting decades for an accurate diagnosis) and, on average, a patient needs to visit a doctor 7.3 times before diagnosis of their rare condition is made. Since the Regulation was implemented, new tests have been developed that improve the diagnosis of rare diseases. When new treatments are introduced, interest in the condition grows and this encourages clinicians to review existing and new cases, improving diagnosis. In addition, as noted by academics and research centre representatives, the Regulation led to new resources for physicians and increased development of clinical practice guidelines for rare diseases.

The Regulation has also established a favourable legislative environment for policies on rare diseases. In particular, NRDPs have contributed, among others initiatives, to the creation of patient disease registries, facilitating a better understanding of rare diseases and the diagnosis pathway (the number of patient registries for rare diseases increased by 36% between 2011 and 2016). More recently we have seen the development of European Reference Networks (ERNs). The first ERNs were launched in March 2017, involving more than 900 highly specialised healthcare units from over 300 hospitals in 26 Member States. There are now 24 ERNs working on a range of disease areas including metabolic conditions, bone disorders, childhood cancer and immunodeficiency.

***Impact on the efficiency of the healthcare system:* <u>The Regulation has increased efficiency through improvements to diagnosis and by effective treatments reducing the cost of hospitalisation.</u>** Patients with rare diseases often have serious medical conditions with a correspondingly large impact on healthcare resources. There is little data on this issue, however, we highlight case studies in Chronic Lymphocytic Leukemia (CLL), Differentiated thyroid carcinoma (DTC) and Invasive Aspergillosis (from our sample of OMPs approved since 2015) showing the benefits from diagnosing patients earlier thus preventing disease progression and reducing the cost of care. Effective treatments can reduce the average period of hospitalisation delivering off-setting savings in healthcare expenditure. This is also linked to the problem of delayed and misdiagnosis.

During the 4.3 years prior to an accurate diagnosis, patients are commonly misdiagnosed with the result that they are prescribed unnecessary treatments with little clinical effect. Finally, the targeted nature of OMPs for rare diseases means that healthcare spending is used more effectively.

Economic impact

The Regulation also has an impact on the economy, through its influence on the European R&D environment, on growth and employment for SMEs, and on the productivity of patients.

Impact on European R&D environment: **The Regulation contributed to the creation of a favourable environment for research and development and the establishment of research networks.** Drawing on our interviews with researchers, centres of excellence and the industry and analysis of published data, we found that:

- There is an increase in basic research projects for rare diseases in the EU. In particular, recent statistics show that the average size of EU-funded projects has increased considerably compared to the 2000–2004 period.
- The number and share of scientific publications reporting on basic and clinical research on rare diseases has grown significantly over the years since the Regulation was implemented.
- The number of companies involved in OMP research continues to increase, with faster growth since the Regulation. The most recent data shows 298 companies with EU headquarters are undertaking some OMP activity and 142 companies have an OMP compound in clinical development (i.e. Phase I or later); 23 companies are reported as exclusively researching OMPs.
- The number of specialist centres for rare diseases has grown considerably in recent years. These are often associated to OMPs developed following the Regulation. For example, the development of specialist centres as part of the PNH (Paroxysmal Nocturnal Hemoglobinuria) National Service funded by NHS England in the UK.
- The introduction of policies for OMPs in both the US and the EU has encouraged large-scale collaborations between profit and non-profit organisations to foster greater research opportunities. For example, the International Rare Diseases Research Consortium (IRDiRC) was launched in April 2011 at the initiative of the EC and the National Institutes of Health (US) to foster international collaboration in rare diseases research and includes members from industry, government organisations, research institutions, and patient advocacy groups.

As set out in the introduction, we need to be cautious in attributing these changes solely to the Regulation. All interviewers reported that changes in basic research, scientific publications and the number of companies reflect a combination of factors. However, they also reported that the Regulation was an important “part of the puzzle” and made a significant contribution to these trends.

Impact on growth and employment**: The Regulation has contributed to economic growth and employment through the establishment of SMEs and dedicated departments in larger companies researching OMPs in the EU.** We found the following:

- Between 2002 and 2012, 50% of orphan designations were submitted by SMEs and 50% by larger companies. Although it is not possible to compare this directly to the development of medicines for non-rare conditions, according to interviews with researchers and companies, SMEs play a larger role in development of OMPs. The Regulation is particularly important for SMEs. Based on the interviews with SMEs, the orphan designation process is often an important signal for investors (as is getting funding from the EU's framework programmes), and responsible for them securing venture capital funding.
- The OMP Regulation is associated with an increase in the number of SMEs involved with the development and marketing of medicines for rare diseases. Most new companies that started developing OMPs in the first decade [after the Regulation in 2000] focused solely on discovering and developing orphan medicines. An analysis of 252 companies within the EMA SME register shows that 220 were created after the OMP Regulation came into place.
- Collectively, the 252 SMEs involved in orphan medicine development employ 8,739 people. Of these, 77% are employed in SMEs that were created after the OMP Regulation came into force in 2000. Indeed, over 25% are employed by companies created since 2014. We have not been able to estimate the number of employees working in rare diseases in larger pharmaceutical companies but based on interviews, the formation of rare disease groups within larger pharmaceutical companies and increased research and development activity in rare diseases has created more jobs in large companies as well.

***Impact on the productivity of patients*: Patient organisations reported that OMPs increase patient productivity by diminishing the burden of the disease**. Although there is relatively little academic evidence on this issue, we highlight case studies in Fabry disease, Narcolepsy, Precursor B-acute lymphoblastic leukaemia (Ph- B-precursor ALL) and Cystic Fibrosis (CF) (from our review of all of the OMPs approved since 2015) that illustrate how for some OMPs there has been dramatic improvement in patients' health status, often allowing them and/or their families and carers to go back to work.

Conclusions

Prior to the Regulation, there were very few rare diseases with treatments and little prospect of treatments being developed for these severe conditions. Over the last 20 years, there has been a transformation in our understanding of genetic diseases. However, an improved understanding is necessary but not sufficient to improve the lives of patients with rare diseases. The Regulation was required to encourage the development and authorisation of medicines and the improved diagnosis and treatment of patients.

The benefits we have identified go far beyond the numbers of clinical trials, designations or even marketing authorisations (which are typically the focus of assessments of the impact of the regulatory framework). OMPs have changed the lives of patients, the lives of their families and their carers. This has also helped mitigate other healthcare costs (through reduced hospitalisations) and improve productivity. In addition, the Regulation has increased the focus on rare diseases, creating resources for healthcare professionals and encouraging national policymakers to introduce national rare diseases plans and national policies to promote investment in R&D. In terms of the research environment,

there have been significant increases in EU research activity, the number of SMEs being created and the number of employees. Beyond rare diseases, the OMP Regulation has facilitated a supportive environment for rare disease-dedicated policies, including, the role of patients in marketing authorisations, and public–private collaborations to the benefit of all patients in Europe.

However, only a very small proportion of the identified rare diseases (less than 5%) have so far been addressed by OMPs. There is a risk that without incentives in place the development of new treatments for rare diseases will slow and there are still thousands of diseases and millions of people without a treatment. Continued support is a crucial signal for academics, researchers, small and large companies that rare diseases remains a priority going forward.

1. Introduction

Charles River Associates ("CRA") was asked by EFPIA and EuropaBio to conduct an evaluation of the societal and economic impact of the European Union (EU) Regulation on Orphan Medicinal Products (OMP), (which we refer to as the "Regulation" or "EU Regulation" or "OMP Regulation" throughout the report). In particular, the objective is to:

- Develop a set of indicators to measure the impact the Regulation has had on society by improving the treatment and health of patients.
- Use these to review the extent to which the economic and societal benefits of the Regulation have been delivered.

1.1. Background[iii]

Many rare diseases are genetic, and are present throughout a person's entire life, in most cases since childhood. For example, 75% of rare diseases affect children and nearly one-third who are diagnosed will die before their fifth birthday.[1] While an individual disease might be labelled as rare, the total number of persons in Europe suffering from one of the over 6,000-8,000 different identified rare diseases is estimated at over 30 million (an individual rare disease may affect only one person in a million, but all together, rare disease patients comprise 6% to 8 % of the EU population). In addition, rare diseases not only affect the person diagnosed - they also impact families, friends, care takers and society as a whole.[2]

The focus on rare diseases and concern about the lack of innovation for patients originated in the 1980s.[iv] In the United States (US), this resulted in the US Orphan Drug Act in 1983, which pioneered the regulation of these types of medicines. This was seen as a model of legislation[v] in a range of countries across the world, including Japan,[vi] Korea and Australia, which have orphan medicines legislations based to a large extent on the American text.[3] A similar debate occurred in Europe in the 1990s, with some Member States (MS) of the EU adopting orphan medicines policies even before any initiative was promoted at the European Community level resulting in the OMP Regulation.

The European debate can be traced back to the following:

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iii This section draws on "The Regulation of Orphan Drugs: a US-EU Comparative Perspective," Antón Leis García, Licenciado en Derecho, Universidad Carlos III de Madrid, 2003. Available at [last access 4 July 2017]: https://dash.harvard.edu/bitstream/handle/1/8852101/Orphan_Drugs_RTF.html?sequence=2

iv Advocacy efforts by patient organisations like NORD were seen as particularly important in raising this as an issue of debate in Congress.

v This includes a range of measures: seven years of market exclusivity for the designated orphan indication of the product, during which time no identical and competing product will receive a marketing authorisation from the Federal Drug Administration; federal grants to fund clinical trials of designated orphan products and protocol assistance by the FDA; tax credits for such clinical trials. The legislation was subsequently amended in 1985, 1988 and 1993.

vi Japan started its orphan drug program in October 1993 by amending the Pharmaceutical Affairs Law and other ancillary regulations and setting up a complete system for orphan products designation and a full catalogue of incentives for their development and marketing.

- Rare diseases became a focus of attention in 1994, when the BIOMED 2 program, within the context of the Fourth Framework Program for research and technological development, provided funding for 23 research projects.
- A European Commission (EC) department responsible for science, research and development (R&D) and industry was instituted in February 1995; the expert group discussed recommendations on priorities for EU-level research and regulatory action in the field of rare diseases and orphan medicines.
- Rare conditions were further classified as a "priority area" for action by the European Community (henceforth referred to as "the Community") in the context of the Framework for action in the field of public health, after the Commission presented a proposal for a Decision of the European Parliament, and the Council adopted a program of Community action for the period 1999–2003 on rare diseases.

On 27 July 1998, the European Commission adopted a proposal for a European Parliament and Council Regulation on OMPs. The amended proposal was approved by the Parliament in a plenary session held in December 1999, and Regulation (EC) No 141/2000 entered into force in January 2000 (the rules for implementation became applicable in April 2000).[4] The aim of the initiative was clear: to provide, in similar fashion to the US Orphan Drug Act, an attractive environment by offering incentives for the pharmaceutical industry to develop and market medicines for rare diseases in the EU.[5]

The Regulation

The measures and provisions established by the Regulation to stimulate the research and development of OMPs are summarised in Table 1.

Table 1: Provisions in Regulation (EC) No 141/2000[6]

Key measures

• Article 3.1 of the Regulation establishes the criteria for designation of a medicine as an Orphan Medicinal Product, which combines an epidemiological feature (prevalence of the rare diseases in the total Community population is less than 5 per 10,000) with an economic test.
• Article 4 created a new body within the European Medicines Agency (EMA): the Committee for Orphan Medicinal Products (COMP), which is responsible for the scientific examination of applications leading to the designation of an Orphan Medicinal Product
• Article 5 lays out the designation procedure, explaining that a sponsor can submit an application any time prior to marketing authorisation. The opinion from the COMP is sent to the Commission, where the final decision lies.
• The set of incentives and benefits accruing to designated orphan medicinal products in the European Union are established in Articles 6 through 9.
  ○ Article 6: EMA protocol assistance, for sponsors of medicinal products, on the conduct of the tests and trials necessary to demonstrate their quality, safety and efficacy, or regulatory assistance
  ○ Article 7(1): Access to a centralised procedure allowing immediate marketing

authorisation in all Member States and making medicines available to all countries in the EU

- Article 7(2): Designated orphan medicinal products are also eligible for fee reductions for all charges payable under Community rules on marketing authorisation, with advice being free or given in return for reduced fees
  - In addition to these provisions, Commission Regulation (EC) No 2049/2005 established further fee reductions to promote innovation by small and medium-sized enterprises (SMEs)[7]
- Article 8: 10 years of market exclusivity (in which the EMA cannot authorise a similar product for the same therapeutic indication from another industry operator)
- Article 9: A repository of all designated and authorised OMPs was also created.

Source: European Commission

To access these provisions, a medicine needs to be granted the orphan designation status by COMP.[8,vii] To qualify for orphan designation, a medicine must meet a number of criteria:[9]

- It must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating.
- The prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development.
- No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

Some elements of the Regulation have received considerable attention over the last three years, particularly the concept of "significant benefit" and the definition of "similarity".

- *Significant benefit:* In accordance with Article 3(1)(b) of (EC) No 141/2000,[10] a medicinal product may be designated as an orphan product even if a treatment exists for the condition in question, provided that the medicine represents a significant benefit to those affected by the condition. Significant benefit is defined in Commission Regulation (EC) No 847/2000[11] as "a clinically relevant advantage or a major contribution to patient care" (Article 3). A communication from the EC in July 2003[12] (the "2003 Communication") provided an important interpretation of the definition of criteria for significant benefit, which was enhanced in the Notice from the Commission that replaced it in 2016.[13] The Commission Notice observes that significant benefit can only be determined by comparing the medicine with existing products or methods: "[E]stablishing significant benefit takes place in the context of a comparison with an existing authorised medicinal product or method and cannot be limited to an assessment of the intrinsic

vii As discussed later, the orphan designation is also an important signal for investors and for securing venture capital funding.

qualities of the product in question without comparing them with the intrinsic qualities of the authorised methods".

- *Similarity:* In 2016, the Commission initiated a review of the concept of similarity.[14] This considered changing the definition of *active substance,* and re-defining *similar active substances* to recognise the existence of ether and co-valent derivatives.[15] Responses to the public consultation were published on 24 March and the revised guidance is expected during 2017.[16]

A policy focus on rare diseases

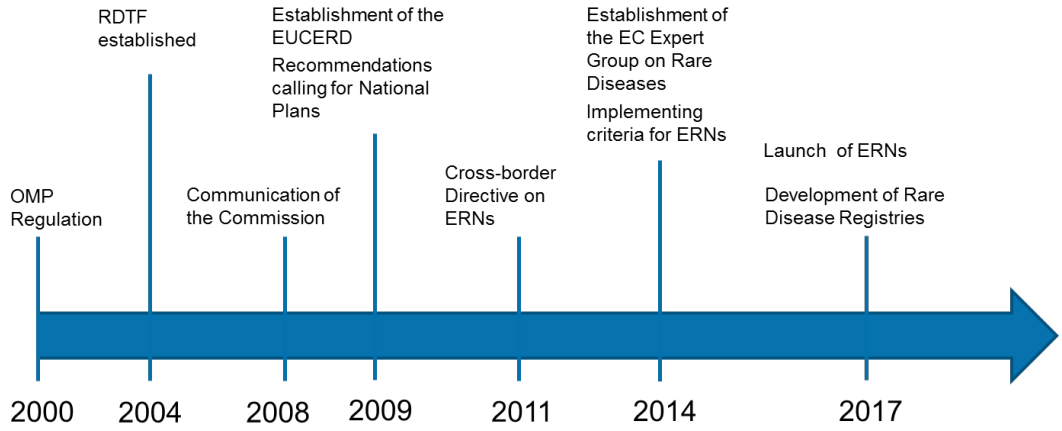
The Regulation was not intended to operate only at the EU level. Indeed, Article 9 of the Regulation requires the EC to publish regularly a detailed inventory of all EU and Member State incentives to support research into, and the development and availability of, OMPs.[viii] In addition:

- In 2004, the Rare Diseases Task Force (RDTF) was established to instigate key collaborative rare diseases initiatives in Europe.[17]
- In 2008, the EC recognised that Member States did not yet ensure full access to each authorised OMP and produced a document ("Communication of the Commission: Rare diseases, Europe's challenge", drafted by the RDTF) giving clear direction to Community activities in the field of rare diseases in order to further improve the access and equity to prevention, diagnosis and treatment for patients suffering from a rare disease throughout the EU.[18]
- The Council adopted a Recommendation on action in the field of rare diseases in June 2009. The Recommendation called for the adoption, before 2013, of national plans and strategies for responding to rare diseases.[19]
- In November 2009, the Commission established the European Committee of Experts on Rare Diseases (EUCERD, which replaced the RDTF) to "assist the Commission in formulating and implementing the Community's activities in the field of rare diseases" and to "foster exchanges of relevant experience, policies and practices between the Member States and the various parties involved".[20]
- In 2011, the Directive 2011/24/EU on patients' rights in cross-border healthcare, with a strong focus on rare diseases, noted that "the Commission should support the continued development of European reference networks between healthcare providers and centres of expertise in the Member States".[21] In 2014, the Commission set out the implementing criteria to support the development of the European reference networks (ERN).[22] The ERN initiative receives support from several EU funding programmes, including the Health Programme, the Connecting Europe Facility and Horizon 2020.

viii The fourth report was published in 2016. "Commission Staff Working Document: Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products — state of play 2015." Available at [last access 4 July 2017]: http://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/orphan_inv_cwd_20160126.pdf

- In 2014, the European Commission Expert Group on Rare Diseases replaced the EUCERD to support EU policy on rare diseases.[23]
- Development of rare diseases registries. The EC had published a Call for proposals for projects on rare diseases registries for approved ERNs on 21 December 2016. The proposals had been evaluated in April – May 2017 and the grant agreement started in August 2017.[24]

Figure 1: Timeline of EU policies for OMPs



Source: CRA

For the purposes of this study we look at the impact of the Regulation, national initiatives, the development of National Rare Disease Plans (NRDPs) and recent efforts to encourage the development of ERNs as a package.

Differences between the EU and US regulations

Given the global nature of R&D, to consider the impact of the Regulation on global incentives we need to put the EU Regulation in the context of the incentives provided in other countries, particularly the US. Although there is a common objective, comparing the regulations in the EU and US there are some differences:[25]

- Definition of a rare disease. In the EU, it is a condition with a prevalence of no more than 5 in 10,000 in Europe, or one for which marketing of a medicine is unlikely to generate sufficient returns to justify the investment needed for its development. In the US, a rare disease is one that affects no more than 200,000 patients (which corresponds to about 6 in 10,000) or, if it affects more than 200,000 patients, there is no expectation that the cost of developing it and making it available in the US will be recovered from sales in the US.
- The US regulation provides specific grants funding clinical and nonclinical trials and tax credits. These are lacking in the European regulation, perhaps because EU institutions have no power over taxation regulations.
- In terms of the incentives, there are differences in the length of the market exclusivity period.

These are summarised in Table 2.

Table 2: A comparison of the EU and the US regulations[26,27]

Incentives	Europe	US
Market exclusivity	10 years; 2-year extension with a paediatric investigational plan	7 years
Protocol assistance	Assistance in development process including individual and parallel protocol assistance	
Fee reduction	Full and partial fee reduction for protocol assistance, initial and follow-up requests; pre-authorisation inspection; initial marketing authorisation and post-authorisation application and fees There are additional fee reductions available exclusively to SME sponsors[28]	Exempt from paying application fees[29]
Tax credits	At national level	Tax credit in the amount of 50% of clinical investigation expenses
Grant funding	Eligibility for EU research grants – e.g. Horizon 2020 program, E-rare (mainly for researchers and public institutions)	Yes

Source: Adapted from Taymor and Kanavos; EFPIA and EuropaBio

Existing reviews of the performance of the Regulation

Unlike more recent regulations,[ix] there is not an impact assessment setting out the anticipated impact of the Regulation or what attributes should be measured. However, the Regulation was reviewed in a report by the Commission in 2006[30] and it has also been discussed in each of the Commission reports on European and national initiatives. The Commission identified that "there has been impressive progress, in particular as regards generating significant activity by the pharmaceutical industry in this field".[x] The review provides insight about the number of designations, protocol assistance, products, fee waivers and research projects, but does not set out the wider benefits to patients or society.

ix For example, if we compare the OMP Regulation to the Paediatric Regulation that was introduced in 2006. The Paediatric Regulation had an initial impact assessment. This has been used in subsequent reviews of the impact. In 2013, the Commission published a first report on the Paediatric Regulation referencing back to the original impact assessment, and while it revealed some promising signs of progress, it found that, due to the length of medicinal products' development, it would take at least 10 years to gain a full understanding of the situation. Under Article 50(3) of the Regulation, the Commission's second report is due in 2017. Source: European Commission website [last access 29 May 2017]: https://ec.europa.eu/health/human-use/paediatric-medicines/developments/2016_pc_report_2017_en

x The first inventory was published in January 2001 and updated versions were issued in 2003 and 2005. Most recently: "Commission staff working document: Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products — state of play 2015" Available at [last access 4 July 2017]: http://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/orphan_inv_cwd_20160126.pdf

There are many papers supporting the view that the Regulation has been successful. As pointed out by EURORDIS, the association for rare diseases patients in Europe, "the regulation can be considered a success."[31] However, recently there has been more criticism about the environment/context around OMPs.

- In June 2016, the Council of the European Union adopted a set of conclusions on strengthening the balance in the pharmaceutical systems in the EU and its MS.[32] Among the several considerations about the EU pharmaceutical market, the Council invited the European Commission to "prepare as soon as possible and with the close involvement of the Member States, while fully respecting Member States competences, the following:
    - an overview of the current EU legislative instruments[xi] and related incentives that aim to facilitate the investment in the development of medicinal products and the marketing authorization of medicinal products given to the holders of a marketing authorisation as implemented within the EU: Supplementary Protection Certificates (Regulation EC 469/2009), [provisions for] medicinal products for human use (Directive 2001/83/EC and Regulation EC 726/2004), [specific provisions for] orphan medicinal products (Regulation EC 141/2000) and paediatrics (Regulation EC 1901/2006);
    - an evidence based analysis of the impact of the incentives in these EU legislative instruments […] on innovation, as well as on the availability […] and accessibility of medicinal products, including high priced essential medicinal products for conditions that pose a high burden for patients and health systems […]. Among those incentives, particular attention should be given to […] the data exclusivity for medicinal products and the market exclusivity for orphan medicinal products."
- A report by the Organisation for Economic Co-operation and Development (OECD), published in January 2017, is concerned that OMPs typically enter the market with "very high prices" and it notes: (1) the extent to which the general public supports decisions reflecting a higher willingness to pay for patients with rare diseases is not clear. (2) Companies are accused of "salami-slicing strategies" by marketing new medicines with narrow indications to claim an orphan status and a high price and then developing other indications (orphan or non-orphan). (3) Orphan medicines may be performing too well, which suggests that they may not need additional public subsidies to be commercially viable. The OECD concludes orphan legislation should be reassessed to make sure incentives are not diverted from their initial vocation to encourage R&D investments in areas that would not be explored otherwise.[33]

xi The EU legislative instruments are: Supplementary Protection Certificates (Regulation EC 469/2009), provisions for medicinal products for human use (Directive 2001/83/EC and Regulation EC 726/2004), provisions for orphan medicinal products (Regulation EC 141/2000) and paediatrics (Regulation EC 1901/2006).

1.2. Methodology

The purpose of this report is not to replicate existing studies but to develop evidence to assess the *economic* and *societal impacts* of the Regulation. In particular, the societal impact regarding the impact on different stakeholders: patients, their families, healthcare professionals and the wider healthcare system. To gather evidence on the impact of the Regulation, we have:

(1) Set out a range of indicators that can be used to assess the impact of the Regulation. The set of indicators has been endorsed by the project Steering Committee, composed of EFPIA and EuropaBio representatives, representatives from six biopharmaceutical companies and a national trade association.

(2) Reviewed the existing literature on the impact of the Regulation:

   a. We first took stock of the existing studies on the impact of the Regulation. These include the Commission's 2006 report[34] on the experience acquired as a result of the application of the Regulation and an assessment of the impact of OMPs on the European economy and society conducted by the Office of Health Economics (OHE).[35]

   b. Next, we carried out a literature review using academic and open source databases (including PubMed, EconLit, and Google Scholar). The literature review focused on: academic peer-reviewed articles, discussion papers, white papers and grey literature that have examined the impact of the Regulation on the indicators identified in step 1. CRA has reviewed the existing literature including:

      - 75 peer-reviewed articles which assess the impact of the regulation;[xii]
      - Analysis of the Regulation commissioned by EFPIA ("Dolon report" – data on file).

(3) A comparison was made between the experience of the US and EU.

(4) 14 interviews were conducted by CRA with wider stakeholder groups (Table 3). They were conducted between 28 April 2017 and 15 June 2017 and undertaken on the basis that we would not directly associate statements to particular organisations but would associate comments to the type of organisation. One of the objectives of the interviews was to clarify the extent to which the Regulation was responsible for the observed changes in the indicators.

Table 3: List of organisations interviewed

Organisation
Patient Groups and clinicians
ACHSE eV, Germany
Cystic Fibrosis Europe
European Gaucher Alliance
EURORDIS
Genetic Alliance UK

[xii] The relevant articles are listed in the bibliographic appendix to this report.

Academic Research Network/Clinical centres of excellence
Institut national de la santé et de la recherché médicale (Inserm), France
Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Italy
University of Leuven, Belgium
Industry
bluebird bio
Lysogene
Novartis
Pfizer
Sobi
Vertex

Note: These organisations were suggested by the Steering Committee on the basis of their involvement in the topic.

Source: CRA

1.3. Structure of the report

The rest of this report is structured as follows:

- Chapter 2 describes the potential indicators to measure the impact of the Regulation.
- Chapter 3 reviews the direct indicators relating to number of orphan designations and regulatory approvals.
- Chapter 4 describes the societal impact of the Regulation on the health of patients, the impact on their families, healthcare professions and wider healthcare system.
- Chapter 5 describes the economic impact of the Regulation by looking at the benefits the Regulation has brought to research and the macroeconomic environment.
- Chapter 6 presents our conclusions.

2. Indicators of the impact of the Regulation

Although there was not an impact assessment undertaken before the Regulation was introduced nor any stated expectations regarding the impact of the Regulation, the impact of the Regulation and the extent to which it has achieved its objectives have already been assessed – in 2006 by the "2006 Commission Report" (briefly summarised in Table 4) and in 2010 by the "2010 OHE report on societal impacts" (briefly summarised in Table 5).

Table 4: The 2006 Commission Report[36]

The 2006 Commission Report
This assessment, which took place after only five years of experience with the Regulation, found that more than 1 million patients suffering from orphan diseases in the Community may potentially benefit from the 22 orphan medicines that were authorised during the first five years of application of Regulation (EC) No 141/2000. The main conclusion was that "the true impact of the EU orphan initiative on public health will only be revealed progressively as longer-term experience is accumulated". In addition, they concluded that there are good grounds to assume that the legislation has stimulated industrial activity, leading to the creation of companies with promising high-tech potential. The assessment looked at a range of indicators including the number of designations and authorisations; the amount of protocol assistance, public health benefits and access to treatment in terms of number of products and patients affected; economic impact; growth in terms of number of start-ups, jobs and innovation; and impact on public health-care expenditure in terms of spending on orphan medicines.

Source: European Commission

Table 5: The 2010 OHE report on societal impacts[37]

The 2010 OHE report on societal impacts
This report was commissioned by EBE/EFPIA and EuropaBio. It drew on a literature review and a survey of industry participants. The report focused on 17 indicators of activity around OMPs in the EU identified by the Associations.[xiii] The indicators provided information on how much impact the Regulation had had on the following: • Company creation, growth and investment, in terms of number of start-ups, growth in R&D spending • Employment and company structure, in terms of employment growth • Science and innovation, in terms of number of clinical trials and therapeutic areas, number of specialist centres and funded projects • Patients, through innovation in healthcare delivery, in terms of patient

[xiii] This was based on a (confidential) survey completed by companies active in the area of orphan medicines. Eighteen companies (out of 51 who were sent the survey) responded to the survey.

organisations and in terms of particular OMP case studies

- Wider benefits accruing to the patient's family members or carers
- Medical expertise on rare diseases, and in terms of particular OMP case studies and number of clinical trials
- Research networks and infrastructures facilitating knowledge exchange
- Improving diagnostic tools and time to diagnosis, in terms of average time to diagnosis and access to medicines.

Source: OHE

Drawing on these reports, the original objectives of the Regulation, some initial interviews with industry participants, and discussions with the project Steering Committee, we developed a set of indicators to use in our assessment of the impact of the Regulation. These indicators have been used to structure the evidence collection on the direct impact of the Regulation (in Chapter 3), the societal impact of the Regulation (in Chapter 4) and economic impact of the Regulation in Chapter 5. The indicators are summarised in Table 6 below.

Table 6: Indicators capturing the direct impact of the Regulation, the societal impact and economic impact (* denotes an indicator suggested by Commission or OHE)

Area of Impact	Impact	Possible indicators
Direct impact of the Regulation	Has the OMP Regulation stimulated the research, development, and bringing to the market of appropriate medications?	• Number of clinical trials* • Number of applications for orphan designations and • Number of OMP designations* • Number of OMP marketing authorisations* • Protocol-assistance requests* • Number of rare diseases with new treatments • Range of therapy areas with orphan designation and prevalence of conditions*
Societal impact	Has there been improvement in the health of patients with rare diseases?	• Number of patients benefitting from OMPs* • Case Studies of increased life expectancy • Case Studies showing improved quality of life
	Is there a decrease in reliance on supportive care?	• Change in reliance on carers for rare diseases
	How has the role of patients been affected?	• Number of Europe-wide patient organisations • Number of Member State patient organisations

	Is there increased medical expertise on Rare Diseases?	• Improved training • Guidelines
	Have better treatment protocols been developed?	• Improved diagnostic tools and time for diagnosis
	Has there been an impact on efficiency of the healthcare system?	• Case Studies of average period of hospitalisation
Economic impact	How has research and development been impacted?	• Number of research projects initiated for rare diseases* • Number of EU-funded research projects* • Number of scientific publications* • Number of companies with compounds in development*
	How has the coordination and innovation eco-system been impacted?	• Number of centres of excellence* • Number of rare diseases research networks • Number of public–private partnerships between industry sponsored clinical research and academia • International cooperation of the EMA on OMPs
	Has there been an impact on growth and employment?	• Number of SMEs involved in OMP development • Number of people employed in OMP-related activities in Europe
	Has there been an impact on productivity?	• Case Studies of increase in patients' (and caregivers') productivity • Case Studies of increase in caregivers' productivity

Source: CRA analysis

Our report focuses on the societal and economic benefits from the Regulation and does not focus on spending associated to orphan medicines. This has been recently discussed in the EURORDIS reflection paper which discusses cost of OMP and the plateauing of orphan expenditure as a share of total pharmaceutical expenditure (predicted to stabilise between 4% and 5% by 2020).

3. Direct indicators to measure the impact of the Regulation

In this chapter, we review the evidence on the direct impact of the Regulation by looking at a set of indicators that measure how successful it has been in promoting and encouraging OMP development across Europe, its core objective (Table 7). As well as setting out data on each of these indicators, we contrast the most recent evidence with the assessments in 2006 and 2010, to see what has changed in the last seven years and to identify trends.

Table 7: Indicators that reflect the core objectives of the OMP Regulation (* denotes an indicator suggested by Commission or OHE)

Objective of the Regulation	Types of impact	Possible indicators
To stimulate research, development, and bringing to the market of appropriate medications	Development of new medicines	• Number of clinical trials for rare diseases* • Number of applications for OMP designation • Number of OMP designations* • Number of OMP marketing authorisations • Protocol-assistance requests*
	Types of products	• Number of rare diseases with new treatments • Range of therapy areas with orphan designation and prevalence of conditions*

Source: CRA analysis

3.1. Development of new medicines

3.1.1. Clinical trials

The OHE study identified a total of 2,553 clinical trials for OMPs reported in Orphanet as of January 2009 and showed that number of clinical trials with at least one site in an EU Member State in the area of orphan drugs had increased rapidly after 2001 until 2006. They noted that nearly 80% of all trials were conducted in European countries where a National Plan for Rare Diseases exists.[38] We have updated this analysis by examining the EU Clinical Trials Register and identifying ongoing trials for rare diseases by phase. **Relative to the numbers reported in 2009, there has been a 19% increase in European clinical trials for rare diseases over the past eight years** (Table 8). In comparison, using the same data base to examine the total number of clinical trials in Europe we find this has declined over the same period (2009 to 2017) by almost 24%.

Table 8: Total number of ongoing European clinical trials for rare diseases[xiv]

Phase	January 2009 (% of total trials associated to each development phase)	June 2017 (% of total trials associated to each development phase)
Phase 1	40 (2%)	234 (8%)
Phase 2	959 (38%)	1,423 (47%)
Phase 3	927 (37%)	1,064 (35%)
Phase 4	189 (7%)	289 (10%)
Non-specified	418 (16%)	-
Total	**2,533**	**3,010** ***(+19% compared to 2009)***

Source: CRA analysis of OHE (2010) and EU Clinical Trials Register

This represents a significant increase compared to the period prior to the Regulation. The increase in the total number of trials over the last ten years is consistent with the interviews we have undertaken, indicating that **the Regulation continues to foster clinical trials**, as originally intended.

3.1.2. Orphan designations and marketing authorisations

Since the implementation of the Regulation there have been more orphan designations and more authorised OMPs:

- During the first five years of implementation (April 2000 – April 2005), 458 applications for orphan designation were submitted, resulting in 268 products being designated as OMPs. Of these, 49 (19%)[xv] have applied for a marketing authorisation; 44 of these filed through the centralised route and 5 via national procedures.[39]
- Within the first decade of the OMP Regulation (April 2000 – December 2010), more than 850 positive opinions for orphan designations had been adopted from the 1,235 applications, resulting in 63 authorised OMPs across the EU.[40]

xiv Clinical trial data as of June 2017 is from the EU Clinical Trials Register and filters all European countries by trial status (Ongoing) and trial phase for those targeted at rare diseases. The data from January 2009 is from OHE (2010), which uses clinical trial data from Orphanet. This trial data sub-categorises phases into I-II, II-III and III-IV. For the purposes of comparison in this report, trials that fall into these sub-categories are grouped in the latter trial phase.

xv Although it did not provide an explanation of why only 19% of the designated OMPs applied for a marketing authorisation, the 2006 Commission Report noted that the number of applications was expected to increase in the coming years. This is likely to have resulted from the immaturity of the Regulation at the time, and the time it takes for designated products to apply for a marketing authorisation.

- Given the length of the development process, we would expect the impact of the Regulation to be more observable over time.[xvi] By May 2017, the EC had granted 1,868 orphan designations, and 133 OMPs had obtained marketing authorisation across the EU (Table 9).

Table 9: Number of orphan designations and marketing authorisations by year since the implementation of the OMP Regulation

Year	Number of applications submitted for orphan medicine designation	Number of positive opinions issued by COMP	Number of orphan designations by EC[xvii]	Number of marketing authorisations for OMPs
2000	72	26	14	0
2001	83	62	64	3
2002	80	43	49	4
2003	87	54	55	5
2004	108	75	73	6
2005	118	88	88	4
2006	104	81	80	9
2007	125	97	98	13
2008	119	86	73	6
2009	164	113	106	9
2010	174	123	128	4
2011	166	111	107	5
2012	197	139	148	10
2013	201	136	136	7
2014	329	196	187	15
2015	238	177	190	14
2016	330	220	209	14
2017[xviii]	58	61	63	5

xvi The process for researching and developing new medicines is difficult and lengthy. On average, it takes at least ten years for a new medicine to complete the journey from initial discovery to the marketplace, with clinical trials alone taking six to seven years on average. Therefore, the incentives from the Regulation may have taken some time to materialise and have an additional impact on the number of marketing authorisations (as also noted in the 2006 Commission report).

xvii The number of positive opinions issued by COMP differs from the number of orphan designation by EC because in some cases the COMP produces a positive opinion towards the end of the calendar year and this is adopted by the EC in the next year.

xviii As of COMP 189th plenary meeting on the review of applications for orphan designation 10–12 May 2017.

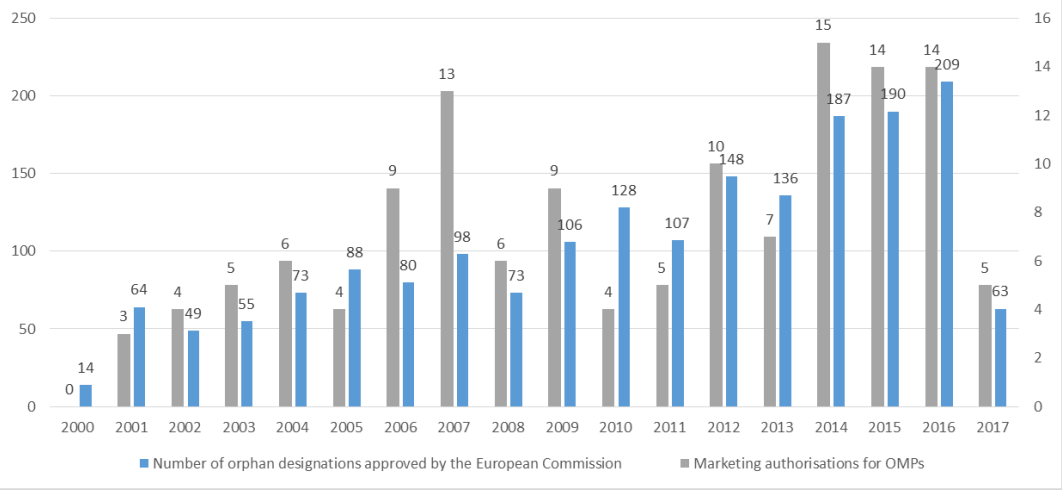
Total	**2,753**	**1,888**	**1,868**	**133**

Source: CRA analysis of European Medicines Agency[41]

A study of the orphan designations between 2002 and 2012[42] 304 orphan designations (representing 44% of the sample) were granted to medicines for conditions where there were no satisfactory method of diagnosis, prevention or treatment (and therefore no comparison with existing treatments was possible). Therefore, **in a large proportion of the cases, OMPs address diseases where no alternative treatment is available**. In the other cases (406 orphan designations), the medicines provided 'a clinically relevant advantage or a major contribution to patient care'.

Up until April 2000, when the Regulation was implemented, only eight products that would fit the definition of an OMP had been granted marketing authorisation in the EU.[43] In 2006 the European Commission stated that "*the orphan legislation in the EU has far exceeded initial expectations*"[44] and since then the trend in the number of OMPs authorised has continued (Figure 2).[xix]

Figure 2: Number of orphan designations and marketing authorisations for OMPs since implementation of the OMP Regulation[45]

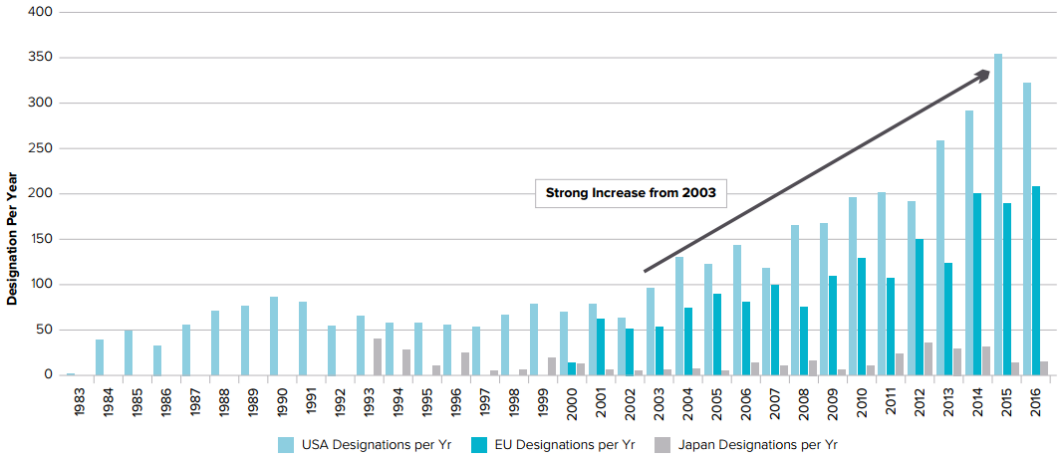


Source: EMA data [note:2017 reflects a partial year]

xix We tested this result with a simple linear regression and found that there is a statistically significant positive trend.

Figure 3 shows the number of orphan designations in Europe, the US and Japan (regions with orphan medicine legislations).[xx]

Figure 3: Number of US, EU and Japan orphan designations per year (1983–2016)[46,xxi]



Source: EvaluatePharma

While the increase in the number of designations after 2003 seems to be consistent with the introduction of the EU Regulation, it was emphasised in the interviews that the increase in global orphan medicine development was due to a number of factors and although **the Regulation played an important role in stimulating global development**, it was not the only reason for this. Interviews with both academic research networks and industry suggested that this increase was the result of the combined impact of the legislations in the US, Japan and EU and the scientific advances in the last two decades. Specifically genomic sequencing and an improved understanding of the molecular mechanisms of genetic diseases were systematically identified in the interviews as a fundamental driver of medicine development for many rare diseases.[47]

Use of protocol assistance

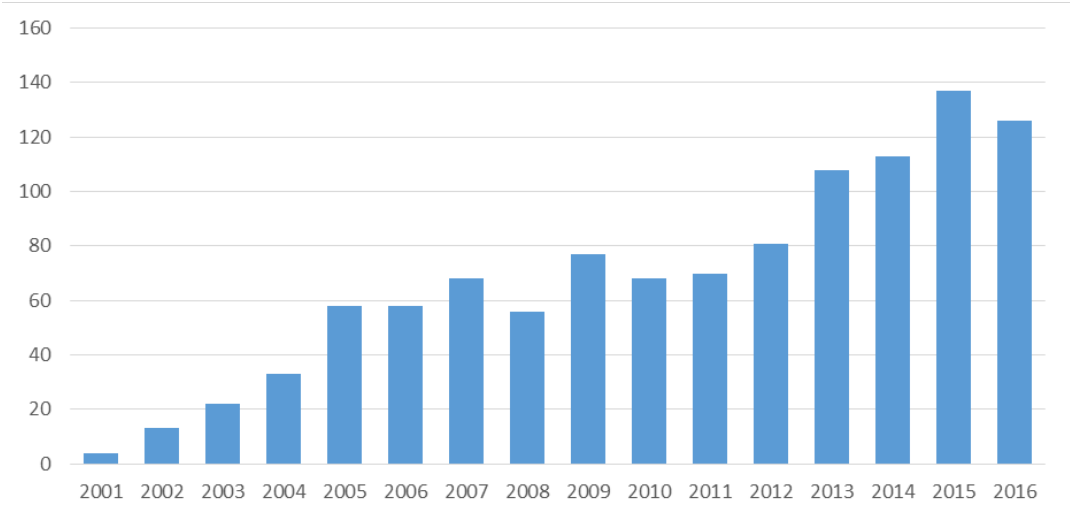
During the process of applying for orphan designation and subsequently for marketing authorisation, manufacturers have the opportunity to benefit from scientific advice from the EMA. In the case of manufacturers developing designated OMPs, the scientific advice provided by the Agency is referred to as protocol assistance and is offered free of charge. As Figure 4 illustrates, these too have increased over the years, with protocol assistance requests up from 4 in 2001 to 126 in 2016 (in total, there have been 1,092 requests

xx It would appear that there was a significant increase in the growth of orphan medicines designations also in the US shortly after the EU OMP legislation. This is consistent with an increase following the introduction of EU Regulation and could be interpreted as suggesting that the introduction of the EU Regulation helped facilitate global development of orphan medicines, likely through the additional incentives for manufacturers. The change is statistically significant, with no significant yearly increase pre-2001, but a yearly increase of 15 designations a year post-2001, at a 1% significance level (we used US data because it allows us to compare the trend before and after the Regulation was implemented. This result however does not hold for Japan, however we could not identify any evidence that would explain why this is the case).

xxi Note the data presented by EvaluatePharma and EMA are not identical.

between 2001 and 2016). The number of protocol assistances is a measure of the positive impact the Regulation has on OMP development.

Figure 4: Protocol-assistance and follow-up requests received by the EMA[48]



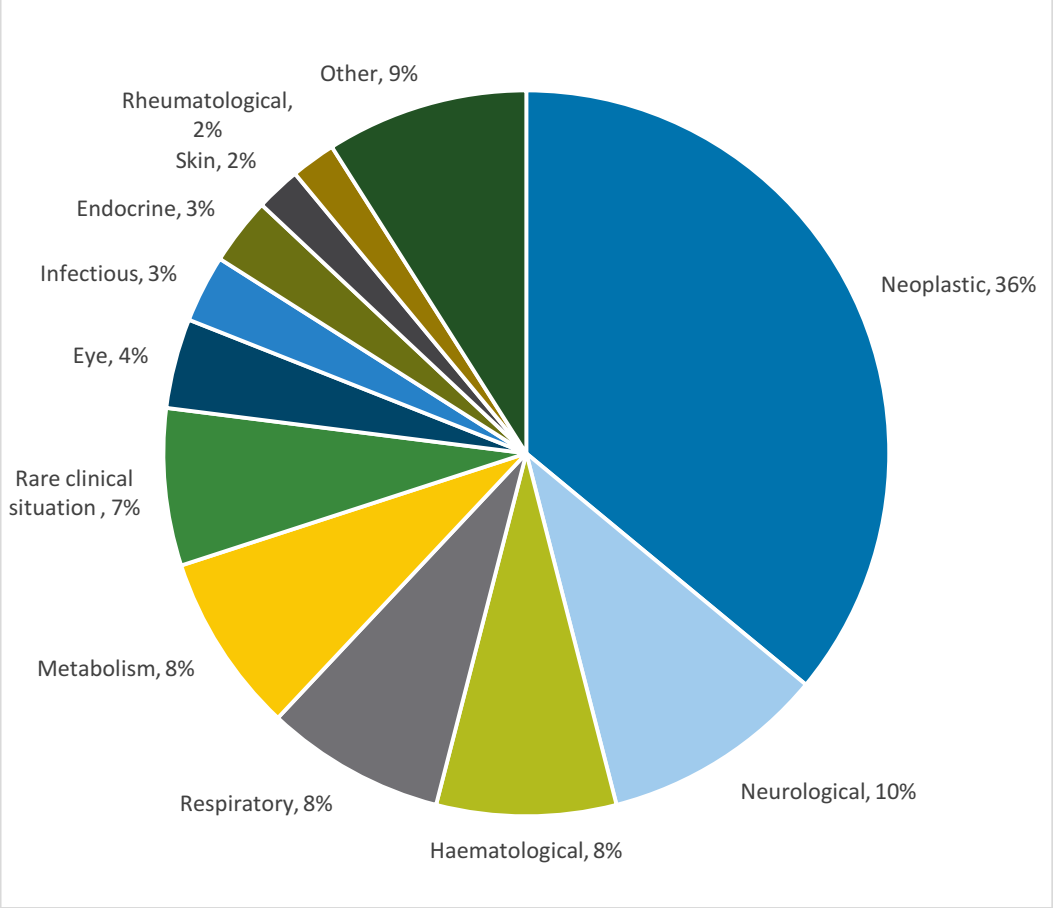
Source: European Medicines Agency

3.2. Types of products receiving orphan designation and marketing authorisation

While it is clear the overall number of authorised OMPs has increased, it is also important to look at what therapeutic areas are covered by these new medicines. In its five-year review the EC examined the therapy area targeted by each of the designated OMP. They found these were primarily rare cancers (36%), metabolic disorders (11%), immunologic disorders (11%), cardiovascular and respiratory disorders (10%), neurological (8%) and infectious diseases (4%).[49]

Although it is not possible to compare every therapy area, it appears the distribution has remained broadly similar. Rare cancers are still the largest category. Figure 5 illustrates an analysis of 605 orphan designations granted between 2002 and 2012, representing the most common diseases.

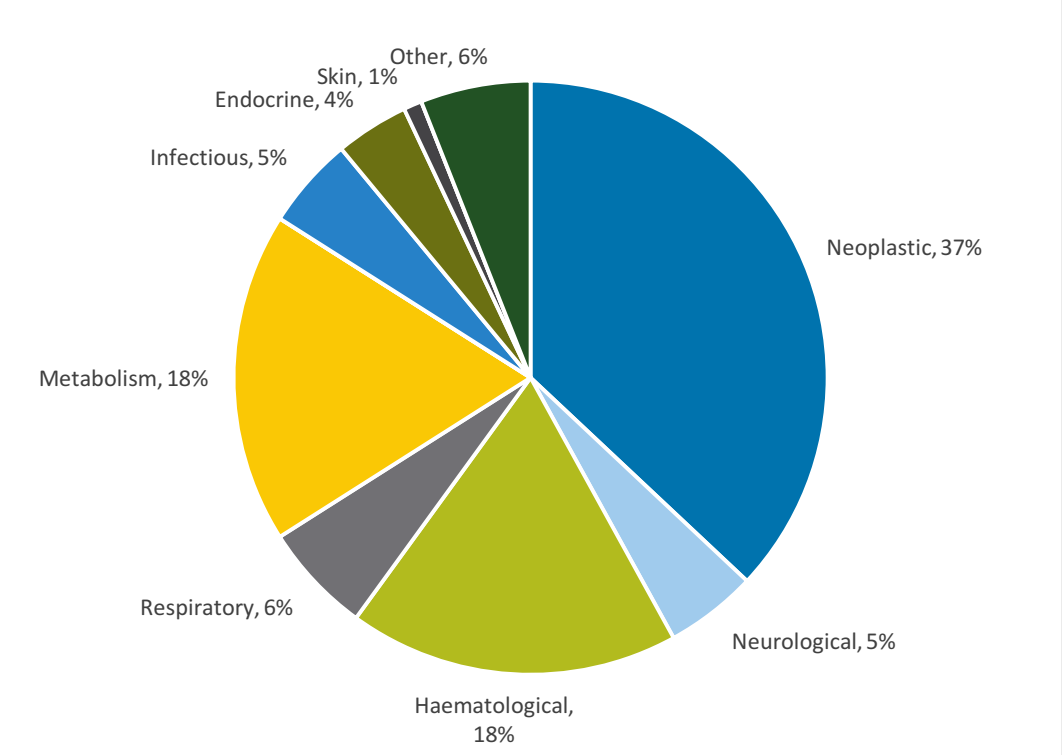
Figure 5: Analysis of orphan designations (2002–2012)[50]



Source: Morel et al.

Figure 6 illustrates an analysis of the marketing authorisation for OMPs, showing a similar pattern for approvals.

Figure 6: Analysis of OMP approvals (2000–2015)[51]



Source: Giannuzzi et al.

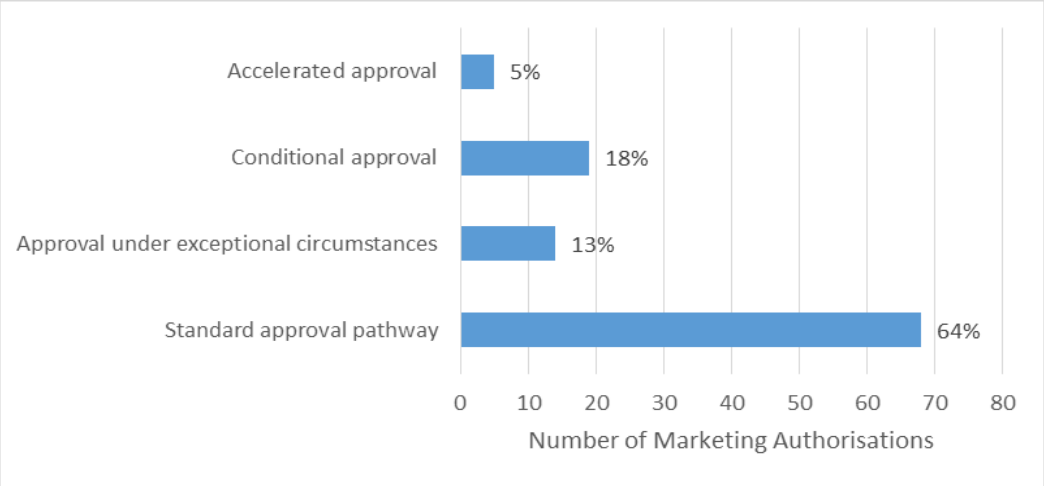
We can also look at the size of patient population the products are intended for and its relative rarity. **In 2006 the Commission found that 43% of granted designations were for conditions with a prevalence below 1 in 10,000.[52] This percentage has increased over the years: recent data show that about 60% of designations are for conditions that affect fewer than 1 in 10,000 patients.[53,54] This is inconsistent with the perception that the focus of development effort is on the largest populations within the rare diseases category.**

The number of rare diseases for which there is an orphan designation in Europe was 370 as of the end of December 2015.[55] This has increased from 200 in 2006, indicating that OMP research is targeting an increasing number of rare diseases.[56] Of these rare diseases, 319 affect children (86.2%) and 161 are genetic (43.5%).

Finally, we can look at the type of product by considering the regulatory pathway that OMPs have used. As OMPs are filed for marketing authorisation through the centralised procedure, it is possible for OMPs to be eligible for either an *accelerated approval*, a *conditional approval* or an *exceptional approval* (i.e. authorisation under exceptional

circumstances).[xxii,xxiii,xxiv] As shown in Figure 7, between 2006 and 2016, 64% of OMPs went through the standard approval pathways and 36% used other pathways for marketing authorisation. In particular, the vast majority (19 out of 21) of conditional approvals and a large proportion (14 out of 32) authorisations under exceptional circumstances granted over that period by the EMA were for OMPs.[xxv] This reflects the fact that, compared to non-orphan medicines, OMPs target diseases where immediate availability of treatments is of public interest (conditional approval) and where it is difficult to collect data (authorisation under exceptional circumstances).

Figure 7: Types of orphan medicinal product approvals (2006–2016)[57]



Source: Regulatory Rapporteur and CRA analysis of EMA data

We can also look at this on a year by year basis (Figure 8). Given the short period of time, it is difficult to know if the change in composition reflects a small number of exceptional years or a trend. However, based on the evidence we have, it suggests the EMA is increasingly using conditional approval for OMPs (between 2006 and 2011, five OMPs received conditional approval; between 2012 and 2012, 14 OMPs were conditionally approved) – allowing market access with a corresponding increase in data collection

xxii Accelerated approval is designed to speed up the development and availability of medicines that treat serious diseases. EMA "Marketing authorisation and market exclusivity". Available at [last access 4 July 2017]: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000955.jsp&mid=WC0b01ac05809f843a

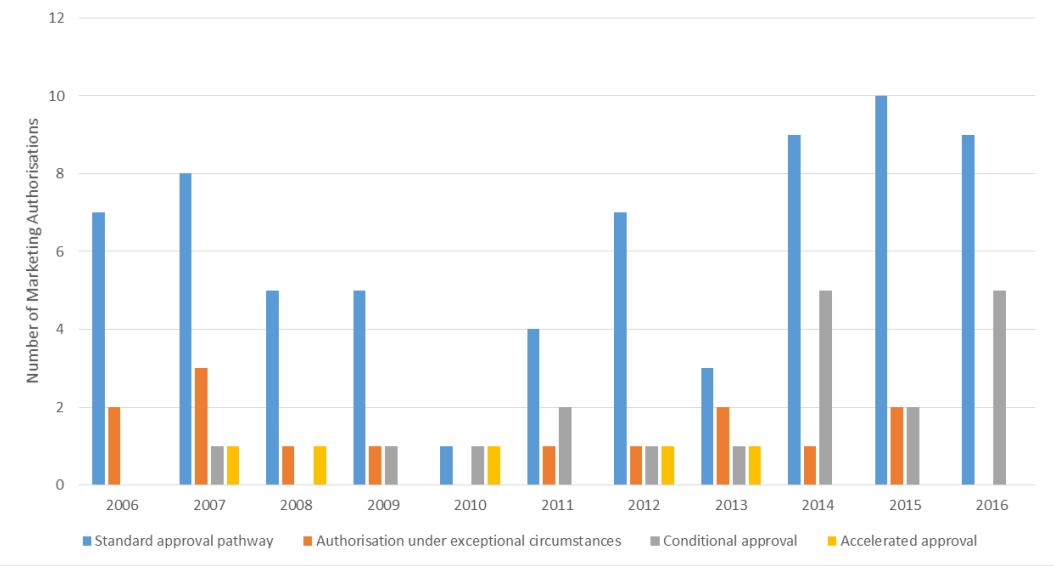
xxiii Conditional approval is granted in the interest of public health, for medicines where the benefit of immediate availability outweighs the risk of using less comprehensive data than normally required. EMA website [last access 26 June 2017]: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp&mid=WC0b01ac05809f843b

xxiv Authorisation under exceptional circumstances is granted where the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because it is impossible or would be unethical to collect full information. EMA website [last access 26 June 2017]: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp

xxv Data are not available to compare accelerated approvals.

requirements. This is consistent with OMPs focusing on most severe diseases, where immediate access to patients is valuable.

Figure 8: Evolution of the types of orphan medicinal product approvals (2006–2016)



Source: CRA analysis of EMA data

3.3. Conclusion

In this chapter we have shown that:

- **There is a positive trend in the number of designations and marketing authorisations over the last 15 years**. The increasing number of clinical trials suggests that is set to continue in the future.
- The OMP Regulation contributed to stimulating the development of medicines for rare conditions where there was no existing treatment. Consequently there are treatments for more patients with chronically debilitating conditions. An analysis of the data shows that the growth rate for designations and marketing authorisations has increased since the EU Regulation. Although it is likely that regulation in other jurisdictions also played an important role and that the underlying science was vital to new medicine development, it is reasonable to associate some of the impact to the Regulation itself. Interviews with industry experts, patient groups and healthcare professionals also validate these deductions. **We therefore conclude that the OMP Regulation has been successful in terms of stimulating the development and authorisation of orphan medicines across Europe; consistent with the 2006 European Commission findings**.[58]
- **The OMPs developed address areas of significant unmet need**. Overall, 304 orphan designations (representing 44% of the sample) were granted to medicines for conditions where there were no satisfactory method of diagnosis, prevention or treatment (and therefore no comparison with existing treatments was possible). In the other cases (406 orphan designations), the medicines provided 'a clinically relevant advantage or a major contribution to patient care'. The number of

conditional approvals suggest OMPs focus on the most severe diseases, where immediate access to patients is valuable.

- **A wide number of diseases have been targeted,** with cancer being the most targeted area (but only 37% of designations and authorisations are for cancer), **and an increase in designations for diseases with lower levels of prevalence** and hence fewer patients (the proportion of designations for conditions affecting fewer than 1 in 10,000 patients increased from 43% in 2006 to 60% today).

4. Societal impact of the Regulation

In the last chapter we focused on the direct indicators and compared the recent data with the results from the previous studies. As the 2006 Commission report noted, the full impact of the EU orphan initiative on public health could not be properly observed at that time (five years after the Regulation was implemented), as the benefits of the Regulation would be delivered progressively, and would become more fully observable as longer-term experience was accumulated.

The goal of this chapter is therefore to consider all the longer-term benefits that the Regulation has delivered to the health of the patients, their families and carers and to healthcare professionals and the healthcare system. We will focus on the economic impact of the Regulation in the next chapter.

4.1. Impact on patients

According to the interviews with patient organisations and the industry, it would have been much more challenging to develop and authorise effective treatment options for rare diseases in the EU without the Regulation. Moreover, interviewees also say that OMPs that were developed because of the Regulation have improved patients' health and quality of life, and decreased their reliance on supportive care. However, the nature of rare diseases is that each medicine affects a small number of patients, and the diseases affected are heterogeneous. It is therefore difficult to aggregate data from different diseases and instead we need to look at evidence from specific disease areas. Therefore the analysis of the impact of the Regulation on the patients (Table 10) focuses on indicators derived from case studies. In order to develop the case studies discussed in this chapter, we systematically reviewed the relevant information on OMPs authorised by the EMA in 2015 (14 marketing authorisations), in 2016 (14 marketing authorisations) and in 2017 (5 marketing authorisations) – totalling 33 potential case studies.[xxvi] We have drawn on evidence from the EMA (included in the EPAR), academic evidence and health technology assessment reports from HTA agencies in France, Germany and the UK.

Table 10: Indicators capturing the impact of the Regulation on patients (* denotes an indicator suggested by Commission or OHE)

Area of Impact	Impact	Possible indicators
Impact on patients	Is there improved health of patients with rare diseases?	• Number of patients benefiting from OMPs* • Case Studies of increased life expectancy • Case Studies showing improved quality of life
	Is there a decrease in reliance on supportive care?	• Case Studies of change in reliance of carers for rare diseases

[xxvi] A complete list of the OMPs reviewed is provided in Annex A.

Role of patients	• Number of Europe-wide patient organisations • Number of Member State patient organisations

Source: CRA analysis

OMPs improved the lives of a larger number of patients

Although each OMP aims to address a medical need affecting a small patient population, in aggregate the number of patients treated is significant and growing. In 2006, the EC illustrated that after five years the Regulation had made successful steps in meeting its core objectives:[59]

- In terms of public health benefits, the first 22 orphan medicines had been authorised for the treatment of 20 different life-threatening or chronically debilitating rare diseases.
- As a consequence, more than 1 million patients suffering from these rare diseases in the Community may have potentially benefited from the availability of these new treatments authorised since Regulation (EC) No 141/2000 came into force.[xxvii]

To update this, we have estimated the number of patients with diseases that could now be treated by the authorised OMPs,[xxviii] taking the number of different life-threatening or chronically debilitating rare diseases treatable with OMPs (99) and applying an average level of prevalence (1.38 in 10,000[xxix]) to the population of the EU (510 million). This is an over-estimate as each medicine will have an indication for a proportion of the population with the disease – but it is still comparable to the estimate provided by the Commission in 2006. On this basis, there are 7 times as many patients with diseases where an OMP has been approved compared to the population in 2006.[xxx]

It should be noted that the existence of an OMP for a given condition does not mean that all patients have access to this medicine. A 2017 study by OHE shows that differences in

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xxvii Although the 2006 Commission report does not provide the details of the calculation, we assume it took into account the fact that there are diseases where there are multiple treatments approved.

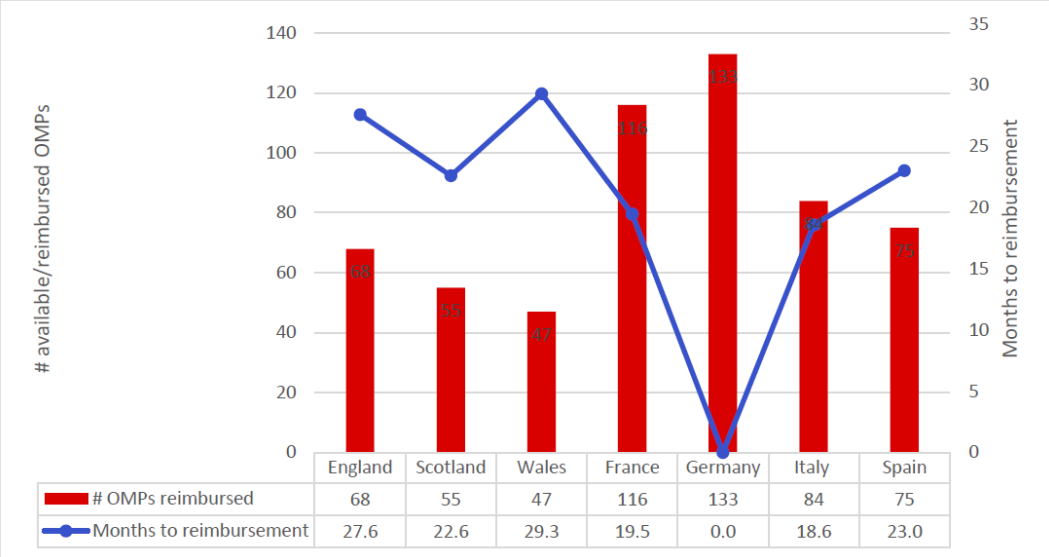
xxviii We have counted the number of different life-threatening or chronically debilitating rare diseases treated by the 133 authorised OMPs authorised since 2000. This takes into account if OMPs treat the same diseases or if they treat the same patient population (after showing significant benefits)

xxix As already noted on page 26, 60% of the rare diseases have prevalence below 1 in 10,000 (we assume it is 0.5 in 10,000), 26% have prevalence between 1 and 3 in 10,000 (we assume it is 2 in 10,000), and 14% have prevalence between 3 and 5 in 10,000 (we assume it is 4 in 10,000). The weighted average is 1.38 in 10,000.

xxx Given the 99 distinct diseases, the average level of prevalence of a rare disease in Europe is 1.38 in 10,000 and applying this to the population in the EU of 510 million, the number of treated patients is 510,000,000 x 99 x 1.38 : 10,000, is approximately 7 million. Applying the same approach to the situation in 2006, we estimate 1.3 million have OMPs relevant for their disease, which is consistent with the Commission estimate. Even using a very conservative approach (i.e. assuming that: 60% of the rare diseases have prevalence 0.01 in 10,000; 26% have prevalence between 1 in 10,000, and 14% have prevalence between 3 in 10,000), calculations indicate that OMPs had been approved for than 4 million patients.

reimbursement systems in selected European countries have a large effect on access to OMPs.[60] As shown in Figure 9, OMPs are most widely available in Germany and France, due to immediate reimbursement of medicines in Germany and that in France orphans are generally fully reimbursed. If Germany is excluded from this analysis, the average time between granting of marketing authorisation and the final reimbursement decision for the remaining six countries[xxxi] is 23.4 months.[61] It should be noted that pricing and reimbursement decisions are strictly the responsibilities of individual Member States, these issues are beyond the scope of the OMP Regulation and the mandate of COMP.

Figure 9: Comparison of access indicators for OMPs across seven EU countries



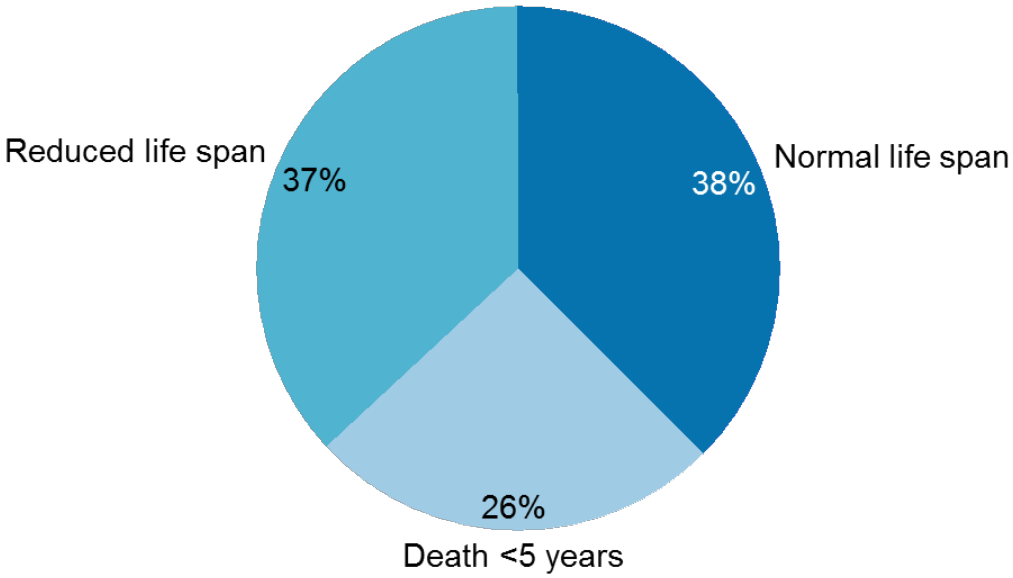
Source: Office of Health Economics[62]

OMPs improved the life expectancy of patients with rare diseases

Rare diseases are often severe and have a significant impact on the patients expected survival (as illustrated in Figure 10). For example, 75% of rare diseases affect children and nearly one-third who are diagnosed will die before their fifth birthday.[63]

xxxi Countries included in the analysis are England, Scotland, Wales, France, Italy and Spain.

Figure 10: Life expectancy for patients with rare diseases



Source: EURORDIS

Interviews with patient associations have highlighted that, given the difficulty in showing aggregate impact on patients with rare diseases, case studies are the best approach to show the benefits that medicines have brought to particular patient groups. In particular, case studies can illustrate the life-changing impact of the medicines. For some life-threatening rare diseases, OMPs give patients the opportunity to enjoy a normal life expectancy, in other cases, they provide a significant improvement in survival, allowing time to be spent with their families that would otherwise not occur, even though life expectancy remains short. We consider the most recent (i.e. since January 2015) orphan designations and launches of OMPs in the EU to show these benefits (Table 11).

Table 11: Impact of OMPs on life expectancy

OMPs (year of approval)	Disease area	Impact of OMPs on disease
Dinutuximab beta Apeiron (2017)	Paediatric neuroblastoma	78% of the patients whose neuroblastoma had not improved with other treatments were still alive 2 years after treatment with Dinutuximab beta Apeiron. Of the patients whose neuroblastoma had come back, 69% were still alive 2 years after treatment (compared to expected mortality in case of non-treatment).[64]
Darzalex (2016)	Multiple myeloma	Examined in different studies, Darzalex showed a benefit for patients in progression-free survival with (in one study) 78% of patients living for 1.5 years without their disease getting worse; in another study, 61% of patients lived for one year without their disease progressing (comparison data to other treatments are not yet available).[65] These results give hope to patients that otherwise would have a

		life expectancy shorter than 3 years.
Gazyvaro (2016)	Chronic lymphocytic leukaemia (CLL)	Gazyvaro allows CLL patients to live 1.3 years longer without disease progression than they would with other treatments.[66] German GBA also backs their approval of Gazvaro with the argument of the drug significantly improving PFS.[67]
Latruvo (2016)	Advanced Soft Tissue Sarcoma (STS)	The median survival time in patients with metastatic STS is 11 to 15 months when treated with Doxorubicin monotherapy (a non-orphan medicine). In combination with the chemotherapeutic Doxorubicin, Lartruvo prolongs life for a median duration of 11.8 more months in comparison to the existing standard of care.[68] The GBA in Germany values the benefits the drugs brings to patients by rating it with the second highest grade "significant benefit".[69]
Strimvelis (2016)	Adenosine deaminase deficiency	Strimvelis is an ex vivo treatment of T-cells for patients with adenosine deaminase deficiency (ADA-SCID). Since their immune systems do not work properly, they rarely survive 2 years (without receiving bone marrow transplant) but when patients were administered with Strimvelis, they were still alive after 3 years of treatment.[70] Having been authorised by EMA in May 2016, the Italian Medicines Agency AIFA granted reimbursement for the medicine only 2 month later (in July 2016) illustrating the high unmet need the medicine is addressing.[71]
Strensiq (2015)	Hypophosphatasia	The perinatal form is almost always fatal within days or weeks. Respiratory complications led to high mortality rates in the infantile form. In clinical trials over a 5-year timeframe, Strensiq was shown to be beneficial for paediatric patients: 4 out of 37 children (10.8%) ≤ 5 years treated with Strensiq group had died, compared with 35 out of 48 patients (72.9%) in the untreated group during the time-period evaluated (the long-term outcome will be measured over 6 years)[72]
Kanuma (2015)	Lysosomal acid lipase deficiency (LAL)	Affected infants rarely live past the age of 6 months, infants surviving the first 6 month have an increased cardiovascular risk and suffer from rapidly developing liver fibrosis and cirrhosis. It was shown that under treatment of Kanuma 6 out of the 9 infants survived to 1 year of age. Growth improvements were also observed in all 6 surviving infants.[73] Kanuma is until now the only available treatment for LAL deficiency.[74]

Source: CRA analysis of OMPs approved since January 2015

OMPs increased patients' quality of life

Rare diseases are generally severe with a large impact on the patient's health. As suggested in interviews with patient associations, OMPs contribute by increasing the

quality of life in patients with rare diseases for patients and their families. We again need to rely on case study evidence to show the impact on quality of life (Table 12) for recently approved OMPs (since January 2015).

Table 12: Impact of OMP on patients' quality of life

OMPs (year of approval)	Disease area	Impact of OMPs
Darzalex (2016)	Multiple myeloma	Myeloma patients experience a variety of disease-related events and symptoms, such as bone destruction leading to pain, height reduction and body-shape changes; and bone marrow failure, renal failure and immunodeficiency; as well as the psychosocial burden of a diagnosis of cancer. These aspects may have different importance for the patient in different periods of the disease. Darzalex is a fast-acting drug – in many cases tumours shrank in just a month. As a result of shrinkage and slower tumour growth, patients had less pain and a better quality of life.[75]
Coagadex (2016)	Hereditary factor X deficiency	Hereditary FX deficiency persists for life and can result in severe debilitation in the quality of life due to the increased tendency for bleeding, seen especially in states of hemodynamic stress. Treatment of bleeding episodes by Coagadex was rated as "excellent" or "good" for 98.4% of bleeding episodes, improving patients' quality of life.[76]
Wakix (2016)	Narcolepsy	Patients with narcolepsy have considerably lower scores in quality of life domains recorded using the 36-item short-form Medical Outcomes Study (SF-36). In particular, scores are poor for the dimensions "physical role", "vitality", and "general health perception". Forty-eight percent of the patients reported problems in the dimension "usual activity" (63.8% of them), "pain/discomfort" (61.7% of them) and "anxiety/depression" (41.1% of them). Difficulty maintaining "self-care" was documented only by 6.8% of them. There is a reduction in daytime sleepiness in patients with narcolepsy taking Wakix. There is also a 75% reduction of cataplexy, a concomitant side effect of narcolepsy in 60%-70% of narcolepsy patients.[77]
Idelvion (2016) Alprolix (2016)	Haemophilia B	A study found that 48% of patients who were diagnosed with haemophilia also had arthritis, 43% had osteoporosis, 29% had acute pain, 13% had chronic pain, 23% suffered from anxiety and 22% had depression. More than half of caregivers reported at least mild depression; just under half reported mild anxiety. Idelvion and Alprolix have a prolonged half-life allowing for fewer injections compared to the other existing, conventional prophylactic treatments

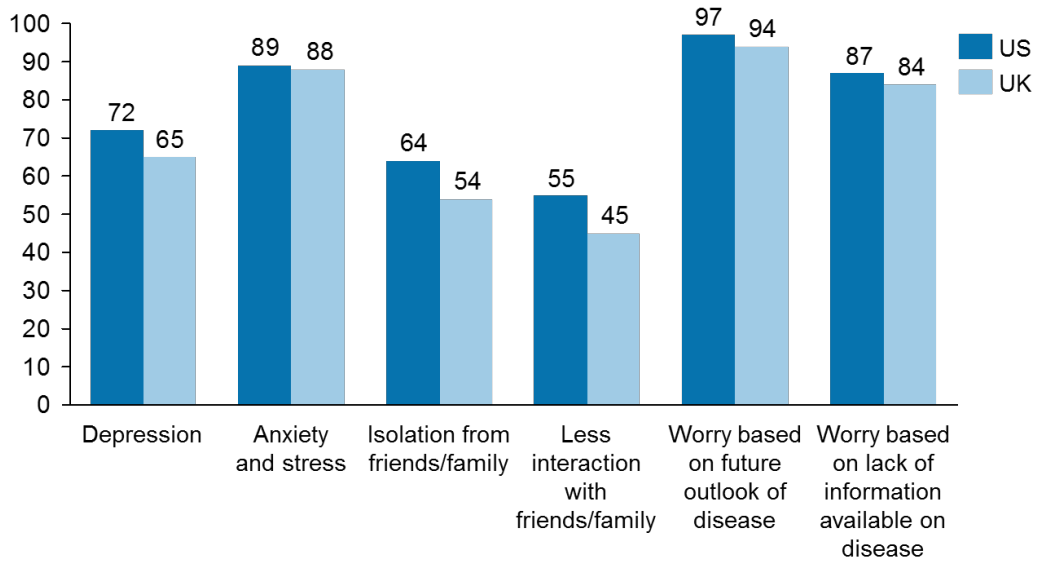
		and, therefore, have a positive impact on patients' quality of life. For instance, the decrease in injection frequency with both Idelvion and Alprolix is beneficial in children who often have difficult venous access (and often have to use portacaths, which can also pose infection-related issues).[78,79]
Hetlioz (2015)	Non-24-hour sleep-wake disorders in blind people with no light perception	Blind people suffering from this disease often have one or more of the following symptoms: insomnia, anorexia, incoordination, memory impairment, mood attacks. The disease deprives affected patients from the ability to follow their normal daily schedule. 20% of patients who received Hetlioz (8 out of 40) were able to adjust to the 24-hour clock after 1 months of treatment, compared with around 3% of patients on placebo (1 out of 38).[80]

Sources: CRA analysis of OMPs approved since January 2015

Decrease in reliance on supportive care

Interviews with patient organisations indicated that rare diseases often have a significant impact not just on the patients but also on their families and carers. As illustrated in Haemophilia B case study above, where more than half of caregivers reported at least mild depression; just under half reported mild anxiety. This is also shown in a EURORDIS survey (and summarised in Figure 10).

Figure 11: Impact of rare diseases on caregivers[81]



Source: EURORDIS

Reviewing the OMPs authorised over the last three years we found very limited evidence to document the impact of OMPs on relieving the burden on carers. However, according to our interviews with patient organisations on cystic fibrosis (CF) and Gaucher disease, the impact on carers is an important element of the wider benefits. These include the carers' quality of life, their own health and ability to continue caring on a sustainable basis. For example, interviewees reported that patients affected by CF have

unpredictable pulmonary exacerbations which, on many occasions, prevent them and their families from conducting normal lives (for instance, planning holiday and family activities is problematic as pulmonary exacerbations would imply patient hospitalisation). By reducing pulmonary exacerbations, new medicines for CF help patients and their families to enjoy normal lives.

The Regulation contributed to the establishment of patient organisations

The final indicator refers to the empowerment of patients in raising awareness of rare diseases among stakeholders and stimulating research priorities and policy initiatives. The 2010 OHE report identified a number of benefits delivered to patients by patient groups, and our interviews suggest these areas continue to be impactful:[xxxii]

- Encouraging product development by identifying very specific research areas that are relatively close to clinical development[82]
- Advocacy in the national healthcare system to raise awareness of the diseases and ensure access to available treatment(s)
- Establishing and reinforcing partnerships and linkages with key stakeholders with an interest in the disease in question, including researchers, medical staff and industry
- Disseminating information on the diseases through publications, websites and other media
- Fully collaborating with COMP to develop the regulatory framework – a unique example in the EU of collaboration between patient groups and regulatory authorities
- Supporting clinical trial recruitment.

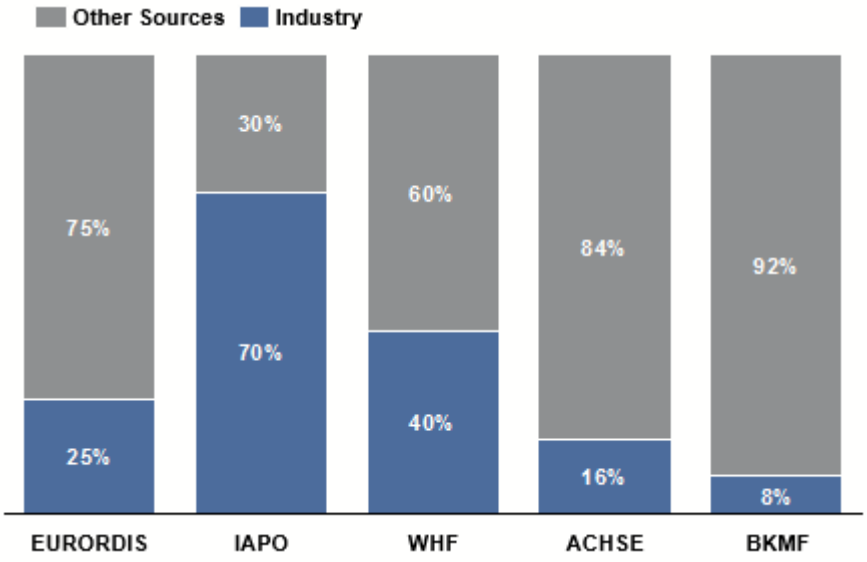
According to the interviews with patient organisations and the industry, the Regulation and the consequent increased awareness around rare diseases helped patient organisations in the EU to expand their activities. EURORDIS – the European patient advocacy group for rare diseases founded in 1997 – reports a significant increase in the number of patient organisations dedicated to rare diseases as well as an increase in membership since the Regulation. This has resulted in a broader diversity of rare diseases being covered and a wider scope of activities.[83] Nowadays, EURORDIS represents more than 755 rare diseases patient organisations (including from beyond the EU).[84]

Over the last seven years, patient organisations have also become more active in the assessment of medicines for rare diseases, through their involvement in health technology assessment processes and by working with other stakeholders to develop innovative solutions to market access challenges (for example the development of managed entry agreements).

xxxii The OHE report also emphasised the role of particular patient groups, such as those in Pompe and multiple myeloma. These still represent good examples of the role of patient groups, but we could equally include examples for cystic fibrosis or Duchenne muscular dystrophy.

As the industry has become more involved in rare diseases as a result of the Regulation, its interaction with patient groups has also increased. For instance, the industry provides support to patient advocacy groups through multiple different means, including by providing data/networks (e.g. medical information to help inform patient associations on recent discoveries and a platform to connect to experts), by direct sponsorship (Figure 12), and by helping the patient advocacy groups become more established organisations with increased capabilities.[85]

Figure 12: Industry versus other sources of funding for various patient organisations (2015)



Source: Respective organisations 2015 annual report. Note: IAPO = International Alliance of Patients' Organizations, WHF = World Hemophilia Foundation, ACHSE = Alliance of chronic rare diseases (Germany), BKMF= German Association for People of Short Stature and their Families

Overall, the Regulation has contributed to the funding and support of an ecosystem of stakeholders (including patient organisations[xxxiii]) that add value to the care paradigm of rare diseases.

The patients' voice has been amplified by the institutional structures. The COMP is the first scientific committee in the EU to include representatives of patients' organisations as full members. Three seats of COMP have been assigned to patients' organisations since its creation in 2000. This has not only stimulated dialogue with patient groups but it has also had a positive impact on triggering the committee's work from the perspectives of patients' need and public health, structuring patient groups' work at EU level, and it has supported patients' demands for greater transparency in decision-making.[86]

xxxiii For instance, although directly linked to the Innovative Medicine Initiative, the European Patients' Academy (EUPATI) was created also in response to the increased activity and availability of patient organisations. It is a pan-European project implemented as a public–private partnership by a collaborative multi-stakeholder consortium from the pharmaceutical industry, academia, not-for-profit, and patient organisations. EUPATI has already trained 96 patient experts on medicines development, clinical trials, medicines regulations, and health technology assessment. Source: EUPATI website [last access 27 June 2017]: https://www.eupati.eu/what-is-eupati/

4.2. Impact on treatment provided by healthcare professionals and the efficiency of the healthcare systems

According to the interviews with patient organisations and clinician groups, the Regulation also helped to increase the expertise of healthcare professionals (HCPs), the treatment protocols and, in turn, the efficiency of the healthcare system. We examined a number of different indicators that can describe the potential impact of the Regulation on HCPs (Table 13).

Table 13: Indicators capturing the wider impact of the Regulation on HCPs and healthcare system

Area of impact	Impact	Possible indicators
Impact on healthcare professionals and healthcare system	Is there increased medical expertise on rare diseases?	• Improved training • Guidelines
	Have better treatment protocols been developed?	• Improved diagnostic tools and time for diagnosis
	Is there an increase in efficiency?	• Case Studies of average period of hospitalisation

Source: CRA

The Regulation helped to improve HCPs' training and expertise

The 2010 OHE report noted that the incentive to acquire specialist knowledge to diagnose rare conditions is reduced when there are no therapy options available to treat them once diagnosed, beyond palliation of symptoms. Our interviews with clinician groups support this, suggesting that when new treatments are introduced, clinicians gain interest in the condition and this encourages them to review existing and new cases. Therefore, when a new OMP is developed and launched, there is more general awareness of the targeted disease, and an improvement in medical skills. For instance, in the case of Pompe disease, since the launch of alglucosidase alfa, the Erasmus Medical Centre in the Netherlands has hosted the "Pompe Expert day" every six months.[87]

Given the nature of rare diseases, the number of clinical experts is often limited and they are often focused on particular hospitals or research institutions. Interviews with clinicians and patient groups reported that the pharmaceutical industry has an important role in: proactively providing medical information to physicians and sharing information on successful approaches to diagnosis (in the form of congresses and trainings on both diagnostic procedures and treatments). The result of this is that physicians improved their ability to recognise patients with severe and typical forms of the condition in areas where treatments have been made available. In addition, the ability to recognise patients with mild forms of the disease improved, meaning the disease is diagnosed earlier benefiting patients and potentially preventing progression of the disease and associated costs to patients, their family and the healthcare system.[88]

Finally, as noted in the interviews with academics and research centres, the Regulation did lead to new resources for physicians, for instance Orphanet (Table 14).

Table 14: The creation of Orphanet

The Regulation also supported the development of Orphanet

Orphanet is a resource intended to improve knowledge on rare diseases so as to improve the diagnosis, care and treatment of patients with rare diseases. It aims to provide high-quality information on rare diseases, and ensure equal access to knowledge for all stakeholders. Orphanet also maintains the Orphanet rare diseases nomenclature (ORPHAnumber), essential in improving the visibility of rare diseases in health and research information systems.[89]

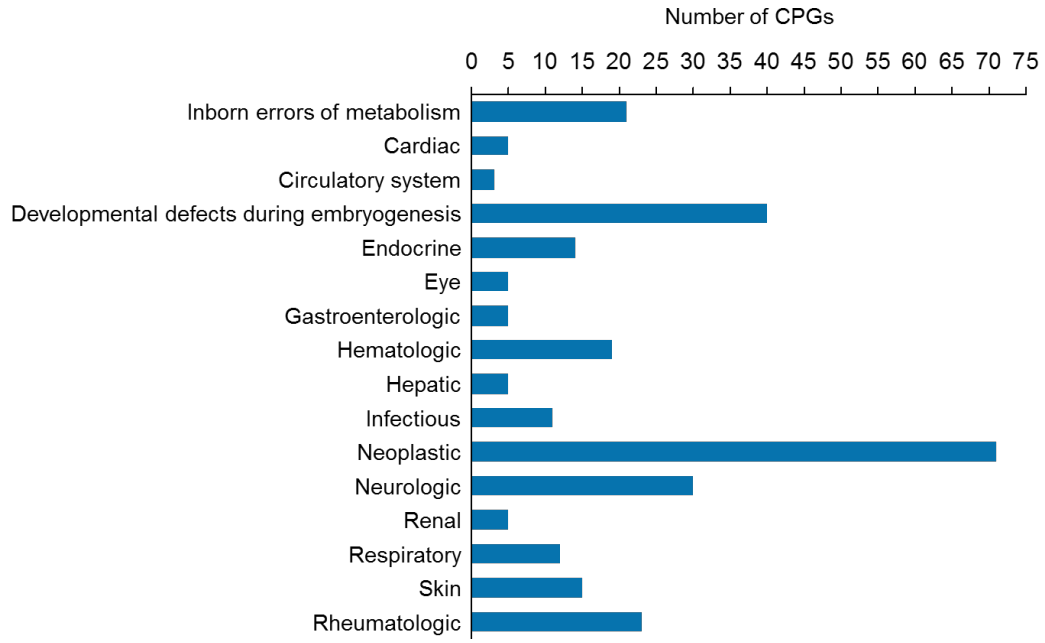
Orphanet was established in France by Inserm (the French National Institute of Health and Medical Research) in 1997.The initiative became a European endeavour from 2000, supported by grants from the European Commission: Orphanet has gradually grown to a consortium of 40 countries within Europe and across the globe.[90]

Source: CRA analysis

Improved guidelines

Although many clinical practice guidelines (CPGs) have been developed in the last 25 years, most of them are aimed at common diseases; recommendations dedicated to rare diseases remain scarce. However, the contribution of CPGs to shortening the time to diagnosis and improving of the quality of care is now widely acknowledged, and several European countries have included CPG development as a priority in their respective national plans on rare diseases.[91] A recent analysis of CPGs found that 277 CPGs for rare diseases were disseminated on the Orphanet database from January 2012 to July 2015.[92] In particular, distribution of CPGs among medical specialties showed that the most represented diseases were rare neoplastic, neurologic, hematologic, rheumatologic and developmental diseases (Figure 13).

Figure 13: Clinical practice guidelines distribution on Orphanet by medical speciality[93]



Source: Pavan et al.

Improved diagnosis

In interviews with patient associations and clinician groups, it was pointed out that, beyond the impact of the disease itself, another fundamental problem for rare disease patients is the difficulty in receiving a timely and correct diagnosis.. The extent of the problem is illustrated by the following:

- 40% of rare diseases patients are misdiagnosed at least twice and diagnosis is delayed.[94]
- It is common for patients to be misdiagnosed with a more common disease before they are eventually diagnosed with a rare condition.[95]
- It can take on average 4.8 years for a person with a rare disease to receive the correct diagnosis, after a number of visits to the doctor.[96] In the meantime, the disease is misdiagnosed and patients often receive the wrong treatments while unnecessarily suffering from the disease.[97]

This evidence was also supported in the 2010 OHE report, which found that for rare diseases diagnosis can take between 5 and 30 years.[98]

Several EU policy documents have emphasised the importance of developing improved diagnostic and genetic testing for rare diseases.[xxxiv] As noted in the interviews with clinical centres, several initiatives have been undertaken since then to improve diagnosis. One of the most important is the industry has worked with HCPs[99] through the development of the following:

- Raising awareness
- Patient and new born screening
- Establishment of patient registries
- Development of rare disease plans

We examine each of these initiatives in turn.

Raising awareness. Specific programmes have been initiated and aim at raising awareness, among healthcare professionals and people diagnosed with rare diseases, of the importance of a family history evaluation (for example, by offering information for healthcare professionals on genetic testing). For instance, in the UK, the NHS has developed a strategy to work with clinicians to establish appropriate diagnostic pathways which are accessible to, and understood by, professionals and patients by 2020.[100]
Patient and new born screening. New initiatives also support the clinical community to evaluate different screening methodologies to support early detection of these devastating conditions. In particular, new born screening programme have been established to improve the long-term outcome of the treatments for the children with genetic disorders.[101]

xxxiv In particular, the need of testing is noted in: (1) the Council Recommendation on an action in the field of Rare Diseases (2009/ C151/02); (2) the Commission Communication on Rare Diseases: Europe's Challenge (COM(2008) 679); (3) Directive 2011/24/EU on the application of patients' rights in cross-border healthcare.

Patient registries. The establishment of patient disease registries allows a better understanding of rare diseases and the diagnosis pathway. In particular, the number of patient registries for rare diseases increased by 36% between 2011 and 2016. However, the largest expansion occurred for registries at national level (vs European registries), indicating that there is still a need for further European integration (see Table 16 below). This need is also noted by the EMA, which stated that the current regulatory approach to registries is suboptimal, as there is a lack of common protocols, data sharing and transparency and sustainability.[102] This shows the on-going need of increased cooperation at European level and the maintenance of an appropriate approach supporting common actions.

Table 15: Distribution of registries by country: comparison between 2011[103] (in parentheses) and 2016[104]

Country	Regional	National	European	Global
Austria	3 (1)	26 (12)	5 (2)	2 (0)
Belgium	2 (2)	16 (16)	0 (1)	3 (1)
Bulgaria	0 (0)	11 (4)	0 (0)	0 (0)
Cyprus	0 (0)	2 (1)	0 (0)	0 (0)
Czech Republic	0 (0)	4 (4)	0 (0)	0 (0)
Germany	9 (4)	78 (57)	3 (20)	34 (5)
Denmark	1 (1)	3 (3)	0 (0)	0 (0)
Estonia	0 (0)	2 (2)	1 (0)	0 (0)
Spain	11 (4)	31 (25)	3 (3)	1 (0)
Finland	0 (0)	7 (5)	0 (0)	0 (0)
France	20 (17)	97 (92)	13 (11)	4 (2)
Greece	0 (0)	2 (2)	0 (0)	0 (0)
Croatia	0 (0)	1 (1)	0 (0)	0 (0)
Hungary	0 (0)	5 (3)	0 (0)	1 (0)
Ireland	4 (4)	11 (6)	0 (0)	1 (0)
Italy	10 (9)	51 (35)	4 (2)	7 (5)
Lithuania	0 (0)	1 (1)	0 (0)	0 (0)
Luxembourg	0 (0)	1 (1)	0 (0)	0 (0)

Latvia	0 (0)	1 (1)	0 (0)	0 (0)
Malta	0 (0)	2 (1)	0 (0)	0 (0)
Netherlands	1 (1)	12 (6)	5 (3)	8 (5)
Poland	3 (3)	5 (6)	2 (0)	0 (0)
Portugal	5 (1)	11 (8)	0 (0)	0 (0)
Romania	0 (0)	2 (2)	0 (0)	0 (0)
Sweden	0 (0)	14 (15)	1 (3)	3 (0)
Slovenia	0 (0)	2 (2)	0 (0)	0 (0)
Slovakia	0 (0)	2 (2)	0 (0)	0 (0)
United Kingdom	5 (13)	54 (38)	17 (6)	8 (1)
TOTAL	***74 (60)***	***454 (351)***	***54 (51)***	***72 (19)***

Source: CRA analysis from Orphanet and EC data

National rare disease plans. The development of patient registries is also closely connected to the development of National Rare Disease Plans (Table 16); the activities of the EUCERD and the Commission Expert Group on Rare Diseases;[105] and the EU Joint Action on Rare Disease ("RD-Action").[xxxv,106] The EC and the MS have also been supporting the development of National Rare Disease Plans together within the European Project for Rare Diseases National Plans Development (EUROPLAN).[xxxvi]

Although not directly resulting from the Regulation, interviews with patients groups and companies linked the environment created by the Regulation, with the development of rare disease plans, greater awareness of rare diseases and the encouragement of registries.

Table 16: The development of National Rare Disease Plans

The Regulation helped to create a favourable environment for the development of National Plans for Rare Diseases
Based on a 2008 EC report and the wide-ranging objectives it set for the European

xxxv The current Joint Action on rare diseases, RD-ACTION, started on 1 June 2015 for a three year duration. It is the continuity of both the EUCERD Joint Action (March 2012 – November 2015) and a former Orphanet Joint Action.

xxxvi EUROPLAN is a project co-funded by the EU Commission (DG-SANCO) to promote and implement National Plans or Strategies to tackle rare diseases, to share relevant experiences within MS, linking national efforts with a common strategy at European level. Since its inception in 2008, EUROPLAN National Conferences promote and accompany the development and adoption of National Plans or Strategies for Rare Diseases in the EU MS.

community, the European Council of Health Ministers in 2009 adopted a Recommendation on an action in the field of rare diseases.[107] This Recommendation has served as a catalyst in the development of national plans and strategies for rare diseases in EU countries. Whereas only 5 countries had developed such a plan or strategy at the time of its adoption (2009), by the end of 2013 (the date by which the Council Recommendation encouraged countries to adopt a plan), 16 countries had adopted a plan/strategy and the others were in advanced stages of elaborating a plan/strategy.[108]

As of June 2017, 24 of the 28 countries in the EU have adopted national plans as a result of the increased awareness around rare diseases generated by the Regulation. Only Estonia, Malta, Poland and Sweden have not implemented a plan yet.[109]

In addition to these initiatives, the industry also contributed to the development of diagnostic testing, which helped:[110]

- Alerting significant clinical co-morbidities
- Reducing mortality/saving lives
- Avoiding invasive diagnostic procedures
- Confirming targeted therapy
- Allowing early diagnosis, avoiding multiple hospital appointments/procedures
- Avoiding irreversible harm
- Allowing discharge from follow up for a risk family members

As noted in the interviews, the development of diagnostic and genetic testing cannot be directly linked to the Regulation. The human genome project in the '90s and consequent scientific advances have been pivotal in the development of new diagnostics. However, according to the interviews with research groups, the increased EU focus on rare diseases was crucial to motivating this research and in encouraging its commercialisation. In particular, at the end of 2014, there were tests for 2,557 genes and 3,378 rare diseases (see **Error! Reference source not found.** below).

Table 17: Impact of the Regulation on the number of diagnostic tests[111]

Availability of genetic testing for rare diseases in the EU
At the end of 2014 there were 1,674 laboratories registered in Orphanet in Europe, providing tests for 2,557 genes and 3,378 diseases. This has increased significantly since the Regulation, however, the Orphanet data also demonstrates the significant differences between countries of comparable size, for example: • Germany (testing for 2,116 rare diseases-associated genes) • Spain (1,708 genes) • France (1,579 genes) • Italy (1,148 genes)

- United Kingdom (896 genes).

For medium and smaller-sized countries the extent of genetic testing also varies substantially, ranging from 18 to 1,171 genes tested. Furthermore, as of December 2014, 915 rare diseases – 27% of the diseases for which a genetic test exists – can only be tested for in laboratories located in one country in Europe.

Source: Commission Expert Group on Rare Diseases

OMPs improve the efficiency of the healthcare systems

In addition to providing better diagnosis and treatment options for patients, OMPs could also improve the efficiency of the healthcare system. OMPs treat some of the severest diseases that without treatment impose significant costs on the healthcare system.

The academic evidence analysing improvements in healthcare efficiency due to the OMPs encouraged by the Regulation is relatively weak. However, using the sample of case studies developed above, there are examples where this is the case. A recent study shows that 89% of patients with rare diseases require hospitalisation, with an average duration of 19 days a year, and 60% of patients with rare diseases are highly dependent on others to help them in their daily activities.[112] OMPs can displace hospital costs by reducing the average hospitalisation associated to some rare diseases (Table 18).[xxxvii]

Table 18: Impact of the Regulation on the efficiency of the healthcare system

OMPs (year of approval)	Disease area	Impact of OMPs
Gazyvaro (2016)	Chronic Lymphocytic Leukemia (CLL)	Based on a 39% reduction in numbers of refractory patients treated with Gazyvaro (in combination with chlorambucil) compared to rituximab (in combination with chlorambucil) cost savings per year per patient (in Germany) range between €2,555 and €8,318, which leads to maximum cost savings for the whole eligible population (1,302 patients in 2013) up to €10,830,036.[113]
Lenvima (2015)	Differentiated thyroid carcinoma (DTC)	Lenvima had evidence showing potential cost savings due to fewer hospitalisation and physicians visits. On average there were judged to be judged significant.[114]
Cresemba (2015)	Invasive Aspergillosis	Base case analysis showed that Cresemba was associated with a $7,418 lower total cost per patient than voriconazole. In both incremental costs per death avoided and incremental costs per additional clinical responder, Cresemba dominated voriconazole.[115]

Source: CRA analysis

xxxvii We reviewed data from OMPs approved since 2015 and included international studies when EU data are not available.

4.3. Conclusion

In this chapter, we have shown that:

- **The Regulation has fostered treatments for many patients with rare diseases.** In 2006, the Commission found that more than 1 million patients suffering from rare diseases in the EU might potentially benefit from the availability of these new treatments authorised since the Regulation came into force. We have updated this estimate. In 2017, 7 million EU patients have diseases where OMP medicines have received a marketing authorisation. This demonstrates the scale of the improvement for patients with rare diseases but we note that these medicines may not be effective for all patients with the disease and not all patients have effective access to these treatments. There is considerable variation in terms of access to treatment in Europe. Access however is a national competence is and cannot be attributed to the Regulation.
- **Since the Regulation was implemented, new tests have been developed that improve the diagnosis of rare diseases**. Although the information derived from understanding of human genome in the '90s have been pivotal in the development of new diagnostics, the increased focus on rare diseases in Europe played a role in motivating this research and its commercialisation (at the end of 2014, there were tests for 2,557 genes and 3,378 rare diseases).
- **The Regulation and the consequently increased awareness around rare diseases helped patient organisations in the EU to expand their activities**.
- **The Regulation led to new resources** (e.g. Orphanet) for physicians and increased development of clinical practice guidelines for rare diseases.
- **The Regulation has also established a favourable legislative environment for policies on rare diseases**. In particular, it supported the development of National Rare Disease Plans. This further encouraged awareness about rare diseases, the development of registries creating a self-reinforcing environment.

All these activities fostered by the Regulation had implications for the society:

- There are many case studies showing the benefit of OMPs in terms of survival. For many life-threatening rare diseases, OMPs improve life expectancy by several years, in some cases offering near normal life expectancy to people with otherwise life-limiting conditions or they provide a significant improvement in survival, even though life expectancy remains short.
- OMPs improve patients' and caregivers' quality of life (e.g. OMPs help to reduce the pain, discomfort and anxiety associated with rare diseases and allow patients and their families to enjoy normal lives, such as planning family activities or holidays).
- OMPs can also provide wider benefits to the healthcare system, delivering off-setting savings in healthcare expenditure by reducing the average period of hospitalisation. There are recent case studies illustrating this but it is not the case for all products.

5. Economic impact of the Regulation

In addition to benefiting the patients' health and the society by supporting the development of OMPs, the Regulation could also have had an impact on the economy, through its impacts on the European R&D environment for large and smaller companies, on fostering the growth of SMEs and jobs,[xxxviii] and on the productivity of patients.

The objective of this chapter is therefore to consider the economic impact of the Regulation and, when available, compare recent findings with the statistics reported in the previous studies.

5.1. Impact on European R&D environment

Beyond the impact on clinical trials (discussed in Chapter 3) the Regulation could have encouraged a more fundamental change in the research environment and impacted on basic research. The Regulation required Member States to introduce incentives for research in their countries.[116] This could also result from pull-factors, as the prospect of commercialising products encourages clinical development or the creation of research groups, which further creates an environment that encourages basic research. Table 19 lists the indicators that can be used to analyse this impact.

Table 19: Indicators capturing the impact of the Regulation on the environment for R&D (* denotes an indicator suggested by Commission or OHE)

Area of impact	Impact	Possible indicators
Impact on the environment for R&D	How has research and development been impacted?	• Number of research projects initiated for rare diseases* • Number of EU-funded research projects* • Number of scientific publications* • Number of companies with compounds in development*
	How has the coordination and innovation ecosystem been impacted?	• Number of centres of excellence* • Number of rare disease research networks • Number of public–private partnerships between industry sponsored clinical research and academia • International cooperation of the EMA on OMPs

Source: CRA

xxxviii We explicitly looked at SMEs as promotion of SMEs activities is considered a key economic objective by the European Commission. According to the EC, SMEs represent 99% of all businesses in the EU and they are the backbone of its economy. They generate 2 out of every 3 jobs. In 2013, over 21 million SMEs provided almost 90 million jobs throughout the EU. They stimulate a sense of entrepreneurship and innovation, helping to foster European competitiveness, economic growth and employment. Source: EC website [last access]: http://eur-lex.europa.eu/summary/EN/n26026

5.1.1. Impact on European research

The increase in R&D on genetic diseases and specifically rare diseases reflects advances in scientific understanding. As noted in the previous chapter, the increased understanding of genomics opened up many different research avenues relevant for rare disease, as most rare diseases are genetic disorders. This resulted in a better understanding of common disease mechanisms and research into potential medicines and improvement in testing possibilities for many rare diseases.[117]

However, according to our interviews with the industry and the centres of excellence, in addition to supporting clinical development of OMPs, the Regulation contributed to changing the environment for R&D by creating a favourable environment for basic research and the establishment of research networks.[xxxix]

Research projects for rare diseases increased after the Regulation

The 2010 OHE report found that there were, or had been, 15,208 funded research projects in the EU Member States in 2010 (however, the data did not allow the information to be stratified by calendar year). Although we could not access more recent European statistics, the Orphanet data is available for Italy: this shows a positive trend with annual research projects increasing from 650 in 2001 to 820 by 2015.

Interviews with centres of excellence support the idea that the Regulation helped to develop a favourable environment for funding EU research. For instance, in October 2010, the European Commission and the US National Institutes of Health announced their intention to join forces on rare diseases research. The two institutions planned to coordinate their research funding on rare diseases and to make major investments in this research field in the years to come. The International Rare Diseases Research Consortium (IRDiRC) was established in 2011 and teamed up researchers and organisations investing in rare diseases research in order to achieve two main objectives by the year 2020, namely to deliver 200 new therapies for rare diseases and means to diagnose most rare diseases.[118]

EU funding of basic research projects increased after the Regulation

Funding is available from the European Commission and other sources to support research in rare diseases. For instance:

- Horizon 2020, the EU Framework Programme for Research and Innovation specifically covering new therapies for rare diseases in Work Programme 2016–2017[119]
- E-Rare, a European transnational project for research programmes on rare diseases (which collaborates with the above EU Framework Programme).[120]

The EU has also demonstrated a strong commitment to rare diseases research through the EU Framework Programme for Research and Innovation. Under the Seventh Framework Programme for research (2007–2013), over €620 million in support was

xxxix In practice, both factors are likely to be true and created a virtuous circle, where the Regulation supported the advances in scientific understanding and vice versa. It is therefore impossible to unpick the relative importance of the Regulation and the changes in underlying scientific opportunities.

granted to more than 120 collaborative research projects in rare diseases. Compared to FP5, which operated from 1998-2002, investment in research for Rare Diseases increased considerably (Table 20).

Table 20: Public investment in research for Rare Diseases

Initiative	Public investment in research for Rare Diseases	Number of projects
FP5 (1998-2002)	€64 million	47
FP6 (2003-2006)	€230 million	59
FP7 (2007-2013)	€620 million	120
Horizon 2020 (2014-2016 period only)	€220 million *[€510 million*]*	40 *[90*]*
*Project impact on the 2014-2020 period assuming constant investment rate		

Source: CRA analysis from EC data

The funding allowed the formation of multidisciplinary teams with members from universities, research organisations, industry, and patient organisations from across Europe and beyond.[121] However, we cannot find any direct link between the increase in funding and the Regulation. However, it is the case that rare diseases companies who achieved funding under the Framework Programme were then able to use this to access other funding sources.[122]

The 2010 OHE report showed that, after the implementation of the Regulation, EU-funded basic research projects for rare diseases over the period 2000–2005 (when data was available) had remained relatively stable, although the average value of the projects funded, in financial terms, increased significantly over time. Although based on a different dataset,[xl] a selection of funded activities shows that the average size of the EU-funded projects for basic research, and the EU funding per project has increased considerably in the period 2007-2013 (Table 21).

Table 21: EU-funded basic research projects for rare diseases: 2000–2004 compared to 2007-2013

Year	Funded projects	Grant / subsidy per project (€)
Average 2000-2004	***5.8***	***379,310***
Average 2007-2013[123]	***14.4***	***4.42 million***

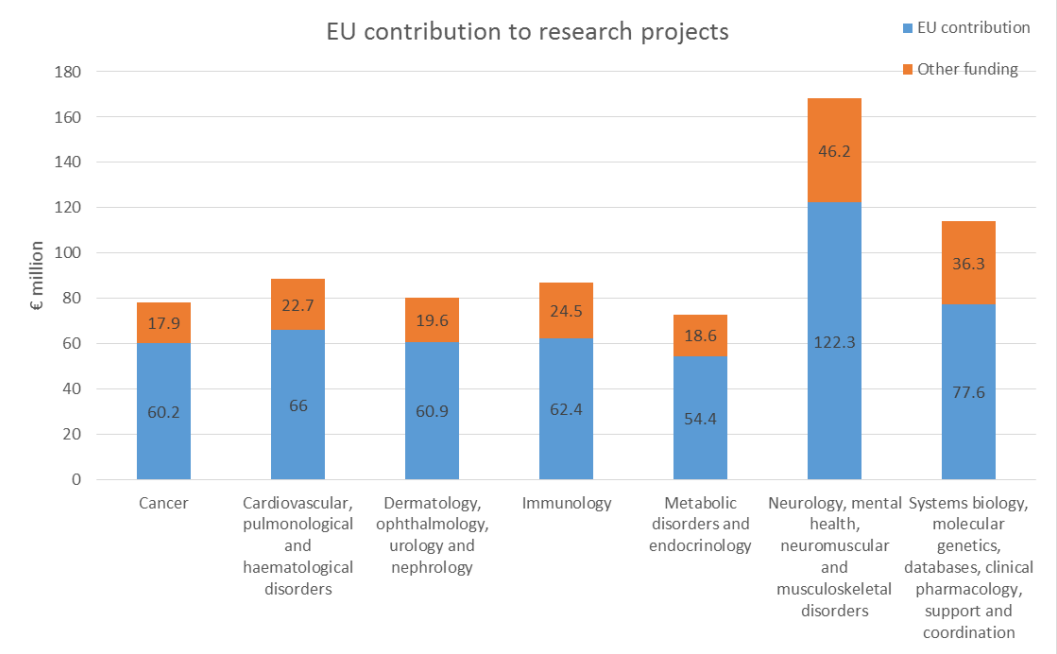
Source: 2010 OHE report and CRA analysis from EC data

Indeed, the EU funds provided after the Regulation are responsible for funding over 70% of the cost of several basic research projects in different disease areas (Figure 14) in

xl The EC dataset does not provide the breakdown of the funding per year; however, the total funding per project is available.

Europe. It is important to note that basic research is applicable to a very broad range of therapy areas (i.e. it is not disease specific) and is useful only when combined with other, disease-specific research.

Figure 14: EU contribution to basic research projects in rare diseases (2007–2013)[124]



Note: Other funding refers to non-EU contributions (i.e. funding from individual Member States), funding from charitable organisations and private funding.

Source: CRA analysis from EC data

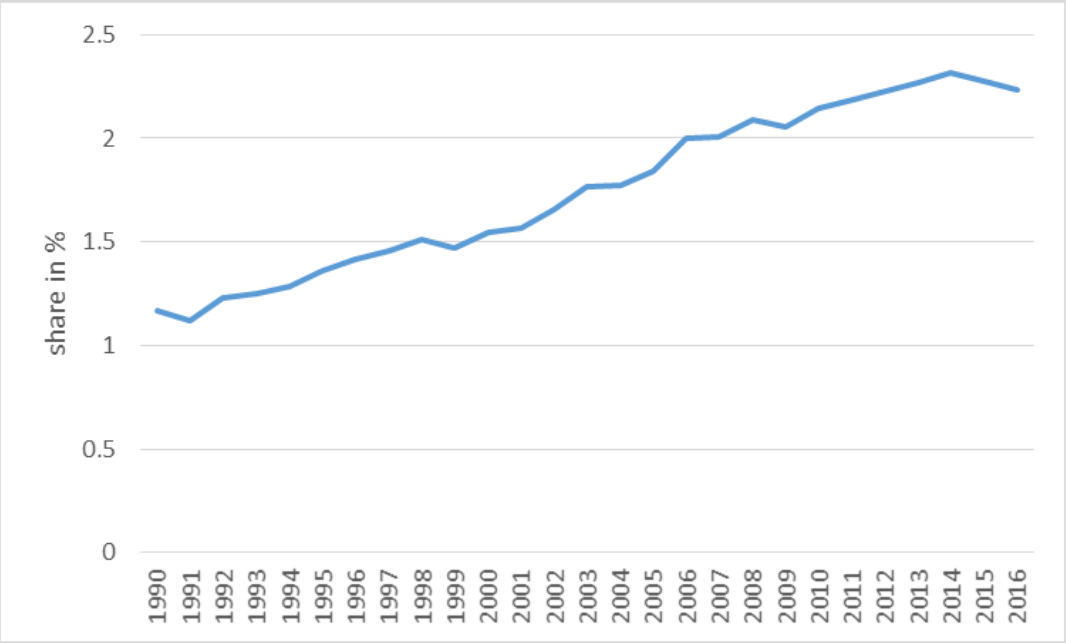
The Regulation impacted the number of scientific publications

The 2010 OHE report suggested looking at the number of scientific publications but did not provide any relevant data. However, a bibliometric study by Heemstra et al. evaluated the scientific output of a large group of rare diseases.[125] The disease dataset consisted of 588 rare diseases, distributed over 3 prevalence classes. For each disease, the study determined the number of publications in four time periods: 1976–1983, 1984–1991, 1992–1999 and 2000–2007. The average number of publications per disease increased over time for all 588 diseases in the study, from 330 publications in the period 1976–1983 to 1,319 publications in the period 2000–2007, indicating a consistent increase in scientific output from 1976 to 2007. However, comparison with the general increase in number of publications on overall biomedical research from 1976 to 2007 reveals that the observed increase is not statistically different from the general trend.

We have updated this analysis using data up to 2016 but used a more simplistic approach. Whereas Heemstra et al. looked at a range of therapy areas, we have counted

the number of articles with a range of key words.[xli] We found that the number of scientific publications on rare diseases as a proportion of the total number of publications has significantly[xlii] increased over the years (Figure 15).

Figure 15: Estimation of the share of scientific publications on rare diseases as a percentage of all scientific publications



Source: CRA analysis of PubMed data. Note the analysis is based on a simplistic approach.

We also found that the worldwide number of scientific publications on rare diseases has statistically significantly[xliii] increased since the implementation of the EU Regulation in 2000 (Figure 16).[xliv]

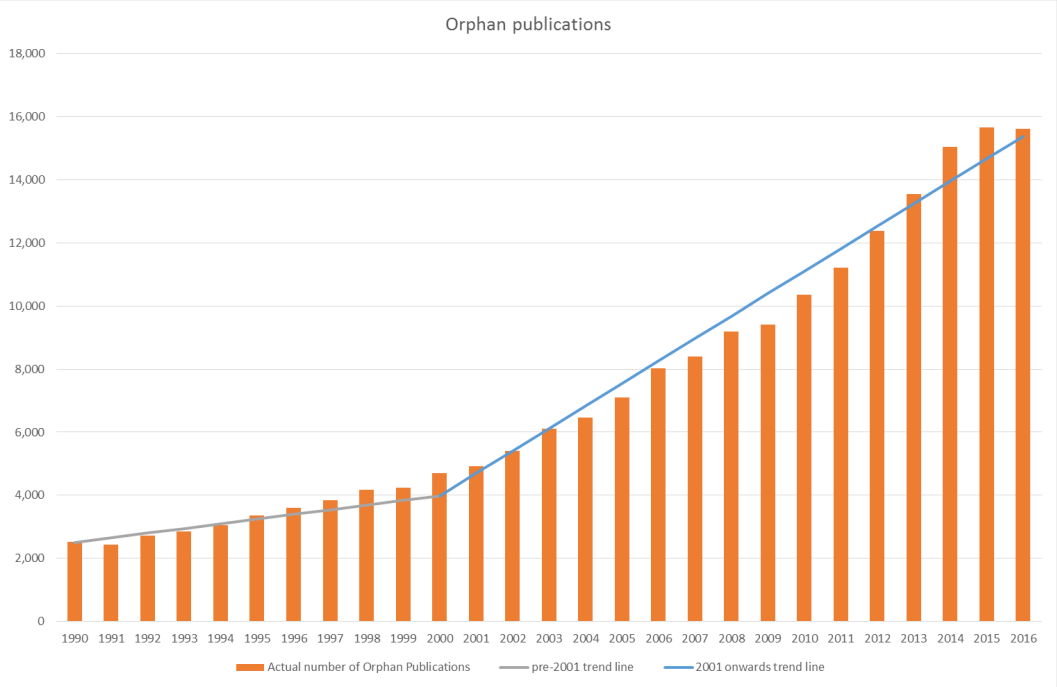
xli Data include publications between 1990 and 2016 that contain combinations of key words such as: "rare disease"; "rare condition"; "rare cancer"; "orphan medicine"; "orphan drug"; "rare disorder"; "rare mutation" in the title or abstract. Our sample is therefore a subset of the sample considered by Heemstra but consistent over time.

xlii The average share of orphan publications out of all scientific publications is 1.75% and is significant at the 1% level.

xliii Pre–2001, there is an average yearly increase of 147 publications at a 1% significance level. From 2001 onwards there is an average yearly increase of 565 publications at a 1% significance level.

xliv There are a number of caveats to this type of analysis. It is not possible to show any causality to the Regulation apart from any change at the time of introduction. It is not possible to allocate these to European research. In reality, research is often conducted in international teams and papers are jointly authored by academics from different regions. This is therefore only a proxy for the amount of research.

Figure 16: Scientific publications on rare diseases[xlv]



Source: CRA analysis of PubMed data

However, as noted above, we cannot attribute this entirely to the Regulation (although the Regulation certainly contributed to creating a favourable environment for the scientific development). 80% of rare diseases have a genetic origin[126] and the fully decoded genome sequence was released in June 2000 creating a huge number of research opportunities.[127] The increase in publications was made possible by the scientific advances, however, the Regulation played a crucial role (in pulling through the scientific activity) and was timely in ensuring this led to the development of OMPs benefiting patients.

Number of companies researching OMPs

The amount invested in R&D for OMPs is an obvious indicator. Based on the information provided in a confidential survey, the 2010 OHE report found that the increase in OMP R&D investment in the EU is considerable. Between 2000 and 2004, OMP R&D investment in Europe increased by more than one half (51%), and more than doubled between 2004 and 2008 (104% increase). Over the entire 2000–2008 period, the growth was 209%.[xlvi] In absolute terms this increased from €150 million in 2000 to over €490 million in 2008. However, it is important to note that the results only represent 18 out of

xlv Data include publications between 1990 and 2016 that contain combinations of key words such as: “rare disease”; “rare condition”; “rare cancer”; “orphan medicine”; “orphan drug”; “rare disorder”; “rare mutation” in the title or abstract.

xlvi In absolute terms this increased from €150 million in 2000 to over €490 million in 2008. However, it is important to note that the results only represent 18 out of the 51 companies who were sent the survey and therefore is likely to represent a significant under-estimate of the level of R&D in Europe. Given this, it is not a sound basis to extrapolate changes in R&D over the last seven years.

the 51 companies who were sent the survey and therefore is likely to represent a significant under-estimate of the level of R&D in Europe. We have not been able to collect up to date data on the amount of investment undertaken in the EU and the 2006 estimates do not provide a sound basis to extrapolate changes in R&D over the last seven years.

An alternative is to look at the number of companies. Given the change in the R&D environment, this could encourage the development of companies in Europe or companies to set up European affiliates. The 2010 OHE study found that as of September 2008, 33 companies with EU headquarters were lead partner in the development of medicines for rare diseases (considering 10 EU Member States). As of May 2017, we found[xlvii] that OMP research activity in Europe as measured by the number of companies has increased considerably (considering the 28 Member States): 298 companies with EU headquarters are undertaking some OMP activity and 142 companies have an OMP compound in clinical development (i.e. Phase I or later); 23 companies are reported as exclusively researching OMPs (Table 22).

Table 22: Orientation of OMP R&D activity[xlviii]

Indicator	EU Total # (%)	US Total # (%)	Worldwide Total # (%)
Companies analysed	2,751	4,669	10,287
Companies with orphan designation activity	298 (10.8%)	492 (10.5%)	927 (9%)
Companies with OMP compounds in development	142 (5%)	139 (3%)	336 (3.3%)

Note: The EvaluatePharma dataset identified all products that have orphan medicine designations filed in the US, EU or Japan. Given the different definitions of OMPs, any comparisons between EU and US statistics can only be indicative.

Source: CRA analysis of EvaluatePharma

5.1.2. Impact on coordination and innovation ecosystem

The Regulation helped establish centres of excellence and rare diseases research networks

The 2010 OHE report found that, as of 2005, in terms of specialist centres for rare diseases, France, with 296, was the country with the highest number of them, followed by Italy and Germany, with 186 and 129 respectively. Although we again rely on different dataset making a direct comparison challenging; we can make a comparison for some

xlvii We used the EvaluatePharma dataset, which has some limitations.

xlviii The analysis considers the pharmaceutical companies tracked by EvaluatePharma, considering the headquarters of the parent company.

countries. The available data for Italy show that the number of specialist centres has increased considerably in recent years (from 186 in 2005 to 1028 in 2015).[xlix] In France, it has also been reported that in 2013 there were over 600 centres that coordinated research, trained HCPs, and facilitated diagnoses.[128]

Interviews with patient organisations highlighted that centres of excellence have been developed as a result of the favourable legislative environment that the Regulation has created in the EU. The concept of dedicated and comprehensive centres for rare diseases was originally developed by France for its first National Rare Disease Plan (NRDP).[129] In addition, EUCERD (see Table 23) issued recommendations on quality criteria for Rare Disease Centres of Excellence in EU Member States as a core element of all National Plans on rare diseases that the MS were encouraged to adopt by the end of 2013.[130] While many Member States already had provisions in place for national networks of Rare Disease Centres, this initiative resulted in significant progress in some countries. For example in Bulgaria, where the Ministry of Health established a working group, which prepared a draft regulation, containing criteria for designation of centres of expertise and reference networks for rare diseases, as well as rules and procedures for their implementation, monitoring and evaluation.[131]

Table 23: The establishment of EUCERD

The European Union Committee of Experts on Rare Diseases (EUCERD)
In 2009, the Commission established the European Union Committee of Experts on Rare Diseases (EUCERD) by Decision (2009/872/EC).[132] The committee was charged with aiding the European Commission with the implementation of activities in the field of rare diseases at EU and Member State level, including enhancing research for rare diseases and identifying centres of excellence by the end of 2013 and fostering their participation in European Reference Networks.[133] EUCERD was then replaced by the European Commission Expert Group on Rare Diseases from 2014 onwards.[134]

The European Reference Networks (ERNs)

In 2014, the EU issued criteria for designating European Reference Networks (ERNs) across the EU for treating rare medical conditions.[135] ERNs are virtual networks involving healthcare providers across Europe, which aim to tackle complex or rare diseases and conditions that require highly specialised treatment and concentrated knowledge and resources.[136] The creation of ERNs has been described as essential, both to share knowledge and to identify where patients should go when expertise is unavailable in their home country.[137] This is however a recent trend. The first ERNs were launched in March 2017, involving more than 900 highly specialised healthcare units from over 300 hospitals in 26 Member States. There are now 24 ERNs working on a range of thematic issues including bone disorders, childhood cancer and immunodeficiency.[138]

xlix For Italy only, Orphanet provides reports [in Italian] indicating the number of specialist centres. Source: Orphanet website [last access 5 July 2017]: http://www.orpha.net/consor/cgi-bin/Education.php?lng=EN

However, there are several examples of initiatives being driven to help develop networks for particular rare diseases:

- ECORN-CF was initiated in 2007 with funding from the EU as a pilot project, to build a model of a 'European Centres of Reference Network for Cystic Fibrosis' (ECORN-CF).
- CARE-NMD is an EU-funded project to implement best-practice standards of care for Duchenne Muscular Dystrophy (DMD) across Europe, by bringing together a network of leading care centres. The project ran from 2010 to 2013 to implement newly agreed international consensus care recommendations and evaluate their impact on patients' quality of life. Results of the program were illustrated in a cross-sectional survey of 1,677 patients contacted via the TREAT-NMD patient registries, showing that neuromuscular centre care shortened unplanned hospital stays and provided care according to standard guidelines, which ultimately prolonged the ambulatory phase in DMD patients.[139]

The establishment of the ERNs responds to the need highlighted in a technical and scientific report from an expert group of the rare diseases Task Force of the Commission.[140] The report identified three categories of countries: those which had a specific policy regarding rare diseases and have established centres of reference in this framework (Bulgaria, Denmark, France, Italy, Spain, Sweden); those which had established centres of reference but not specifically for rare diseases (Belgium, Czech Republic, Finland, Greece, Ireland, UK) and those which have no centres with these denominations, although they have centres with all the characteristics of a centre of reference (Austria, Cyprus, Estonia, Germany, Hungary, Lithuania, Netherlands, Poland). The recommendation of the report was that "networks of centres of expertise are identified and funded at European level." Interviewees also supported the idea that research networks will help reduce inequalities across Member States and this initiative would not have been developed in the absence of the Regulation providing the framework for developing OMPs.

Impact on industry–academia collaboration

Although not analysed in previous studies, it was noted in the interviews with the industry and centres of excellence that the introduction of policies for OMPs in both the US and Europe has encouraged large-scale collaborations between profit and non-profit organisations to foster greater research opportunities. For example, as discussed above, the International Rare Diseases Research Consortium (IRDiRC) was launched in April 2011 at the initiative of the European Commission and the National Institutes of Health (US) to foster international collaboration in rare diseases research and includes members from industry, government organisations, research institutions, and patient advocacy groups.[141]

Impact on international cooperation facilitating research

As noted in the 2006 report from the Commission, on an international level, the COMP has developed an international liaison with medicines agencies in North America and Japan on orphan medicinal products, and at the same time the COMP has cooperated with the World Health Organization (WHO) and other NGOs on neglected diseases.[142] Since then, the international collaboration between regulators has further developed. The EMA has established regular contacts with the Office for Orphan Products Development

of the FDA (OOPD FDA) and the Japanese authorities (PMDA and MHLW). The purpose of these contracts is to facilitate exchange of information and discussion of regulatory issues in order to respond to the globalisation of product development and research.[143] In particular:

- EU–US collaboration in the field of OMPs. The EU, including the European Commission and the European Medicines Agency, has had arrangements with the United States Food and Drug Administration (FDA) since September 2003. As part of this arrangement, the EMA and the FDA launched several joint initiatives to increase collaboration in the field of OMPs: as a result, more than 80% of the applications for orphan designation have been using the EMA/FDA common application form, which is facilitating parallel submission and decreasing the administrative burden for sponsors.
- Agreement with Japan (2012). Under the arrangement, advance drafts of legislation and regulatory guidance documents, scientific advice on medicine development, assessments of applications for marketing authorisations and information concerning the safety of marketed medicines may be exchanged between the two agencies, reducing the duplication of effort (22% of the submissions for OMPs have been made in parallel).

According to the interviews, these agreements and collaborations have reduced the burden of authorisation process and supported a faster approval of OMPs.

5.2. Impact on growth and employment

To consider the impact on growth and employment, we have first looked at the evidence on SMEs and then consider the wider implications for employment. This impact was not analysed in previous studies.

In particular, interviews with the industry supported the idea that the Regulation was crucial to the establishment of SMEs researching OMPs in the EU. This section analyses a series of indicators to measure this impact (Table 24).

Table 24: Indicators capturing the impact of the Regulation growth and employment for SMEs

Area of impact	Impact	Possible indicators
Impact on growth and employment for SMEs	How has the Regulation affected EU SMEs researching OMPs?	• Number of SMEs involved in OMP development • Number of people employed in OMP-related activities in Europe

Source: CRA

Creation of SMEs

In terms of stimulated economic growth, the European Commission places considerable attention on the creation and development of SMEs.[144] It has been reported that in the EU, many applications for orphan designations come from young or start-up companies, sometimes created to develop orphan medicines as their first products – as a direct result of the EU OMP Regulation.[145] Here we examine the impact of the OMP Regulation on

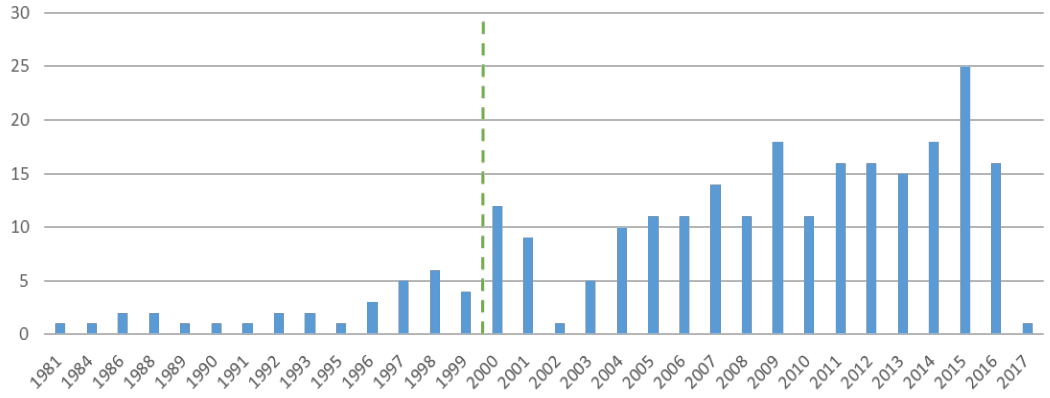
SMEs through the number of orphan designations belonging to SMEs and the ability of the Regulation to foster innovation and encourage development of SMEs.[l]

The number of SMEs

Based on the interviews everyone agrees that small companies play an important role in the development of OMPs (and are responsible for a large percentage of the orphan designations). SMEs can benefit from specific rules when developing medicines with orphan designation, including administrative and procedural assistance from the Agency's SME office and fee reductions.[146] As of May 2017, the SME Office reports 1,233 companies registered in human medicine development, with 252 registered under the development of Orphan medicines in accordance with the OMP Regulation (EC) No 141/2000.[147]

Within the first decade following the implementation of the OMP Regulation, there was a 30% increase in new biotech companies involved in OMP development across Europe.[148] Most companies that have started developing OMPs after 2000 focus solely on discovering and developing orphan medicines. Moreover, nearly all of these companies have their R&D activities and staff located in the EU.[149] This trend has continued. An analysis of the 252 companies within the EMA SME register shows that 220 were created after the OMP Regulation came into place (Figure 17). The majority of start-ups have been created more recently: 25 were created in 2015.

Figure 17: Creation date of small and medium-sized enterprises focusing on orphans under the OMP Regulation[li]



Note: the analysis of the data and a search of the literature did not provide any explanations for why the figure for 2002 is considerably smaller compared to the other years – a possible explanation could be that most SMEs anticipated the benefits of the Regulation and accelerated the establishment process in 2000 and 2001.

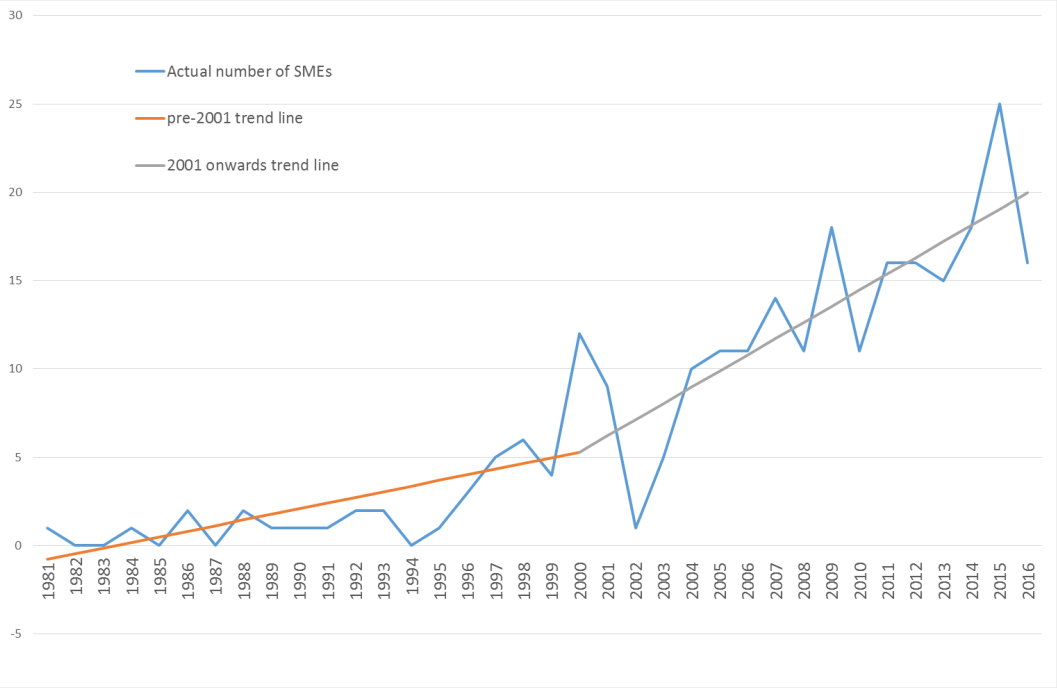
Source: CRA analysis of EMA SME Register

l It is however important to mention that larger companies have established orphan R&D dedicated units as a result of the Regulation.

li Data up to end May 2017 for registration of companies in SME database. No information available to suggest reasoning for decline in companies created in 2002.

In particular, there is a statistically significant[lii] increase in the number of SMEs researching OMPs after 2000 (Figure 18).

Figure 18: Trend in the per-year creation of SMEs developing OMPs



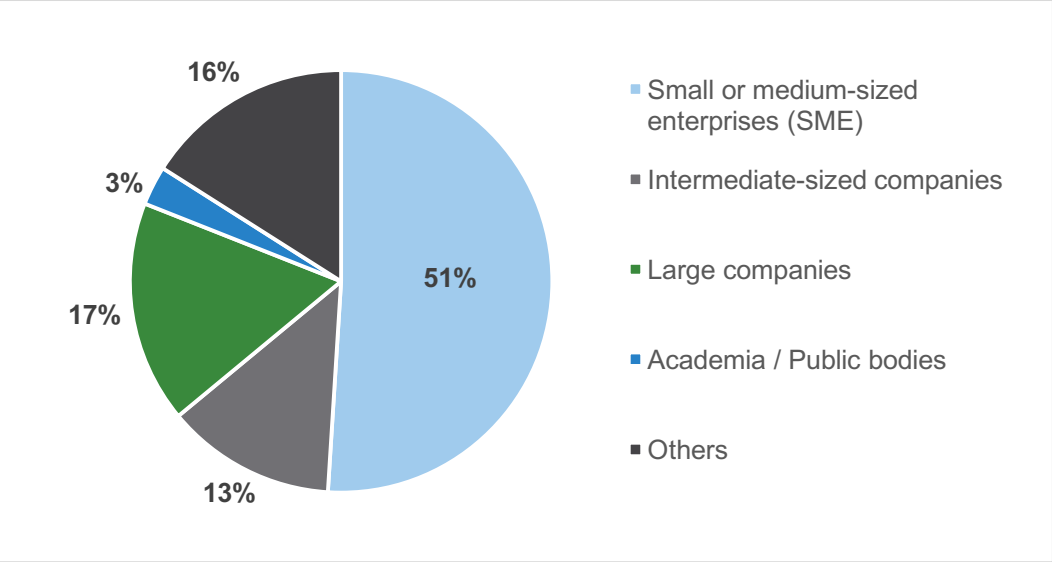
Source: CRA analysis of EMA SME Register

Types of manufacturers with orphan designations

In terms of disease areas covered by SMEs, a recent study of 502 orphan designations for the period between 2002 and 2012 illustrated SMEs were responsible for more than half of the designations for rare neoplastic disorders and, although they also compose the largest category of applicants for other rare conditions, their involvement was significantly lower compared to in rare neoplastic disorders.[150] Overall, over 50% of orphan designations belonged to SMEs (Figure 19) – however, it should be noted that companies may have lost their SME status once the designated OMP obtain regulatory approval and start generating sales.

lii There is a yearly increase of 0.3 orphan SMEs pre–2001 at a 1% significance level, though post–2001 there is a yearly increase of an additional 0.6 orphan SMEs at a 1% significance level.

Figure 19: Types of manufacturers with orphan designations in ongoing development (2002–2012, n=502)[151]



Source: CRA analysis of Nature

In 2015, the number of protocol assistance procedures for orphan medicines developed by SMEs represented 44% of all protocol assistance procedures.[liii,152] For orphan-designated medicines, the scope of protocol assistance often related to the demonstration of significant benefit, a key aspect of the evaluation of marketing authorisations for orphan-designated products.

The funding of SME

Based on the interviews, the orphan designation process is often an important signal for investors, indicating that the OMP Regulation has been particularly useful for securing venture capital funding. Throughout the designation application process there are frequent conversations with investors, and the timing of the orphan application becomes a crucial part of the company's development strategy from an investment perspective.[153] The certification of orphan designation serves as a strong quality signal to investors in a number of ways:

- It provides observable information, providing some certification to the investors.
- It helps differentiate between companies allowing the investing firm to finance innovations at an earlier stage. Studies have shown that venture capitalists investing in OMP start-ups typically do so on average one year before non-orphan-designated medicines.[154]

liii This statistic is broadly compatible with the fact that SMEs are responsible for over 50% of the orphan designations. The lower number is likely due to larger companies taking over the development of OMPs as the product develops, as well as the awareness of regulatory process, such as protocol assistance, being lower for SMEs.

- It is indicative that the asset will have market exclusivity which is seen as helpful in determining whether it will be able to recover the cost of investment and achieve an adequate return.[155]

We might therefore expect the amount of venture capital funding to increase following the Regulation. However, we could not find statistics on funding in Europe specifically for companies involved in rare diseases.

Impact on employment

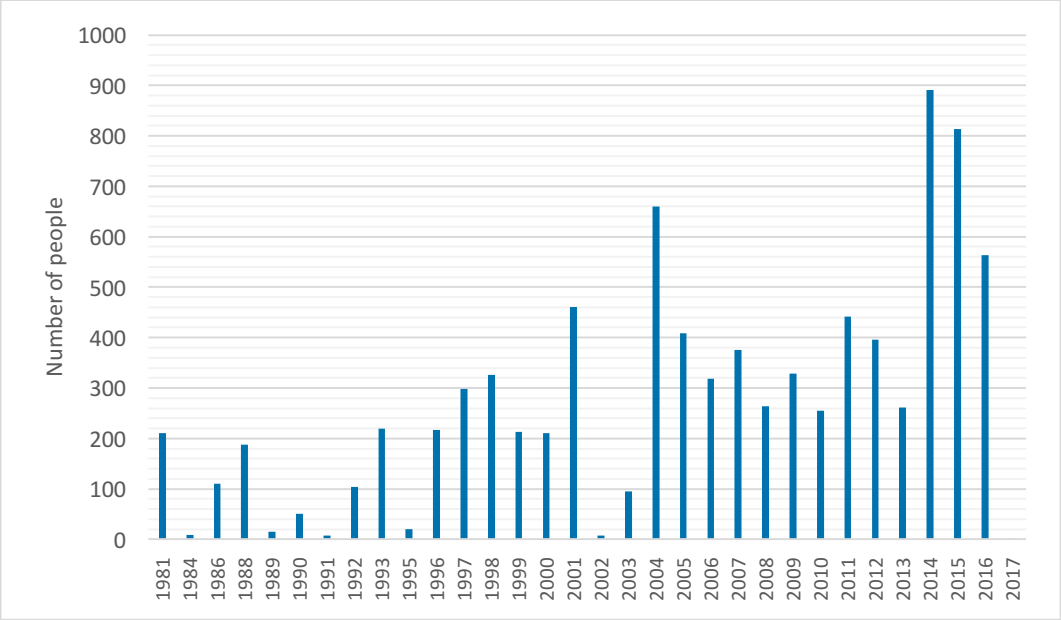
The initial 5-year review by the European Commission first examined the economic impact of the Regulation in terms of growth, jobs and innovation. It explained that although reliable statistics related specifically to OMP investments and their economic benefits were not yet available, some preliminary indications of broad trends could be observed.[156] The review identified that jobs related to OMPs seemed to have increased at a faster pace than general industry trends, in both R&D and commercial areas, as companies producing orphan medicines proceeded to bring their products to the market. According to the 2006 Commission study, all the companies surveyed had increased their total number of employees in the EU by 43% on average between 2000 and 2004. In 2010, the OHE examined employment trends and found that employment in OMP-related activities across Europe more than doubled between 2000 and 2008, with a 158% increase.[157] In absolute terms, this was an increase from 2,046 to 5,285 employees (full-time equivalent).

Since then there have been no studies to identify how employment in OMP-related activities has changed across Europe. However, we can examine the impact on changes in employment in SMEs. Collectively, the 252 SMEs involved in orphan medicine development employ 8,739 people.[liv] Of these, 77% are employed in SMEs that were created after the OMP Regulation came into force in 2000 (Figure 20). This growth has continued (although erratically over time) with 25% employed by companies created since 2014.

We have not been able to estimate the number of employees in larger pharmaceutical companies. It is tempting to use the growth in employment in SME as a proxy for growth in the industry as a whole. However, given the changes in industry structure, for example, the role of contract research organisations and the out-sourcing of some elements of development, the rate of growth in SMEs is unlikely to be comparable to that in large pharmaceutical companies. Nonetheless, based on interviews, the formation of rare disease groups within larger pharmaceutical companies and increased activity in rare diseases has created more jobs in large companies as well.

liv According to data from the SME office as of May 2017. This figure is not directly comparable with the findings in the 2010 OHE study as based on a different dataset.

Figure 20: Number of people employed in SMEs focusing on orphan medicinal products by SME creation date



Note: companies may have lost their SME status once the designated OMP obtain regulatory approval and start generating sales.

Source: CRA analysis

5.3. Impact on the productivity of patients

Finally, although a different kind of economic contribution, the Regulation could have contributed through improving the health of patients. Interviews with patient organisations supported the idea that OMPs increase patient productivity by diminishing the burden of the disease on patients and on carers and families. We need to return to the case studies developed in Chapter 4 (i.e. the analysis of OMPs approved since 2015) to investigate this (Table 25).

Table 25: Indicators capturing the impact of the Regulation on productivity and efficiency

Area of Impact	Impact	Possible indicators
Impact on productivity and efficiency	Is there an increase in productivity?	• Case Studies of increase in patients' productivity • Case Studies of increase in caregivers' productivity

Source: CRA analysis

OMPs increase patients' productivity

In addition to patients' health, OMPs also have a wider impact on the society. Given most rare diseases are severe, often genetic, and particularly likely to affect children, we should not necessarily expect large increases in the number of patients who can return to or continue in employment. However, for some OMPs there has been dramatic

improvement in patients' health status, often allowing them and their caregivers to go back to work[158] (Table 26).

Table 26: Impact of the Regulation on patients' productivity

OMPs (year of approval)	Disease area	Impact of OMPs
Galafold (2016)	Fabry disease	Galafold stabilises kidney function to the same extent as enzyme replacement therapy (ERT) but is administered in oral form rather than by infusion. ERT infusions every 2 weeks can have a major impact on a person's home and work life. An oral treatment allows people with Fabry disease freedom from these frequent infusions and allows them to save the time needed to attend the hospital for the infusions (and dedicate it to other activities, including work).[159]
Wakix (2016)	Narcolepsy	Treating patients with Wakix reduced the weekly cataplexy rate by 75% (compared to 38% of those patients who received placebo) and other symptoms of the disease such as hallucinations and enhanced patients' assessment of their quality of life, increasing their productivity.[160]
Blincyto (2015)	Precursor B-acute lymphoblastic leukaemia (Ph- B-precursor ALL)	Adult patients diagnosed with Ph- B-precursor ALL have a median age of 34 to 39 years and dying, on average, 30 years prematurely. These life years lost (YLL) estimate far exceeds those seen in other more common haematological and solid tumour malignancies, such as chronic lymphocytic leukaemia (10 years), prostate (6 years), colorectal (10 years), lung (12 years) and breast (14 years) cancers. This means that the long-term societal and economic consequences of each premature death, including the substantial number of working years lost, are much greater than in many other oncologic diseases. Blincyto prolongs patients' lives, diminishing the societal and economic consequences of the disease.[161]
Kalydeco (2012)*	Cystic Fibrosis (CF)	A study estimated loss of labour productivity ranged from €1,094 (Bulgaria) to €12,443 (UK): if half of this productivity is recovered, this will allow substantial earning to the economic systems.[162]

**Note: although this case study predates the relevant sample, it provides a useful quantification of the economic impact of productivity loss.*

Source: CRA analysis

5.4. Conclusion

In this chapter, we have shown that:

- **The Regulation contributed to changing the landscape for R&D by creating a favourable environment for basic research and (indirectly) the recent establishment of research networks.**
- **The number of scientific publications on rare diseases has grown significantly over the years since the Regulation was implemented** (although this result can primarily be attributed to the scientific developments in genetic research, the Regulation played a role) and grown as a percentage of overall publications.
- As of May 2017, **we found that OMP research activity in Europe has increased considerably** compared to the past: 298 companies with EU headquarters are undertaking some OMP activity and 142 companies have an OMP compound in clinical development (i.e. Phase I or later); 23 companies are reported as exclusively researching OMPs.
- Within the first decade following the implementation of the OMP Regulation, there was a 30% increase in new biotech companies across Europe. **Most new companies that started developing OMPs in the first decade [after the Regulation in 2000] focused solely on discovering and developing orphan medicines** (they also expanded to non-OMP activities over time). This trend has continued, and our analysis of 252 companies within the EMA SME register shows that 220 were created after the OMP Regulation came into place.
- **Collectively, the 252 SMEs involved in orphan medicine development employ 8,739 people**. Of these, 77% are employed in SMEs that were created after the OMP Regulation came into force in 2000. We have not been able to estimate the number of employees in larger pharmaceutical companies but based on interviews, the formation of rare disease groups within larger pharmaceutical companies has created more jobs in large companies as well.
- In terms of the economic impact, the health benefits to patients should not be ignored. Although based on a small number of case studies, **effective treatments mean that patients can contribute to the labour force and increase their contribution to the economy.**

6. Conclusions

In this report we have set out the economic and societal benefits that can be associated to the Orphan Medicines Regulation. We have assumed, and this has been validated in the interviews with different stakeholders, that the Regulation encouraged and stimulated further policy action, focused on national rare disease plans and research networks.

The benefits we have identified go far beyond the numbers of clinical trials, applications, designations or even marketing authorisations (which are typically the focus of assessments of the impact of the OMP Regulation). An evidence based analysis conducted by the European Commission should consider all these benefits.

In particular, we have also shown the Regulation is associated to the following:[lv]

- A seven-fold increase in the number of patients with medicines relevant for diseases. This has led to significant benefits to patients in terms of improved mortality and quality of life.
- An increased focus on rare diseases, which has created resources for HCPs, created networks for physicians who previously operated in isolation, led to guidelines, and increased information from patient registries. Given the challenges of diagnosing patients with rare diseases, these add to the benefits to patients.
- Significant increases in collaborations and the number of scientific publications.
- There is an economic impact resulting from the number of SMEs being created, the investment in R&D and the number of employees in both SMEs and larger pharmaceutical companies and improvements in productivity.
- The encouragement of national policymakers to introduce national rare diseases plans and national policies to promote investment in R&D.

All these achievements had a life-changing impact on patients (addressing unmet need), their families and their carers, and helped mitigate other healthcare costs (through reduced hospitalisations). Beyond rare diseases, OMP Regulation has pioneered policy development in terms of developing national plans, the role of patients in marketing authorisations, and public–private collaborations to the benefit of all patients in Europe.

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lv Our analysis has drawn together the existing data but there are clearly gaps and areas where more recent and comprehensive data would be valuable. In particular, further research should focus on a number of areas:

- Analysing the impact of OMPs since 2000 was beyond the scope of this project (in terms of life expectancy, quality of life, reliance on supportive care, cost savings, productivity). Completing this database would allow us to consider trends and develop a more accurate estimate of the number of patients treated across the EU.
- Statistics on funding, particularly how venture capital funding in the EU has changed over time and how this compares to the US.
- More recent granular evidence on the activities instigated in the EU, particularly amount of OMP investment undertaken in the EU and data on OMP-related employment in the EU, would be valuable.

However, only a very small proportion of the identified rare diseases (less than 5%) have so far been addressed by OMPs. There is a risk that without incentives in place the development of new treatments for rare diseases will slow and there are still thousands of diseases and millions of people without a treatment. Continued support is a crucial signal for academics, researchers, small and large companies that rare diseases remains a priority going forward.

Annex A: Case studies

Medicine Name	Common name	Marketing Authorisation Holder	Authorisation date	Indication
Dinutuximab beta Apeiron	dinutuximab beta	Apeiron Biologics AG	08/05/2017	Dinutuximab beta Apeiron is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures. In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, Dinutuximab beta Apeiron should be combined with interleukin 2 (IL 2).
Natpar	parathyroid hormone	Shire Pharmaceuticals Ireland Ltd	24/04/2017	Natpar is indicated as adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone.
Chenodeoxycholic acid Leadiant (previously known as Chenodeoxycholic acid sigma-tau)	chenodeoxycholic acid	Leadiant GmbH	10/04/2017	Chenodeoxycholic acid is indicated for the treatment of inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis (CTX)) in infants, children and adolescents aged 1 month to 18 years and adults.
Ledaga	chlormethine	Actelion Registration Ltd.	03/03/2017	Ledaga is indicated for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients.

Cystadrops	mercaptamine	Orphan Europe S.A.R.L.	19/01/2017	Cystadrops is indicated for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis.
Ocaliva	obeticholic acid	Intercept Pharma Ltd	12/12/2016	Ocaliva is indicated for the treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.
SomaKit TOC	edotreotide	Advanced Accelerator Applications	08/12/2016	This medicinal product is for diagnostic use only.After radiolabelling with gallium (68Ga) chloride solution, the solution of gallium (68Ga) edotreotide obtained is indicated for Positron Emission Tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated gastro-enteropancreatic neuroendocrine tumours (GEP-NET) for localizing primary tumours and their metastases.
Venclyxto	venetoclax	AbbVie Ltd	05/12/2016	Venclyxto monotherapy is indicated for the treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B cell receptor pathway inhibitor. Venclyxto monotherapy is indicated for the treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B cell receptor pathway inhibitor.
Ninlaro	ixazomib	Takeda Pharma A/S	21/11/2016	Ninlaro in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple

				myeloma who have received at least one prior therapy.
Lartruvo	olaratumab	Eli Lilly Nederland B.V.	09/11/2016	Lartruvo is indicated in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin (see section 5.1).
Onivyde	irinotecan hydrochloride trihydrate	Baxalta Innovations GmbH	14/10/2016	Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5 fluorouracil (5 FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy.
Zalmoxis	allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (LNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	MolMed SpA	18/08/2016	Zalmoxis is indicated as adjunctive treatment in haploidentical haematopoietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies.
Galafold	migalastat	Amicus Therapeutics UK Ltd	26/05/2016	Galafold is indicated for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (-galactosidase A deficiency) and who have an amenable mutation.
Strimvelis	autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	GlaxoSmithKline Trading Services Limited	26/05/2016	Strimvelis is indicated for the treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available (see section 4.2 and section 4.4).
Darzalex	daratumumab	Janssen-Cilag International	20/05/2016	Darzalex is indicated:

		N.V.		as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone,for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
Alprolix	eftrenonacog alfa	Swedish Orphan Biovitrum AB (publ)	12/05/2016	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). Alprolix can be used for all age groups.
Idelvion	albutrepenonacog alfa	CSL Behring GmbH	11/05/2016	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). Idelvion can be used for all age groups.
Wakix	pitolisant	Bioprojet Pharma	31/03/2016	Wakix is indicated in adults for the treatment of narcolepsy with or without cataplexy (see also section 5.1).
Coagadex	human coagulation factor X	Bio Products Laboratory Limited	16/03/2016	Coagadex is indicated for the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary factor X deficiency.
Ravicti	glycerol phenylbutyrate	Horizon Pharma Ireland Limited	27/11/2015	Ravicti is indicated for use as adjunctive therapy for chronic management of adult and paediatric patients 2 months of age with urea cycle disorders (UCDs) including deficiencies of carbamoyl phosphate-synthase-I (CPS), ornithine carbamoyltransferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase I (ARG) and

				ornithine translocase deficiency hyperornithinaemia-hyperammonaemia homocitrullinuria syndrome (HHH) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.Ravictimust be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).
Blincyto	blinatumomab	Amgen Europe B.V.	23/11/2015	Blincyto is indicated for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).
Kolbam	cholic acid	Retrophin Europe Ltd	20/11/2015	Cholic Acid FGK is indicated for the treatment of inborn errors of primary bile acid synthesis, in infants from one month of age for continuous lifelong treatment through adulthood, encompassing the following single enzyme defects: sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency; 2- (or alpha-) methylacyl-CoA racemase (AMACR) deficiency; cholesterol 7 alpha-hydroxylase (CYP7A1) deficiency.
Kyprolis	carfilzomib	Amgen Europe B.V.	19/11/2015	Kyprolis in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
Cresemba	isavuconazole	Basilea Medical Ltd	15/10/2015	Cresemba is indicated in adults for the treatment of: invasive aspergillosis mucormycosis in patients for whom amphotericin B is

				inappropriate Consideration should be given to official guidance on the appropriate use of antifungal agents.
Raxone	idebenone	Santhera Pharmaceuticals (Deutschland) GmbH	08/09/2015	Raxone is indicated for the treatment of visual impairment in adolescent and adult patients with Lebers Hereditary Optic Neuropathy (LHON).
Farydak	panobinostat	Novartis Europharm Ltd	28/08/2015	Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent.
Kanuma	sebelipase alfa	Alexion Europe SAS	28/08/2015	Kanuma is indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency.
Strensiq	asfotase alfa	Alexion Europe SAS	28/08/2015	Strensiq is indicated for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease.
Hetlioz	tasimelteon	Vanda Pharmaceuticals Ltd	03/07/2015	Hetlioz is indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) in totally blind adults.
Lenvima	lenvatinib	Eisai Europe Ltd	28/05/2015	Lenvima is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hrthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).
Holoclar	ex vivo expanded autologous human corneal epithelial cells containing stem cells	Chiesi Farmaceutici S.p.A.	17/02/2015	Treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement,

				and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1-2 mm2 of undamaged limbus is required for biopsy.
Cerdelga	eliglustat	Genzyme Europe BV	19/01/2015	Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).
Ofev	nintedanib	Boehringer Ingelheim International GmbH	15/01/2015	Ofev is indicated in adults for the treatment of Idiopathic Pulmonary Fibrosis (IPF).

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