Consulting Report

Assessment of the Impact of Orphan Medicinal Products on the European Economy and Society

This report was commissioned from OHE Consulting by the Joint EBE-EuropaBio Task Force on Rare Diseases and Orphan Medicinal Products

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1 Executive Summary

Introduction

Orphan Medicinal Products are intended for the diagnosis, prevention or treatment of life-threatening or serious conditions that are rare. Following the political impetus provided by the OMP regulation EC 141/2000 entering into force in April 2000, which in general terms provides incentives for the research, development and marketing of OMPs, there has been an important increase in the number of OMPs potentially available for patients in Europe compared to the situation before the regulation. Moreover, following this regulation and specifically also the implementation of the National Plan for Rare Diseases in France in 2005, a number of countries have decided to create their own national path. At the same time, further scientific and policy research in the area is needed to better understand the epidemiological, clinical and personal impact of each rare disease in the EU as well as to support sound policy decision-making and enhance several aspects of caring for patients including access to diagnosis, treatment and care.

Methodology

The report combines the results of two phases of study commissioned in 2008 and 2009 from OHE Consulting by the Joint EBE-EuropaBio Task Force on Rare Diseases and Orphan Medicinal Products ("the Task Force").

The first phases involved the collection of data for 17 indicators of activity around OMPs in the EU identified by the Task Force. Several data issues became apparent during this work, namely that data was patchy and scarce and data on activity by companies, such as R&D and employment, were missing.

The second phase consisted of two parts. First, a (confidential) survey to companies active in the area of orphan drugs asking for data on economic indicators, such as R&D and employment for OMPs. Eighteen companies (out of 51) responded to our survey. Second, exploring how the introduction of orphan drugs has impacted on the delivery of health care for patients with rare diseases, based on four case studies.

Fostering economic growth through the development of OMPs

Since the adoption of the EU OMP regulation, the **number of marketing authorisations** in the EU for orphan drugs has increased almost every year: from 8 orphan drugs before 2000 to 68 products by the end of 2009. EU legislation has helped established companies to invest resources in the field of rare diseases, but also the creation of newly formed companies which focus exclusively in researching and discovering orphan drugs within Europe. A significant number of new companies have been created that focus exclusively on researching and developing OMPs. For nearly all these companies all their R&D activities and staff are located in the EU. Given long lead times in biopharmaceutical R&D, we can expect that the EU OMP Regulation will have an even greater impact over the next years.

Overall, **employment** in all departments of companies working on orphan drugs more than doubled between 2000 and 2008 (158% increase).

OMP **R&D expenditure** in the EU has also increased significantly (209%) during the period 2000-2008. Moreover, R&D in OMPs seems to represent an increasing proportion of total R&D in the general biopharmaceutical industry.

Those findings are in line with the 2006 Working Document published by the European Commission[1] where it was highlighted that jobs related to orphan medicinal products seem to have increased at a quicker pace than general industry trends, both those relating to R&D positions and, especially, those around and beyond R&D, as companies producing orphan medicines get ready to bring their products to the market.

The OMP Regulation has also impacted on strategic company decisions in the EU. Companies surveyed primarily target Europe and the US to seek orphan indications and their orphan-designated drugs are predominantly launched in Europe and the US. Moreover, some companies focus their efforts, both in terms of seeking designations and launching orphan drugs, only in Europe – highlighting the importance of the European market. For the companies surveyed the market exclusivity incentive is the most important element of the EU legislation; the second being access to the centralised procedure.

Science and Innovation

Nearly 80% of all **clinical trials** on OMPs are conducted in countries where a national plan for rare diseases exists. The number of clinical trials in the area of rare diseases has been steadily increasing since 1997. Nearly half of all clinical trials are on rare cancers, 8% on diseases of the nervous system and 7% on musculoskeletal disorders. Because by definition cases are rare, patient recruitment for clinical trials on OMPs remains an important issue.

Patients

Patient groups in rare diseases, such as Eurordis, the European Genetic Alliances' Network (EGAN) and Orphanet, have been a key driver in raising awareness of rare diseases among most stakeholders and have been very active in stimulating research priorities and policy initiatives, even before the introduction of the OMP Regulation. There has been an increased confidence in the operation of patient organisations in the arena of rare conditions through the adoption of a more targeted approach. They have focused on identifying very specific research areas including:

- Clinical development and interaction with private companies for funding;
- Advocacy in national health care systems 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 specific diseases, including researchers, medical staff and industry; and
- Disseminating information on the diseases through publications, websites and other media.

Impact on Health Care Systems

In the EU today, altogether about 30 million people are affected by rare diseases for which few or no treatments are available. In many instances newly approved orphan drugs have transformed what were previously acute conditions leading to premature death into chronic/long term conditions and have radically changed the management of these conditions. Additional social benefits not directly captured by clinical outcome measures include:

- Wider benefits accruing to patients' family members or carers;
- Medical expertise on rare diseases;
- Research networks and infrastructures facilitating knowledge exchange;

[1] 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 (2006).

- Improving diagnostic tools and time to diagnosis; and
- Stimulating the creation of patient organisations.

After 2000, following the increasing number of OMPs approved and launched on the market, some European Member States have developed public health policies specific to rare disease, including National Plans which provide across-the-board strategies to manage rare diseases within national health systems. As of January 2009, six EU15 Member States have implemented or are in the process of implementing a National Plan for Rare Diseases.

However the biggest challenge faced currently in respect of orphan drugs is the unequal access to them across Member States following centralised marketing approval. There are large differences in the number of available OMPs across the EU. This can be linked to demographic and economic factors but also to the application of health technology assessment (HTA) methodologies to appraise orphan drugs that can lead to high rates of rejection and significant delay to access to new OMPs. The increasing demand for HTA to inform health care decisions will therefore represent a major challenge in terms of access to OMPs, which are unlikely to meet standard HTA requirements.

Finally in relation to the use of diagnostic techniques, the importance of personalised medicine in the context of rare diseases is increasing. In particular, the work on rare diseases and OMPs can be thought of as a precursor in the development of the personalised medicine field.

Conclusions

The pharmaceutical industry, like most stakeholders in the area of rare diseases, deems the EU OMP Regulation to have been a success and, indeed, one of the most successful EU healthcare policies overall. We argue that the incentives provided in the legislation greatly fostered innovation and entry into market of therapies addressing hitherto unmet medical needs. Increasing activities around OMPs have also led to an improvement in the delivery of health care more widely for rare diseases.

But at the same time, further scientific and policy research in the area is needed to better understand the epidemiological and clinical impact of rare diseases in the EU as well as to support sound policy decision-making to improve, for example, access to treatment and care. A key challenge that remains is to reconcile the increasing efforts in developing new orphan drugs with issues related to HTA and market access. Indeed, ensuring access to orphan drugs in national health care systems in a timely and effective way is important to maintain the positive impact of the OMP developers on the economy and ultimately to continue delivering life-saving therapies for patients.

2 Introduction and Terms of Reference

OMPs are intended for the diagnosis, prevention or treatment of life-threatening or serious conditions that are rare. Under normal market conditions, given the low prevalence of rare diseases, biopharmaceutical companies would not be attracted to develop treatments for orphan diseases. The European Commission (EC) implemented in April 2000 Regulation (EC) No. 141/2000 with the aim of providing incentives for the research, development and marketing of OMPs. In particular, a drug is to be designated as orphan if:

- It is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the EU when its application is made, or
- It is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it would be unlikely that it would generate sufficient return to justify the necessary investment, and
- There exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the EU, or if such method exists, that the product will be of significant benefit to those affected by that condition.

Determining the epidemiological impact of rare diseases is a difficult task. It is estimated that between 5,000 and 8,000 distinct rare diseases exist today, affecting between 6% and 8% of the EU population in the course of their lives. While rare diseases are characterised by low prevalence for each of them, the total number of people affected by rare diseases in the EU is between 27 and 36 million (Council Recommendation, 2009). Orphanet's document "Prevalence of rare diseases in alphabetical order" contains data on prevalence for 1,701 rare diseases[2].

Following the political impetus provided by the OMP regulation EC 141/2000, there has been an important increase in the number of OMPs potentially available for patients in Europe compared to the situation before the regulation. Indeed, since the adoption of this EC regulation, the number of marketing authorisations for orphan drugs has increased almost every year. Before the regulation, only eight orphan drugs "*avant la lettre*" had been approved in Europe. By the end of 2009, more than 500 drugs had obtained orphan designation and 68 products with orphan drug status had been launched.

[2] The interested reader can download this document at:
http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf

3 Methodology

3.1 First Phase

The first phase of this study involved the collection of data on indicators of activity around OMPs in the EU. The members of the EBE-EuropaBio Task Force on Rare Diseases and Orphan Medicinal Products[3] (the Task Force) identified three sets of indicators for collection, covering Patient Management, Competitiveness, and Science and Innovation (see Annex 1 for a complete list of indicators). In total, the Task Force identified 17 indicators; 15 of them being quantitative and two being qualitative[4], the latter two being based on a semi-structured interview programme both with EBE and/or EuropaBio member companies and academics/scientists. The objective of the interview programme was to gather qualitative information about orphan drugs, in terms of the issues around their R&D process, the EU OMP regulation introduced in 2000 and market access.

3.2 Second Phase

3.2.1 Confidential Survey

The second phase of the study consisted of two parts. First, a (confidential) survey was sent to 51 OMP developers asking for specific data on orphan drugs at different points in time (2000, 2004 and 2008) to enable examination of trends. The sample of companies provided by the Task Force included all advised by the Task Force as being active in the area of rare diseases/orphan drugs in Europe (see Annex 2 for a copy of the survey as well as the list of respondents).

Eighteen companies responded to the survey among, which a majority (13) had an OMP launched in Europe by the end of 2008, representing 38% of all companies responsible for (launched) OMPs.

3.2.2 Case Studies

Four case studies were also produced to explore how the discovery, development and use of orphan drugs have improved the way health care is delivered due to the advent of medicines to treat the selected rare diseases. These involved the following four orphan drugs: Myozyme® (alglucosidase alfa), by Genzyme; Revlimid® (lenalidomide), by Celgene; Glevec® (imatinib), by Novartis; and Elaprase® (idursulfase), by Shire.

3.2.3 Literature Review

In parallel, a literature review around orphan drugs was also carried out, guided by our accumulated knowledge and experience on the topic. It also included relevant documents published by the EC on the area of rare diseases, as they provide valuable information on the actions the EC is taking, and has taken in the past, to encourage R&D in the area of OMPs.

[3] Joint EBE/EuropaBio Task Force on Rare Diseases & Orphan Medicinal Products
EBE (European Biopharmaceutical Enterprises) and EuropaBio (European Association for Bioindustries) have established a joint EBE/EuropaBio Task Force on Rare Diseases & Orphan Medicinal Products, comprising companies that have either developed or intend to develop orphan drugs under Regulation EC/141/2000. Together, members of the Joint Task Force represent a large proportion of orphan drugs currently available on the EU market.

[4] This report only contains highlights of the analysis of the selected indicators. The interested reader can request the full set of indicator data by contacting EBE (www.ebe-biopharma.org) or EuropaBio (www.europabio.org).

4 OMPs in Europe: Current Position and Trends to Date

Since the adoption of the EU OMP regulation in 2000, the number of marketing authorisations for orphan drugs has increased almost every year. Before the regulation, only eight orphan drugs "*avant la lettre*" (i.e. before there was an official definition of "orphan") were approved in the EU. After the regulation entered into force, three OMPs were approved in the first year 2001, and by the end of 2009 there were 68 products with orphan drugs status in the EU in total. The highest number of OMPs approved in any one year was 2007, with 14. Some observers have argued that such a high rate of launch of new OMPs is unsustainable. But a number of articles looking in more detail at the OMP pipeline suggest a continuing rate of launch near the 2007/2009 level. For instance, Miles et al. (2007) finds that 113 drugs for 42 very rare diseases are in development; Eurordis analysis shows that between 85 and 105 OMPs will be launched over the next ten years (i.e. between nine and 11 OMPs per year), and the European Medicine Agency (the Agency) has argued that they expect 15 OMP applications for market authorisations a year (EPPOSI Conference Report, 2007).

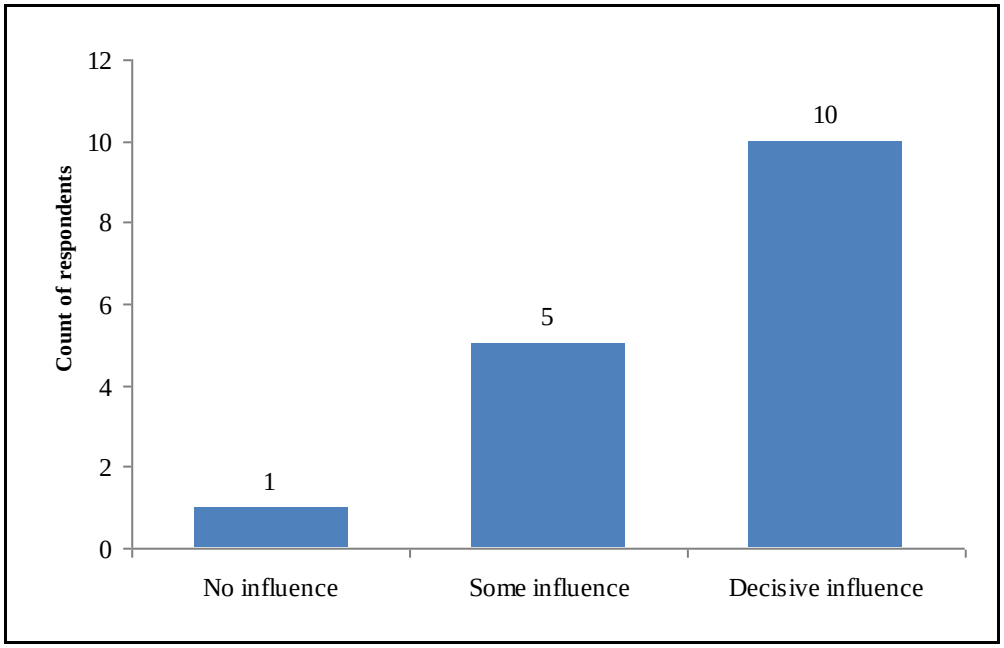
Table 4.1 Number of OMPs in the Community Register of Medicinal Products for Human Use, year by year (2001-2009)

Year of authorisation	Number of orphan drugs
2001	**3**
2002	**5**
2003	**5**
2004	**6**
2005	**3**
2006	**13**
2007	**14**
2008	**7**
2009	**12**
Total	**68**

Source: European Medicine Agency (http://ec.europa.eu/health/documents/community-register/html/orphreg.htm; accessed 17th June 2010)
NB It reflects the situation as of 17th June 2010 – by this date, three OMPs had been included in the Community Register in 2010.

Our survey asked respondents how influential the introduction of the EU OMP Regulation has been in shaping their company's strategic decision making in the EU. Figure 4.1 shows the responses obtained clearly indicating that the EU OMP legislation has been successful at stimulating companies.

Figure 4.1 Influence of EU OMP legislation in shaping company's strategic decision making in the EU

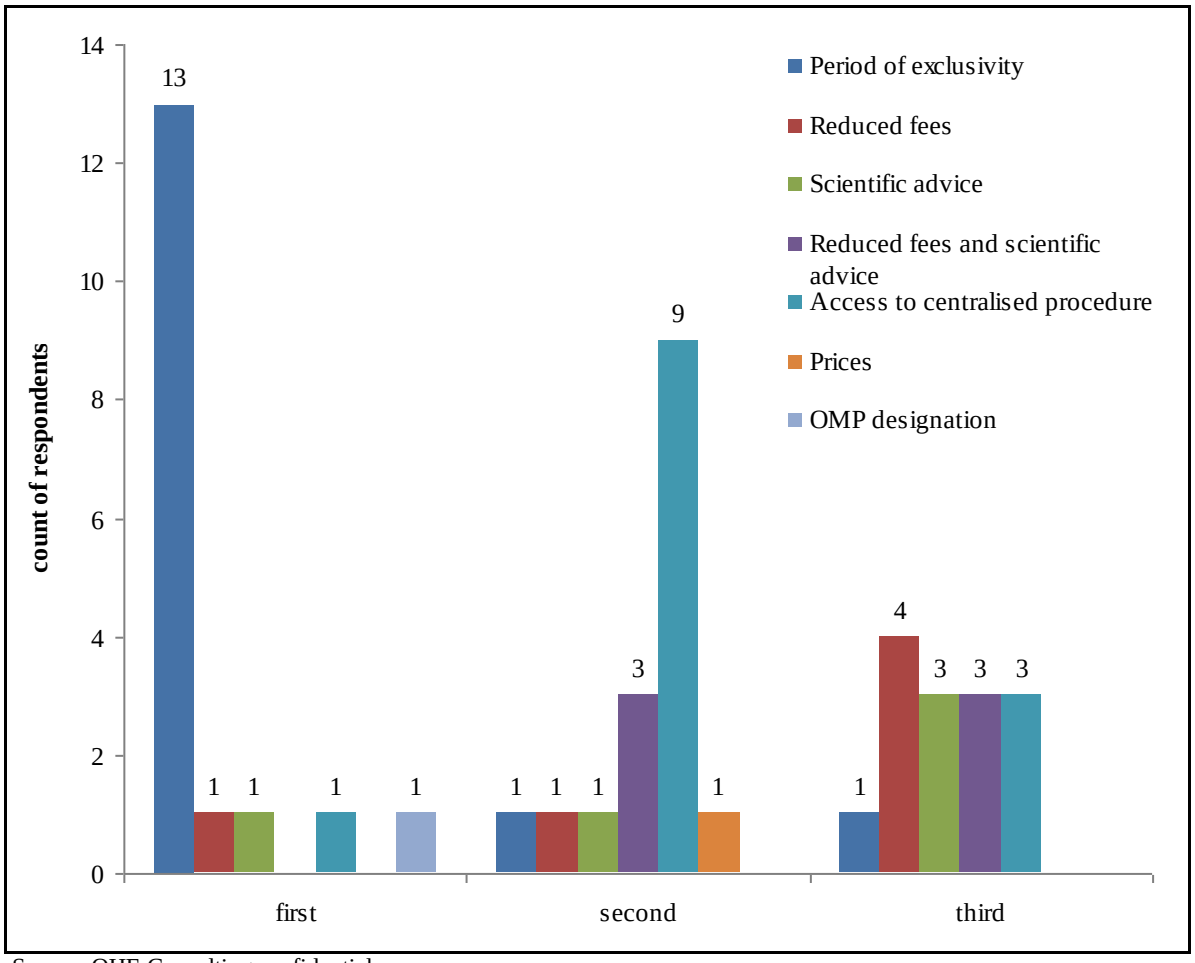


Source: OHE Consulting confidential survey

Nearly all who answered this question (15 out of 16) stated that the EU legislation has had some or a decisive influence in shaping their decisions, and more than half (10/16) said that it has been decisive.

Companies were also asked to rank the three most important features of the EU regulation. As shown in Figure 4.2, the 10-year period of market exclusivity was ranked the highest by most (13/17) companies. Having access to the centralised procedure also seems to be a significant feature of the EU legislation, according to the respondents.

Figure 4.2 Key features of the EU OMP legislation (ranked 'Most important' to 'Third most important)



Source: OHE Consulting confidential survey

5 Economic Impact

5.1 Effect on Company Creation, Growth and Investment

A report published by EuropaBio-EBE in 2005 showed that nearly one third (8/25) of the companies surveyed at the time were start-ups created in or after 2000. In our survey, this percentage was 22% (Figure 5.1) and 25% of the companies started developing OMPs in or after 2000 (Figure 5.2). Most companies that have taken up developing OMPs after 2000 focus solely on discovering and developing orphan drugs. Moreover, for nearly all these companies all their R&D activities and staff are located in the EU.

This result highlights that the EU legislation has not only helped established companies to invest resources in the field of rare diseases, but also has helped the creation of newly formed companies which focus exclusively in researching and discovering orphan drugs within Europe.

Figure 5.1 Company creation

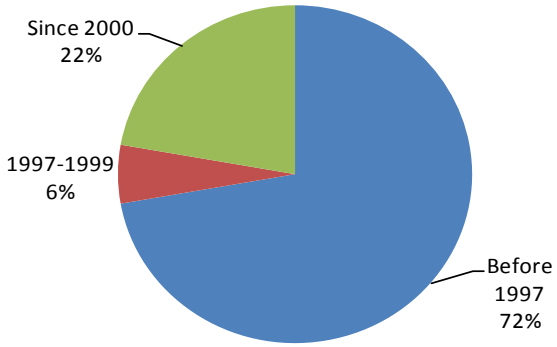
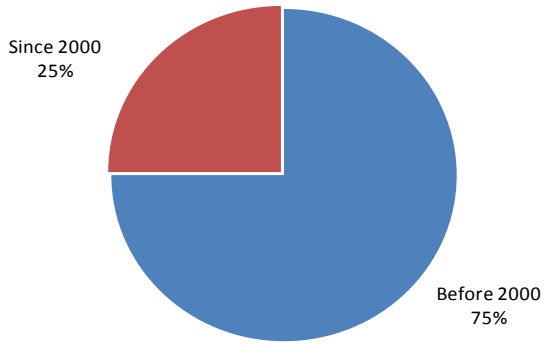


Figure 5.2 Take-up of OMP development

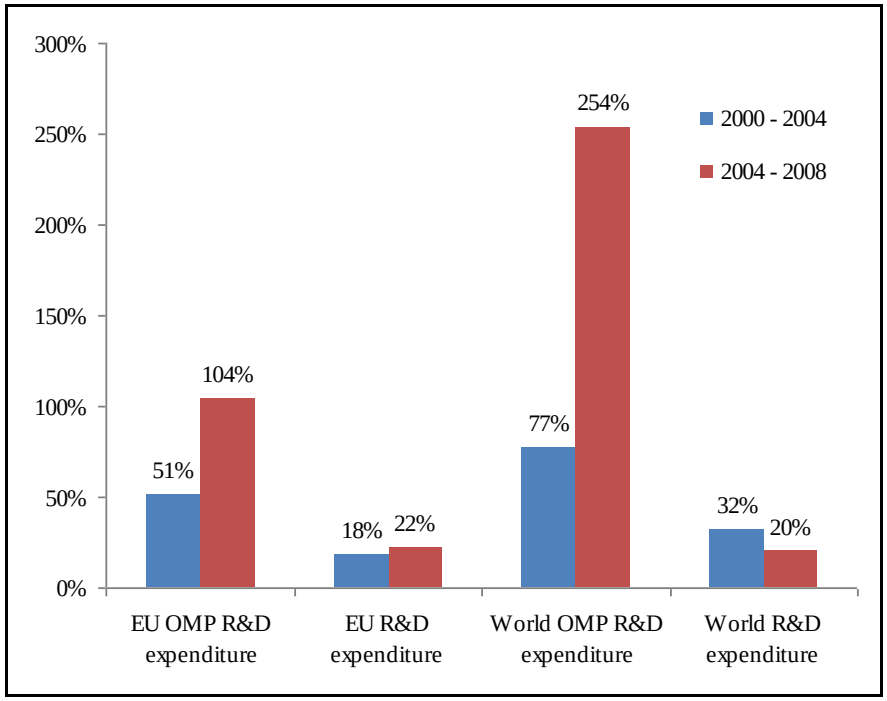


Source: OHE Consulting confidential survey

In addition, all but one company that responded to the question (15 responses in total) 'When did you first launch an OMP?' showed that their first OMP launch was after 1997 – with only 3 of 15 responses saying that their first OMP launch was between 1997 and 1999. The remaining companies (11 of 15) all launched their first OMP in 2000 or after.

When asked about the location of their global headquarters (HQ), and in particular whether it was in the EU at the time of its establishment, more than 50% respondents had their HQ in Europe, demonstrating that, at least when first created, many companies active in the area of orphan drugs have their HQ in the EU.

Figure 5.3 Average growth in R&D expenditure



Sources: EU and World OMP R&D expenditure: OHE Consulting confidential survey; EU R&D expenditure: EFPIA (up to 2007); World R&D expenditure: PICTF
Note: EU OMP-specific R&D expenditure, in absolute terms, (obtained from our confidential survey) represents 1.01%, 1.30% and 2.16% of EU pharmaceutical R&D expenditure (from EFPIA) in 2000, 2004 and 2008 respectively.

Based on the information provided by the respondents, the increase in OMP R&D investment in the EU is formidable. 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%, increasing from €150,000 Millions in 2000 to over €490,000 Millions in 2008. R&D expenditure in OMPs worldwide (including that taking place in the EU) has increased significantly more than in the EU over this eight-year period. This is not surprising as many countries, including the US, have similar legislation with the aim to foster more R&D in the area of rare diseases. Table 5.1 shows the absolute numbers used to calculate the growth rates shown in Figure 5.3 for R&D investment.

Table 5.1 EU and World OMP R&D Expenditure

	R&D Expenditure		
	2000	**2004**	**2008**
EU OMP R&D Expenditure* (in €000's)	158,410	239,962	490,206
EU R&D Expenditure (in €000's)**	15,718,000	18,526,000	22,691,000
World OMP R&D Expenditure* (in €000's)	305,160	540,021	1,912,106
World R&D Expenditure* (in £000's)**	28,033,000	37,547,000	44,668,000

Sources: *OHE Confidential Survey; **EFPIA; ***PICTF

In terms of the proportion of new OMPs relative to the number of new drugs overall, OMPs represent a larger share over time. For instance, in 2001 orphan drugs represented 10% of all new drugs, while this percentage increased to more than 50% by 2006. Except for 2005, there was a year-on-year increase in the proportion accounted by orphan drugs between 2001 and 2006. Although we did not have access to CMR data for 2007, we believe that the trend would have

continued in 2007, when the highest number of OMPs was launched in any one year, but may have fallen back in 2008.

Table 5.2 Share of OMPs vs. overall new product launches

	2001	2002	2003	2004	2005	2006
New product launches	31	28	26	24	28	25
Orphan drugs	3	5	5	6	3	13
Share of orphan drugs	10%	18%	19%	25%	11%	52%

Source: CMR International: New launches, various years (Note that we did not have access to the data for 2007 and 2008); For orphan drugs: European Medicine Agency (Table 4.1above).
Note: CMR International data includes new chemical entities (NCEs) and new biopharmaceutical entities (NBEs) which have not been previously available for therapeutic use. This list includes NCEs/NBEs launched worldwide. It has not been possible to determine from that data source which of the new product launches included in Table 5.1 have been launched in Europe.

5.2 Effect on Employment and Company Structure

Employment both for overall activities and R&D-specific activities in the area of OMPs were also sought from the survey**.**

Figure 5.4 Average total employment growth

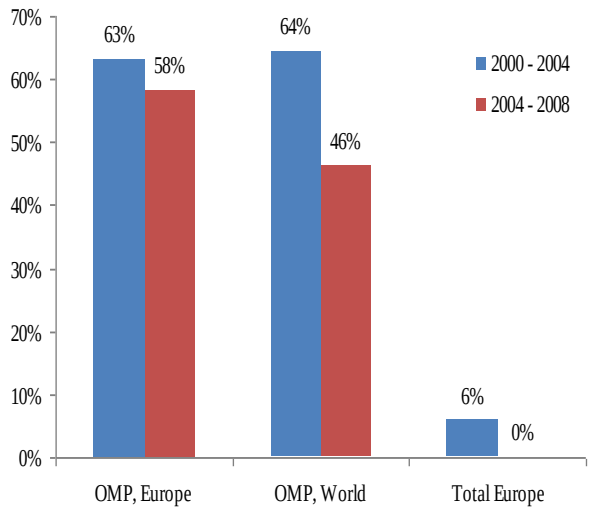
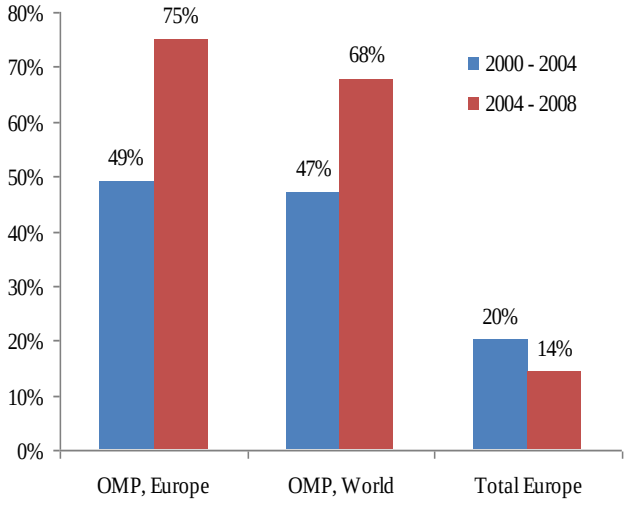


Figure 5.5 Average R&D employment growth



Sources for both Figures: OMP data: OHE Consulting confidential survey; EFPIA for 'Total Europe'

Table 5.3 shows the absolute numbers used to calculate growth rates for average total employment and average R&D employment for OMPs in Europe (first blue bar in Figure 5.4 and Figure 4.5 respectively).

Table 5.3 Employment (whole time equivalents) in Europe (OMPs)

	2000	2004	2008
Number of people employed in OMP-related activities in Europe	2,046	3,341	5,285
Number of people employed in R&D-specific OMP-related activities in Europe	370	551	965

Source: OHE Consulting confidential survey

Overall, employment on OMPs more than doubled between 2000 and 2008 (158% increase). OMP-specific R&D employment (Figure 5.5) has increased by 161% over the total period 2000-2008, and

has grown faster in the latter half of the period than in the first half. While employment in R&D for pharmaceuticals in general in Europe has considerably increased during the 2000-2008 period, the growth rate in the area of OMPs has been even higher. European employment is a key component driving worldwide employment in the field of OMPs.

These growth rates are slightly higher than those quoted by the European Commission report published in 2006 (European Commission, 2006), which are based on the 2005 EuropaBio/EBE survey (EuropaBio – EBE, Joint OMP Task Force, 2005). The EC report cites a 43% increase on average for total number of employees in the European Community between 2004 and 2008 (compared to 63% and 49% for total and R&D-specific activities respectively in our survey). However, results are not directly comparable between the two surveys as we do not know which companies responded to the earlier survey.

6 Effect on Science and Innovation

Nearly 80% of all clinical trials on OMPs (of a total of 2,533 as reported by Orphanet in January 2009) are conducted in countries where a National Plan on orphan drugs/rare diseases exists or is in the process of being implemented (Denmark, France, Germany, the Netherlands, Portugal and Spain). The issue of National Plans is discussed in Section 7, where actions taken by individual Member States are described. France leads with a total of 812 clinical trials, followed by Germany with 769. Trials conducted in these two countries represent more than 60% of all the trials included in Table 6.1. By phase, trials conducted in phase II and III represent a majority.

Table 6.1 Total number clinical trials by EU country by phase (as of January 2009)

	Phase								
	I	**I - II**	**II**	**II - III**	**III**	**III - IV**	**IV**	**Not specified**	**Total**
Austria			2		15			2	**19**
Belgium		2	8		8		3	2	**23**
Czech Republic					2				**2**
Denmark	3		8		14			12	**37**
Estonia					4				**4**
Finland			8		4			1	**13**
France	25	22	266	6	303		75	115	**812**
Germany	6	90	213	15	296		58	91	**769**
Greece							6	4	**10**
Hungary					5				**5**
Ireland			14		6	2	2	4	**28**
Italy		43	69	3	50		12	4	**181**
Malta					2				**2**
Poland			2		2				**4**
Portugal				7					**7**
Romania								1	**1**
Slovakia					2				**2**
Spain	4		31	4	27		4	24	**94**
Sweden			4	2	2				**8**
The Netherlands		2	53		73		12	92	**232**
UK	2	36	86		75		15	66	**280**
Total	**40**	**195**	**764**	**37**	**890**	**2**	**187**	**418**	**2,533**

Source: Orphanet

All clinical trials reported in Orphanet have been classified by ICD category. Table 6.2 shows that the industry is targeting important therapy areas: nearly half of all clinical trials are for cancer orphan medicines; 8% are targeting diseases of the nervous system, while 7% target diseases of the musculoskeletal system and connectivity tissue.

Table 6.2 Clinical Trials by ICD category

ICD	Share of Trials
Neoplasms	46%
Not specified	16%
Diseases of the nervous system	8%
Diseases of the musculoskeletal system and connective tissue	7%
Endocrine, nutritional and metabolic diseases	6%
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	4%
Congenital malformations, deformations and chromosomal abnormalities	3%
Diseases of the circulatory system	3%
Diseases of the digestive system	3%
Others	4%

Source: OHE Consulting analysis based on Orphanet data

We have also classified Orphanet data on clinical trials by ICD disease area and by EU country. Table 6.3 shows this information.

Table 6.3a Clinical trials by ICD disease area in France, Germany and UK

	France		Germany		UK	
	No. of trials	Share of trials for ICD level	No. of trials	Share of trials for ICD level	No. of trials	Share of trials for ICD level
Certain conditions originating in the perinatal period	4	100%	0	0%	0	0%
Certain infectious and parasitic diseases	8	40%	4	20%	0	0%
Congenital malformations, deformations and chromosomal abnormalities	33	43%	24	31%	3	4%
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	38	36%	23	22%	11	10%
Diseases of the circulatory system	17	25%	40	58%	4	6%
Diseases of the digestive system	12	18%	10	15%	12	18%
Diseases of the eye and adnexa	0	0%	16	89%	2	11%
Diseases of the genitourinary system	0	0%	6	50%	0	0%

Diseases of the musculoskeletal system and connective tissue	104	58%	25	14%	8	4%
Diseases of the nervous system	88	43%	40	20%	15	7%
Diseases of the respiratory system	2	6%	2	6%	4	13%
Diseases of the skin and subcutaneous tissue	8	80%	0	0%	0	0%
Endocrine, nutritional and metabolic diseases	53	36%	12	8%	29	19%
Factors influencing health status and contact with health services	2	100%	0	0%	0	0%
Mental and behavioural disorders	0	0%	8	100%	0	0%
Neoplasms	325	28%	399	34%	170	14%
Not specified	118	29%	160	40%	22	5%

Source: OHE Consulting analysis based on Orphanet data

Table 6.3b Clinical trials by ICD disease area in Italy, Netherlands and Other EU Countries

	Italy		Netherlands		Other EU	
	No. of trials	Share of trials for ICD level	No. of trials	Share of trials for ICD level	No. of trials	Share of trials for ICD level
Certain conditions originating in the perinatal period	0	0%	0	0%	0	0%
Certain infectious and parasitic diseases	0	0%	6	30%	2	10%
Congenital malformations, deformations and chromosomal abnormalities	2	3%	6	8%	9	12%
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	12	11%	6	6%	15	14%
Diseases of the circulatory system	4	6%	4	6%	0	0%
Diseases of the digestive system	8	12%	16	25%	7	11%
Diseases of the eye and adnexa	0	0%	0	0%	0	0%
Diseases of the genitourinary system	0	0%	6	50%	0	0%
Diseases of the musculoskeletal system and connective tissue	8	4%	25	14%	10	6%

Diseases of the nervous system	40	20%	10	5%	12	6%
Diseases of the respiratory system	2	6%	2	6%	19	61%
Diseases of the skin and subcutaneous tissue	0	0%	0	0%	2	20%
Endocrine, nutritional and metabolic diseases	12	8%	8	5%	35	23%
Factors influencing health status and contact with health services	0	0%	0	0%	0	0%
Mental and behavioural disorders	0	0%	0	0%	0	0%
Neoplasms	73	6%	113	10%	101	9%
Not specified	20	5%	30	7%	51	13%

Table 6.3c Total Clinical trials by ICD disease area in the EU

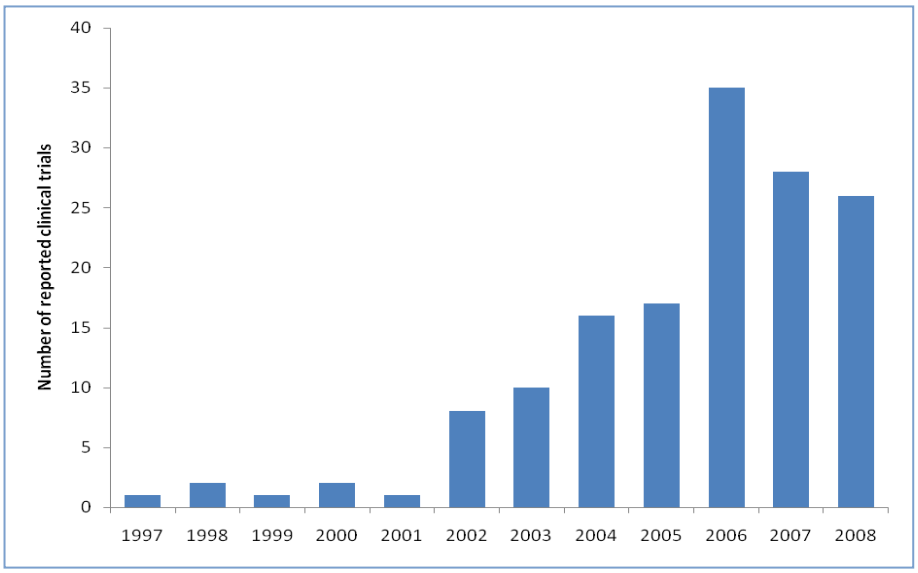
	Total
Certain conditions originating in the perinatal period	**4**
Certain infectious and parasitic diseases	**20**
Congenital malformations, deformations and chromosomal abnormalities	**77**
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	**105**
Diseases of the circulatory system	**69**
Diseases of the digestive system	**65**
Diseases of the eye and adnexa	**18**
Diseases of the genitourinary system	**12**
Diseases of the musculoskeletal system and connective tissue	**180**
Diseases of the nervous system	**205**
Diseases of the respiratory system	**31**
Diseases of the skin and subcutaneous tissue	**10**
Endocrine, nutritional and metabolic diseases	**149**
Factors influencing health status and contact with health services	**2**
Mental and behavioural disorders	**8**
Neoplasms	**1,181**
Not specified	**401**
Total	**2,537**

Based on this, there appears to be a degree of specialism by country for orphan medicines.

Figure 6.1 shows that the number of clinical trials with at least one site in an EU Member State in the area of orphan drugs increased rapidly after 2001 until 2006, and although the number has since

dropped back from the peak level in that year there are still many more clinical trials for orphan drugs than there were before 2001.

Figure 6.1 Number of clinical trials with at least one site in a EU member country included in clinicaltrials.gov for orphan medicines by year initiated



Source: OHE Consulting analysis based on clinicaltrials.gov

We also sought data on numbers of patients recruited for those clinical trials for orphan medicines included in Figure 6.1. Orphanet does not present such data but www.clinicaltrials.gov does. Table 6.4 summarises this information.

Table 6.4 Number of patients recruited for clinical trials for orphan medicines

Total number of trials for orphan conditions with at least one site in an EU member state*	105
Total number of patients recruited	24,053
Average number of patients per trial**	229

Key: * Includes open trials (i.e. currently active as at December 2008) and closed trials (i.e. either not recruiting more patients or finished). It does not include patient registries; ** Average calculated by dividing the total number of patients recruited (24,053) by the total number of trials for orphan conditions with at least one site in EU member country (105).
Source: www.clinicaltrials.gov (accessed 11th December 2008, updated 30th November 2009)
Advanced search: extracted from the combination of "rare diseases, Europe, open trials"; "rare diseases, Europe, closed trials"

Table 6.5 is based on data from the IMS Life Cycle and shows the current number of companies, by nationality of corporate headquarters, with active compounds for orphan indications, as at September 2008. It includes compounds that are anywhere from the Discovery phase to Phase III. The table clearly shows that for most active compounds there is more than one company involved. Among European countries, France is most frequently the country of the corporate headquarters for companies with active compounds in development for orphan conditions. France is the lead partner for nine compounds. The next highest numbers of compounds are for companies headquartered in Germany and Switzerland (with seven and six compounds respectively).

Table 6.5 Current number of companies with active compounds in development for orphan conditions by nationality of corporate headquarters

	Lead partner	Second partner	Third partner	Fourth partner	Fifth partner	Sixth partner	Seventh partner	Eighth partner
Austria	2	1	1					
Belgium	1	1						
Denmark	2	1						
France	9	2	1					
Germany	7	2	2	1	1	1		
Italy	3	2	1					
Netherlands	2	2	1	1				
Spain	1	1	1	1				
Sweden	1							
Switzerland	6	5	2	2	1			
UK	5	3						
USA	41	28	13	6	4	3	2	2
Other	10	7	4	3	2	1	0	0
Total	**90**	**55**	**26**	**14**	**8**	**5**	**2**	**2**

Source: IMS Lifecycle. Search criteria: active programmes from Discovery to Phase III (as at September 2008). 'Other' means non-European countries other than the USA.

We also asked our surveyed companies for information on their current projects in the pipeline. Fourteen companies gave us information on a total of 86 indications that are seeking orphan drug status somewhere in the world (not necessarily Europe). Many drugs have received orphan drug status for more than indication. It is important to note here that receiving orphan drug status does not necessarily imply that the combination product/indication will be launched in the market. This is because many compounds fail to progress through the whole R&D process.

Table 6.6 combines, for the European countries included in Orphanet's database, the numbers of clinical trials begun (based on Table 6.1), specialist centres and research projects. The data do not allow us to decompose this information by calendar year. It shows that a total of 15,208 research projects are, or have been, funded in the EU countries listed. France was the country with the highest number of research projects (4,563) followed by Germany (3,189) and Spain (2,032). The geographical distribution of projects is however very unequal and largely follows the map of the countries where National Plans exist with respect to rare diseases.

Table 6.6 Number of specialist centres established, clinical trials begun or research projects initiated for orphan diseases

	Specialist centres	Trials	Research projects
Austria	31	19	340
Belgium	13	23	362
Bulgaria	4		8
Cyprus	10		29
Czech Republic	25	2	34
Denmark	11	37	79
Estonia	4	4	44
Finland	13	13	85
France	296	812	4,563
Germany	129	769	3,189
Greece	18	10	66
Hungary	10	5	45
Ireland	8	28	200
Italy	186	181	1,429
Latvia	2		
Lithuania	1		
Malta		2	
Netherlands	22	232	302
Poland	3	4	2
Portugal	33	7	818
Romania	8	1	94
Slovakia	4	2	1
Slovenia	5		
Spain	79	94	2,032
Sweden	3	8	3
UK	56	280	1,483
Total	**974**	**2,533**	**15,208**

Source: Orphanet

In terms of specialist centres for rare diseases, France, with 296, is the country with the highest number of them, followed by Italy and Germany with 186 and 129 respectively.

Summary data on current and past EU funded projects for rare diseases is shown in Table 6.6, which is drawn from the EU's webpage on rare diseases. Note that the data are incomplete for 2005 – hence the relatively low values then compared to earlier years.

The European Commission has been funding projects in the area of rare diseases since 2000. Over the period 2000-2005 (when data is available), EU's total funding has remained relatively stable, although the average value of the projects funded, in financial terms, has increased significantly over time. Thus, the EU seems to be funding fewer projects in total but is allocating more money per project.

Table 6.7 Current and past EU funded projects for rare diseases, count and value

	Funded projects	Total value of projects (€)	Total grant/subsidy value of projects (€)	Value per project (€)	Grant/subsidy per project (€)
2000	9	2,190,734.51	1,218,000.00	243,415	135,333
2001	8	2,201,573.26	1,318,685.74	275,197	164,836
2002	7	2,063,024.19	1,270,199.63	294,718	181,457
2003	2	3,998,707.09	2,000,270.84	1,999,354	1,000,135
2004	3	2,106,854.42	1,244,365.46	702,285	414,788
2005	3	269,914.25	161,949		

Source: http://ec.europa.eu/health/ph_threats/non_com/projects_rarediseases_en.htm
Note 1: 2005 data on the value of the projects includes information for one project only.
Note 2: As of January 2009, the EU's webpage contained information only for the period 2003-2005. However, we found data for the period 2000-2002 when we carried out an earlier search.

7 Patients

Eurordis has identified 309 patient organisations across the EU working in the field of rare diseases (as of October 2008) and many other organisations have developed activities in the field. Their distribution is very unequal across the EU. Member States of the pre-2004 EU15, such as France, Germany and Spain, host more than 95% of the rare disease patient organisations; and around 60% of these are located in France, Germany and Spain specifically. Numbers of patient associations are much lower in those Member States that joined the EU in 2004 or later. Table 7.1 illustrates this.

Table 7.1 Indicator 1b Number of national orphan disease patient associations for each EU15 Member State and new EU Member States, where available (as at October 2008)

	Alliance		Patient Organisations
	Yes	No	**Number**
EU15 Members			
Austria	1		**4**
Belgium	1		**15**
Denmark	1		**10**
Finland		✓	**3**
France	1		**95**
Germany	1		**39**
Greece	1		**3**
Ireland		✓	**8**
Italy	1		**25**
Luxembourg		✓	**2**
Netherlands	1		**9**
Portugal		✓	**5**
Spain	1		**44**
Sweden	1		**7**
UK		✓	**29**
New EU members			
Bulgaria	1		**1**
Cyprus		✓	**1**
Czech Republic		✓	**2**
Hungary	1		**1**
Malta	1		**1**
Poland		✓	**1**
Romania	1		**2**
Slovakia		✓	**1**
Slovenia		✓	**1**
Summary	**Alliances**		**Patient Organisations**
Total EU15 Members	10		**298**
Total New EU members	**4**		**11**

Source: Eurordis (search of number of patient associations by EU member countries)
Note 1: Patient groups need to become members of Eurordis to be listed/included in Eurordis' website. This means that in each country there might be more patient organisations than those included in Table 7.1.
Note 2: In the UK, the Genetic Interest Group (GIG) is a national alliance of patient organisations with a membership of over 130 charities which support children, families and individuals affected by genetic disorders, many of which are rare diseases. However, GIG also includes patient organisations for non-rare diseases. Eurordis are not aware of any alliance of organisations in the UK that is limited to orphan diseases.

Through a number of national alliances, rare disease stakeholders have built coordinated fronts against the diseases. This is the case in France and Italy, but many other countries, such as the UK, do not have a national alliance.

According to one interviewee, there has been an increased confidence and professionalism of patient organisations operating in the arena of rare conditions demonstrated by, for instance, following a more targeted approach as compared to the traditional patient organisations. They have focused on identifying very specific research areas which are relatively close to clinical development and interact with private companies for funding. We discuss in more detail the positive effect of patient groups in rare diseases later.

Patient organisations have been very active in influencing research priorities and policy initiatives, even before the introduction of the OMP regulation. The OMP Regulation also empowered patients to have a greater voice in regulatory developments by, for example, providing expertise in the discussions around significant benefit.

Rare diseases patient groups have been effective in various fields, including:

- Product development, as they have encouraged a more targeted approach than traditional patient organisations. They have focused on identifying very specific research areas which are relatively close to clinical development and they interact with private companies for funding;
- Advocacy in national health care 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 the COMP to develop the regulatory framework – a unique example in the EU of collaboration between patient groups and regulatory authorities;
- Supporting clinical trial recruitment.

Pompe disease represents a good example where patients and patient organisations have been particularly active. Whilst patient organisations in other disease areas have collaborated with companies for product development, in Pompe disease there are a few cases where patients have also stimulated and funded the creation of new companies dealing with neuromuscular disorders. A Dutch patient contributed to designing and running an international survey on the natural course of Pompe disease, which led to a scientific publication considered by regulatory authorities when discussing marketing approval of alglucosidase alfa (Rozendaal, 2006).

In the case of multiple myeloma, before the introduction of novel therapies the role of patient groups was focused on one-on-one support of individuals diagnosed with the disease. After the launch of novel therapies, patient groups have also been involved in advocacy activities, particularly in the UK and Belgium, to secure patient access to treatment. Similarly, the development of a treatment for chronic myeloid leukaemia has transformed the composition of existing patient organisations, which are now an active community of patients who have survived and recovered from chronic myeloid leukaemia.

7.1 Why might Orphan Drugs Lead to Innovation in Health Care Delivery?

This chapter focuses on the social benefits generated by orphan drugs that go beyond the clinical effects accruing to patients, measured in terms of clinical efficacy and effectiveness. In particular, we present and discuss the changes that have been brought about in the whole treatment pathway and health care delivery of rare diseases, from diagnosis to treatments, thanks to the development and use of new orphan drugs. These 'wider benefits' captured by the EU society are illustrated using some specific examples of EMA-designated orphan drugs and their impact on European health care systems. These examples are not intended to be exhaustive but offer important insights.

According to the EU OMP Regulation, a product can be orphan-designated if there is no alternative treatment available for a disease (non-existence of intervention) or if the new treatment is of significant benefit for patients. Moreover, the natural history of the disease is usually unknown, as physicians only have limited experience with the disease (Denis et al., 2009). In practice, we found that often a new orphan drug was the first and only treatment for a low-prevalence disease and had radically changed the management of the condition within national health care systems. Indeed, nearly all designations are granted on prevalence, and only one was granted based on the low "return on investment" (a designation for tuberculosis) (Denis et al., 2009).

For some rare types of cancer, newly developed interventions have transformed what were acute conditions leading to premature death into chronic/long term conditions. For example, in the case of multiple myeloma no effective treatment was available for decades. Since the late 1990s, however, novel agents such as thalidomide, bortezomib and lenalidomide have revolutionized treatment in this disease area. Thanks to these, average response rates have been significantly increased and time to progression and overall survival of patients with multiple myeloma have been significantly prolonged. While multiple myeloma still remains an incurable, ultimately fatal disease, patients are now able to live with the disease for substantially longer periods of time.

Multiple myeloma is an example of a rare cancer where a virtuous cycle has been induced. Resurgence of research interest in the area has led to more clinical trials undertaken by private companies and the launch of three new treatments which can also be used sequentially. As patients' survival rates increase, patient numbers and durations of treatment also increase, thus augmenting the market size in multiple myeloma and leading to yet more research interest into this area. Therefore, the market for multiple myeloma becomes more commercially attractive and more companies are willing to invest in R&D. Specialists' (haematologists') knowledge and expertise related to the condition further improves, e.g. through congresses and publications.

Imatinib showed exceptional clinical benefits for the treatment of chronic myeloid leukaemia, another type of cancer with a small patient population. It provided to patients the opportunity to recover and live a normal life. Imatinib was firstly licensed for chronic myeloid leukaemia and successively obtained marketing authorisation for other types of cancers, which are less prevalent than the original indication (for example, malignant gastrointestinal stromal tumours).

In the context of very rare diseases which have a prevalence of less than one in 50,000, the advent of the EU OMP Regulation has stimulated the development of interventions in previously untreated very small groups of patients. Indeed, many orphan drugs are for ultra rare diseases, such as alpha-galactosidase A, laronidase and iduronate-2-sulfatase (Denis et al., 2009).

Iduronate-2-sulfatase was launched in Europe in 2007 and is indicated for the long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). Iduronate-2-sulfatase is an enzyme replacement therapy (ERT) and represents the first and only treatment available for MPS II.

Until recently, there was no effective therapy for MPS II, and care was palliative. ERT with recombinant human iduronate-2-sulphatase (idursulfase), however, has now been introduced. Weekly intravenous infusions of idursulfase have been shown to improve many of the signs and symptoms and overall wellbeing in patients with MPS II (Wraith et al., 2008; Jones et al., 2009).

Another example of a very rare condition is Pompe disease, which affects only a few patients in the whole of Europe. Before the introduction of alglucosidase alfa, patients could receive some palliative and symptom-based treatment which did not address the underlying cause of the disease. Alglucosidase alfa replaces the missing enzyme in Pompe disease patients and can help minimize and potentially avoid some of the supportive treatments. The use of this intervention has changed the treatment pathway of the disease as it is a life-long therapy administered to patients via bi-weekly infusion. In some cases of infantile Pompe disease, it can be life-saving, while in other cases it can alleviate complications or stabilise the disease.

7.2 Positive Effects on Health Care Systems

The following areas are social benefits not directly captured by clinical outcome measures but that may nevertheless accrue to patients, their families and health care systems:

- Wider benefits accruing to patients' family members or carers;
- Medical expertise on rare diseases;
- Research networks and infrastructures facilitating knowledge exchange;
- Improving diagnostic tools and time to diagnosis; and
- Stimulating the creation of patient organisations.

7.2.1 Wider Benefits Accruing to Patient Family Members or Carers

Patients with rare diseases and their families are particularly isolated and vulnerable (European Commission, 2008). There are two main sources of gains generated by orphan drugs and captured by patients' carers, who are frequently patients' relatives:

- Where an old drug administered via intravenous route was available, the development of an oral therapy avoids hospital visits and increase patients' and their carers' convenience;
- For highly debilitating diseases, which have a significant impact on the daily life of patients, new treatments can alleviate symptoms and/or decrease patients' reliance on other supportive treatments and carers' help.

The first case is particularly recurrent in rare cancers where old treatments have been replaced by new, more convenient therapies. For example, lenalidomide for multiple myeloma has an oral formulation which allows patients to take their medicines at home.

The second case is more recurrent in chronic diseases. For example, in the case of Pompe disease in infants, without any treatment one or both parents have to provide full-time care to the affected child. On the other hand, if a child is treated at an early stage the disease complications can be alleviated or stabilised and parents may go back to work or have more time for normal activities.

The use of ERT for lysosomal storage disorders has made an important contribution to improving the quality of life of affected patients, by offering the possibility of receiving home therapy. The treatment, however, is invasive and onerous, involving weekly or biweekly intravenous infusions of product over a 3-4 hour period. Such therapy can be disruptive to normal family life and the provision of safe home treatment is greatly appreciated by affected families. The safety of home

treatment with iduronate-2-sulfatase for MPS II has been demonstrated and careful patient selection, an experienced home care company and a detailed management plan for potential anaphylaxis and infusion-associated reactions are important components in a successful home treatment programme.

Similarly, Little et al. (2009) found that there is a growing move to offer ERT at home, supported by nurse specialists and the community healthcare infrastructure. The authors report their experience of providing ERT to a patient with Hunter syndrome in a school. Through careful planning and the development of close working relationships between nurses, schools, local hospitals and patients' families, the authors found that managing patients outside the hospital setting can greatly benefit their quality of life.

7.2.2 Medical Expertise on Rare Diseases

When no treatment is available, physicians have a limited knowledge of many rare conditions and it may be more difficult and time-consuming to diagnose or to refer to the right specialist patients affected by these conditions. The incentive to acquire specialist knowledge to diagnose rare conditions is weak when are no therapy options available to treat them once diagnosed, beyond palliation of symptoms. But when a major treatment is introduced, clinicians gain interest in the condition and have greater reason to look accurately for new cases. Therefore, when a new orphan drug is developed and launched, there is more general awareness and an improvement of medical skills of the targeted disease.

For example, the treatments of pulmonary arterial hypertension have brought positive changes in this disease area compared to when no treatment was available. As a result of having more than one company addressing the problem with substantial resources, more attention on the management of pulmonary arterial hypertension is devoted to it at medical conventions, such as that of the American Heart Association[5] which is usually attended by 2,000 cardiologists.

In the case of Pompe disease, since the launch of alglucosidase alfa, the Erasmus Medical Centre, which is the European centre of expertise for that disease, based in the Netherlands[6], has hosted "the Pompe Expert day" every six months[7]. The aim is to create a better understanding of the various aspects of Pompe disease and provide an opportunity for physicians involved in the diagnosis and treatment of Pompe patients to discuss and share experiences. Approximately 120 physicians have attended these training days.

The other source of potential improvement of knowledge and expertise on rare diseases is represented by the clinical trials to develop orphan medicines. It can be argued that development work conducted in Europe, especially clinical trials, can not only improve the medical capability to treat certain rare conditions but can also accelerate access in Europe to the new treatments undergoing trials. This access effect has been shown by Corrigan and Glass (2004) and Walley et al. (2004) for more prevalent diseases.

7.2.3 Research Networks and Infrastructures Facilitating Knowledge Exchange

Given the low prevalence of rare diseases, it is crucial to share the limited knowledge and skills of health professionals and encourage research collaborations internationally. This has been acknowledged in a number of new EU policy documents. For example, the European Council

[5] http://www.americanheart.org/presenter.jhtml?identifier=1200000
[6] http://www.erasmusmc.nl/?lang=en
[7] The 6th Pompe disease expert day took place in June 2009 at the Erasmus Medical Centre University Medical Centre Rotterdam.

recommendation on an action in the field of rare disease (Council of the EU, 2009) emphasises the importance for Member States to:

- Identify appropriate centres of expertise and consider the creation of new ones;
- Promote the participation of centres of expertise in European reference networks;
- Foster cooperation among experts and health professionals within countries and across countries;
- Facilitate patients' access to health care through the use of communication technology such as telemedicine.

It has emerged that the introduction of new treatments has not necessarily led to the establishment of new dedicated centres of expertise at the national level. Instead, it has fostered more cooperation and collaboration at the European level and even, in some cases, at a yet wider international level, in order to share resources and skills on rare diseases and avoid duplication of effort. This has also been pointed out by the High Level Pharmaceutical Working Group on Pricing and Reimbursement in its recent policy document on "Improving access to orphan medicines for all affected EU citizens" (HLPWG, 2008). A way to share and harmonise the standard of care across Europe is for main centres of expertise to issue good practice guidelines which can provide advice to physicians and other professionals in the field.

The activities around Hunter syndrome demonstrate the value of creating a research network. Few large-scale datasets exist on the natural history of MPS II. However, the HOS (Hunter Outcome Survey) is a multinational observational database designed to collect data from patients with MPS II on the natural history of the disorder and the long-term safety and effectiveness of ERT with idursulfase. The first report from HOS was published in 2008. At the time of writing, 550 patients have been registered in the HOS, of whom 135 have since died.

7.2.4 Improving Diagnostic Tools and Time to Diagnosis

The better diagnosis of rare diseases is the outcome of the two previous elements discussed: improvements to medical expertise and the growth of research networks.

The availability of treatment heightens the need for better disease recognition and prompt diagnosis, to avoid the development of life threatening forms of the illness. In some cases an accurate diagnosis of a rare disease involves complex procedures starting with a first contact with a physician, who may not recognise the symptoms immediately, and terminating with the confirmation with the appropriate diagnostic test. Often valuable time is lost because of delay or misdiagnosis: it is reported that for rare diseases diagnosis can take between 5 and 30 years (Pescrire, 2006). There is also some evidence on the delay in diagnosis for eight rare diseases in Europe (Eurordis, 2007). They show that 25% of the patients had to wait between 5 and 30 years from early symptoms to confirmatory diagnosis of their diseases. Moreover, 40% of patients first received an erroneous diagnosis, while 25% of patients had to travel to a different region to obtain the confirmatory diagnosis. In principle, nothing can stop achieving a better diagnosis even without an available treatment. In practice, however, the evidence shows that a key challenge for better treatment of rare diseases is both being able to improve diagnosis and reduce the delay in obtaining it. The development of new orphan drugs is one of the most powerful mechanisms to stimulate this.

Although the general level of training is difficult to assess, such delays in diagnosis suggest that there is a dramatic need for more training in rare diseases among health care professionals - both general practitioners and specialists. Countries with stronger national political support, as indicated by having a national plan, seem to have a higher number of centres of reference (adjusted by

population), which could not only provide treatment and care to patients but also professional training for physicians.

Returning to the case of Pompe disease, early treatment prior to the occurrence of irreversible muscle damage may help to minimise and potentially avoid the need for some of the supportive treatments. The introduction of alglucosidase alfa, which is the first and only approved specific treatment for a neuromuscular disease, has led to:

- Shorter treatment pathways due to earlier diagnosis;
- Improved diagnostic techniques, which have historically presented many challenges. The diagnosis of Pompe disease with GAA Activity Assay, although very sensitive, requires an invasive sampling procedure and is time-consuming (4-6 weeks). Newer assay methods using dried blood spots are faster, easier and minimally invasive (Winchester et al., 2008);
- Consolidation of an EU network of genetic tests for sharing knowledge and harmonisation of practice (EuroGentest[8]).

In the case of Hunter syndrome, the availability of ERT requires a greater awareness and understanding of the disease amongst a range of medical specialists and primary care physicians, so that early diagnosis can be made and treatment started before organ damage becomes irreversible (Wraith et al., 2008).

For many rare diseases, particularly metabolic and genetic disorders, population and neonatal screening strategies are crucial and need to be evaluated at the European level to inform decisions of each Member State. This was identified as a future action of the EU Commission in a 2008 communication to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions (2008).

In relation to the use of diagnostic techniques, the importance of personalised medicine in the context of rare diseases is increasing. In particular, the work on rare diseases and OMPs can be thought of as a precursor in the development of the personalised medicine field. For example, imatinib is one of the first successful examples of targeted therapy where the existing test can predict the subgroup of patients more likely to respond to treatment. The benefits of personalised medicine, both in the area of rare and non-rare diseases, imply more effective medicines with less side effects, increasing compliance. They also imply a move away from a "one size fits all" view of where and how health care is delivered.

7.3 Individual Member States Actions on Rare Diseases

After the introduction of the EU OMP Regulation in 2000, followed by the launch of a number of orphan drugs, some European countries have developed public health policies specific to rare disease. They aim at improving the quality of care for rare disease patients and handling the specificities of rare conditions through the whole treatment pathway, from research initiatives to access to available treatments.

One key initiative in this respect has been the creation and implementation of National Plans for rare diseases which provide across-the-board strategies to manage rare diseases within national health systems. For this purpose, we have classified EU countries according to each of the following categories: having both a national policy for rare diseases and centres of reference; having a national policy for rare diseases but no centres of reference; having no national policy for rare diseases but centres of reference; having no national policy for rare diseases and no centres of reference.

[8] http://www.eurogentest.org/

Table 7.2a and Table 7.2b show this information.

Table 7.2a EU15 Member States

Country	National Policy and Centres of Reference	National Policy but No Centres of Reference	Centres of Reference but No National Policy	No National Policy and No Centres of Reference
Austria* **				✓
Belgium*			✓	
Denmark**	✓			
Finland*			✓	
France	✓			
Germany, *****		✓		
Greece*			✓	
Ireland*			✓	
Italy****			✓	
Luxembourg***				✓
The Netherlands, *****		✓		
Portugal*, ******	✓			
Spain******	✓			
Sweden			✓	
UK*			✓	

Key:
* Countries where official centres of reference have been established but not specifically for rare diseases (Source: Alcimed/Novartis)
** National Plan for research only. These Plans support research but do not include aspects linked to healthcare (Source: Alcimed/Novartis)
*** No centre designated as a centre of reference, although many centres act as such (Source: Alcimed/Novartis)
**** National Plan in creation. Note however, that Spain finally introduced the "*Estrategia Nacional de Enfermedades Raras*" (National Strategy for Rare Diseases) in January 2008.
***** No national plan for R&D but rare diseases were considered as a priority in 1998 and major efforts are made to coordinate actions at national level (Source: Alcimed/Novartis)
Sources: DG SANCO Rare Diseases Taskforce (RDTF); Alcimed/Novartis unpublished report

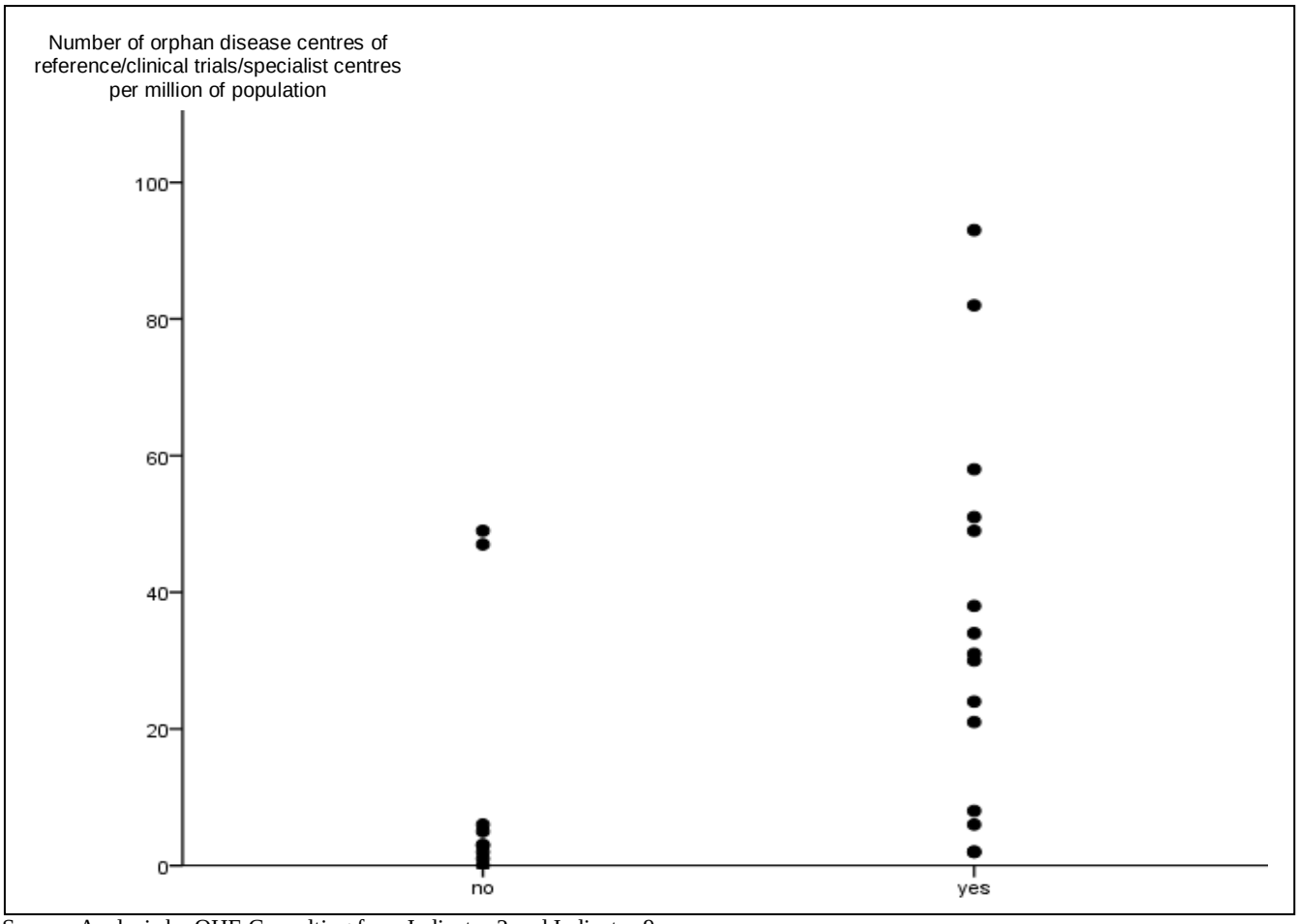
Table 7.2b New EU Member States

New EU Members	Centres of Reference and National Policy	National Policy but No Centres of Reference	Centres of Reference but No National Policy	No National Policy and No Centres of Reference
Bulgaria	✓			
Cyprus				✓
Czech Republic			✓	
Estonia				✓
Hungary				✓
Latvia				✓
Lithuania				✓
Malta				✓
Poland				✓
Romania				✓
Slovakia				✓
Slovenia				✓

Source: DG SANCO Rare Diseases Taskforce (RDTF)

Combining the indicator data at country level does suggest that there is a relationship between activity and national initiatives. As an example, Figure 7.1 plots national initiatives and orphan disease research.

Figure 7.1 National initiatives and orphan disease research: Does the country have a national policy or centres of reference for orphan diseases?



Source: Analysis by OHE Consulting from Indicator 2 and Indicator 9a

In particular, France appears to be the most active country relative to other EU Member States. Nevertheless, it is also true that some exceptions do exist, in that some countries with no national initiatives, e.g. Austria, have higher activity than some countries with national initiatives.

In the confidential survey, companies were also asked to highlight any particular Member State initiative that has had a positive effect. Nearly 40% of the companies mentioned several French initiatives as having a positive effect to encourage R&D in orphan drugs. In particular, both the possibility of having earlier access to the market (via the so-called ATU system) and rewards for building infrastructure around OMPs were mentioned. The second most mentioned factor was the possibility of reduced health technology assessment requirements for orphan drugs (such as not making cost-effectiveness mandatory for market access), which is the case in the Netherlands.

Nine years after the adoption of the EU OMP Regulation, Health Ministers from the 27 EU Member States signed up to a series of political commitments on behalf of Europe's rare disease patients, by

adopting a Council Recommendation on a European Action in the Field of Rare Diseases[9]. In particular, the Member States committed to designing and implementing National Plans for Rare Diseases and Orphan Medicines to be in place by 2013 and to cooperating at a European level on this important and unmet public health priority, increasing the political momentum for rare diseases at both national and EU level.

7.4 Access to Orphan Drugs

Each Member State decides which policies to implement in order to control prices and volumes of medicines launched in their countries. In certain circumstances, pricing and reimbursement negotiations between national payers and manufacturers have been problematic. However, it is the Agency, at the pan-EU level, that grants marketing authorisation (MA) to orphan drugs, which is a necessary step for it to be launched in any Member State.

MA at EU level establishes the quality of a product but does not guarantee patient access as this is determined by each Member State. It is important to note that the OMP Regulation sets in place an EU platform for MA but does not interfere with Member States' competence on access.

As of December 2008, there was one orphan drug with a conditional MA (which required the set up of a registry) and 16 with an exceptional MA (Denis et al., 2009). The remaining orphan drugs, to our knowledge, received a normal MA.

In the case of very rare conditions, such as Pompe disease, where the number of patients in each country is very small, a global registry may be set up. The registry for Pompe disease was set up in 2004 with the purpose:

- "To enhance the understanding of the variability, progression, identification and natural history of the key manifestations of Pompe disease;
- To assist the Pompe medical community with the development of recommendations for monitoring patients and to provide reports on patient outcomes to help optimise patient care;
- To characterize and describe the Pompe disease population as a whole; and
- To evaluate the long-term effectiveness and safety of available treatment options and support measures, including enzyme replacement therapy (ERT)"[10].

A number of studies have been published trying to assess how access to orphan drugs varies across Member States. Eurordis (Eurordis, 2007b) found large differences in the number of available OMPs across different EU countries. They concluded that countries with smaller populations tend to suffer from a longer delay in accessing orphan drugs. Some countries with high average per capita income still only had a small number of OMPs readily available. This unequal access to OMPs is also noted in the recent KCE report (Denis at al., 2009) where it is argued that market access and the utilisation of orphan drugs vary among Member States.

Conditional MA and registries allow for flexibility associated with the development of OMPs. Indeed registries developed in the context of a drug approval on conditional basis can foster patient access. However the availability of OMPs is also dependent on the context in each Member State. Some countries have been particularly flexible in accommodating the use of new orphan drugs in their health care system - for example, France, Germany, Italy, Spain and the Netherlands. In some countries where formal health technology assessment (HTA) is in place, approval for listing or reimbursement of orphan drugs has been more varied. The Netherlands is an exception to this. A

[9] Council Recommendation on action in the field of rare diseases. 2947th Employment, Social Policy, Health and Consumer Affairs Council meeting Luxembourg, 9 June 2009. Available here: http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/lsa/108383.pdf
[10] See http://www.lsdregistry.net/pomperegistry/

recent analysis of coverage decisions in Europe by the Office of Health Economics (Garau and Mestre-Ferrandiz, 2009)[11] shows that almost 30% of the OMPs launched in Sweden were not approved for reimbursement by the national HTA body. In the UK, the Scottish HTA body rejected 13 out of 28 OMPs it had reviewed up to April 2008. This shows that the application of HTA standard methodology to appraise orphan drugs can lead to high rates of rejection and significant delay to access to new OMPs. Garau and Mestre-Ferrandiz argue that, to date, pricing and reimbursement measures implemented in (selected) EU countries have broadly accommodated the introduction of OMPs. But in countries with formal HTA processes, a lower rate of approval is observed. The increasing demand for HTA to inform health care decisions will therefore represent a major challenge in terms of access to OMPs, which are unlikely to meet HTA standard requirements.

[11] This report was partially based on the OHE-organised workshop "Accommodating Orphan Drugs: Balancing Innovation and Financial Stability". A summary of it can be found at: http://www.ohe.org/page/news/article.cfm?articleId=20

8 Conclusions

The pharmaceutical industry, like most stakeholders in the area of rare diseases, deems the EU OMP Regulation to have been a success and, indeed, one of the most successful EU policies overall. We argue that the incentives provided in the legislation greatly fostered innovation and entry into market of therapies addressing hitherto unmet medical needs. Increasing activities around OMPs have also led to an improvement in the delivery of health care more widely for rare diseases.

There seems to be a relation between national initiatives and activity on rare diseases/orphan drugs. France, which was the first country (in 2005) to implement a National Plan for Rare Diseases, seems to be the leader relative to other EU countries in OMP related activity. However, it is also true that exceptions exist in that some countries where there seems to be less political support specifically for rare diseases are nevertheless relatively active in the area.

But at the same time, further scientific and policy research in the area is needed to better understand the epidemiological and clinical impact of rare diseases in the EU as well as to support sound policy decision-making to improve, for example, access to treatment and care. A key challenge that remains is to reconcile the increasing efforts in developing new orphan drugs with issues related to HTA and market access. Indeed, ensuring access to orphan drugs in national health care systems in a timely and effective way is important to maintain the positive impact of the OMP developers on the economy and ultimately to continue delivering life-saving therapies for patients.

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Annex 1 Summary of Indicators

Indicator Number	Description	Source
Patient Management		
Number and role of patients associations		
1a	Current number of Europe-wide orphan disease patient associations	Eurordis
1b	Current number of national orphan disease patient associations for each EU15 Member State	Eurordis
Number and role of dedicated structures providing healthcare services for rare diseases		
2	List of countries falling into each of the following categories: national policy for rare diseases and centres of reference; national policy for rare diseases but no centres of reference; no national policy for rare diseases but centres of reference; no national policy for rare diseases and no centres of reference.	DG SANCO Rare Diseases Taskforce (RDTF) and Alcimed/Novartis unpublished report
Number of diagnosed and treated patients		
3	Prevalence of orphan diseases calculated for Europe for all diseases in the Orphanet database	Orphanet
Number of health professional training courses/modules and attendees		
4a	Past and current list of courses for health professionals	OrphaNews (Orphanet)
4b	Past and current list of congresses for health professionals	OrphaNews (Orphanet)
Competitiveness		
Number of public researchers/investigators involved		
5	Total number of researchers in clinical trials for orphan medicines with at least one site in an EU member country reported by clinicaltrials.gov	www.clinicaltrials.gov
Number of private or public funds that are creating jobs in the field of OMPs		
6a	Total number of research projects by country	Orphanet
6b	Number of OMPs launched per year since 2000	EMEA
6c	Current number of companies with active compounds in development for orphan conditions by nationality of corporate headquarters	IMS Lifecycle
6d	Qualitative description of "success stories"	5 interviews
Science and Innovation		
Number of scientific publications		
7	Number of citations for publications relevant to OMPs by EU15 member state by year	N/A
Number and nature of clinical trials		
8a	Total number of clinical trials for orphan medicines by country by phase	Orphanet

8b	Number of patients recruited for clinical trials for orphan medicines with at least one site in an EU member country reported by clinicaltrials.gov	www.clinicaltrials.gov
Number of R&D programmes (industrial, academic, public/private partnerships		
9a	Number of clinical trials begun, specialist centres established or research projects initiated for orphan diseases for Europe	Orphanet
9b	Past and current EU funded projects for rare diseases, count and value	EC*
9c	Examples of knowledge acquired on some selected rare diseases	1 interview

* http://ec.europa.eu/health/ph_threats/non_com/projects_rarediseases_en.htm; http://cordis.europa.eu/lifescihealth/major/rare-diseases-projects-1.htm; http://ec.europa.eu/health/ph_threats/non_com/rare_3_en.htm (& /rare_4_en.htm; & /rare_8_en.htm)

Annex 2 Confidential Survey and Sample

We received a total of 18 responses, from the following companies: Actelion, Addmedica, Amgen, BioMarin, Celgene, Cephalon, Genzyme, HRA Pharma, MerckSerono, Novartis, NovoNordisk, Orfagen, Orphan Europe, PharmaMar, Roche, Shire, Solvay and Swedish Orphan.

Part 2: YOUR COMPANY

Q1a: Was your company founded in 1997 or later? *(please select from drop down list in box to the left)*

If yes please state year

Q1b: When did you launch your first OMP (if available)?

Q2: Was the global headquarter of your company in the EU at the time of its establishment? *(please select from drop down list in box to the left)*

If no, where was it?

Q3: Did your company become active in the development of OMPs before 2000? *(please select from drop down list in box to the left)*

Q4 What was the value (€000's) of **expenditure on Research and Development** (including basic research and clinical development) by your company, both global total (including EU) and EU only, in total (all R&D) and specifically for OMPs,

In 2008 (or most recent year)

	Global (€000's)	EU (€000's)
Total		
OMP related		

In 2004

	Global (€000's)	EU (€000's)
Total		
OMP related		

In 2000

	Global (€000's)	EU (€000's)
Total		
OMP related		

Q5 What was the value (€000's) of **revenue** for your company, both global total (including EU) and EU only, and how much of that total turnover was for OMPs, in 2008, 2004, 2000?

In 2008 (or most recent year)

	Global (€000's)	EU (€000's)
Total		
OMP related		

In 2004

	Global (€000's)	EU (€000's)
Total		
OMP related		

In 2000

	Global (€000's)	EU (€000's)
Total		
OMP related		

Q6 What was the value (€000's) of **capital assets** (e.g. manufacturing sites, machinery, etc.) for your company, both global total (including EU) and EU only, and how much of that total value of assets relates to OMPs, in the following time periods: 2000-2002; 2003-

In 2006-2008

	Global	EU
Total		
OMP related		

In 2003-2005

	Global	EU
Total		
OMP related		

In 2000-2002

	Global	EU
Total		
OMP related		

Part 2: YOUR COMPANY

Q7 How many people (whole time equivalents if possible) did your company employ, both global total (including EU) and in the EU specifically, and how many of them worked on OMPs, in 2008, 2004, 2000?

In 2008 (or most recent year)

	Global	EU
Total		
OMP related		

In 2004

	Global	EU
Total		
OMP related		

In 2000

	Global	EU
Total		
OMP related		

Q8 How many people (whole time equivalents if possible) did your company **employ in R&D**, both global total (including EU) and in the EU specifically, and how many of them worked on R&D for OMPs, in 2008, 2004, 2000?

In 2008 (or most recent year)

	Global	EU
Total		
OMP related		

In 2004

	Global	EU
Total		
OMP related		

In 2000

	Global	EU
Total		
OMP related		

Note 1 for question 8: You can provide percentages rather than actual numbers.
Note 2 for question 8: If you find it difficult to provide the actual number of employees, or percentages, involved in R&D due to cross-overs across different departments you can alternatively provide "Number of people with post graduate qualifications, including PhDs".

Please go to sheet "Your Company Portfolio"

Part 3: YOUR COMPANY PORTFOLIO

Note: If you feel this is confidential information, please provide for the number (count) of orphan medicines currently in development (Phase I and onwards):

Q9 Please list all **marketed** OMPs in your company portfolio and whether launched in EU, USA and/or other markets

INN name	Tradename	Indication	Launched EU (y/n)	Launched USA (y/n)	Launched Rest of World (excl. EU and US) (y/n)

Q10 Please list all orphan medicines **in development** (Phase I and onwards) in your portfolio. Please include those that have orphan designation in at least one region and those which you intend to, or have, registered for orphan designation

INN name (if available; otherwise project code)	Tradename (if available)	Indication (if available; otherwise target disease)	Orphan designation EU (y/n)	Orphan designation USA (y/n)	Orphan designation ROW (y/n)

Part 4 EU OMP REGULATION

Q11 How influential has the introduction of the EU Orphan Medicinal Products Regulation (2000) been in shaping your company's strategic decision making in the EU? *(list in box left)*

Q12 What three features (e.g. period of market exclusivity; automatic access to centralised procedure; reduced fees and free scientific advise) of the Orphan Medicinal Products Regulation are the most important for your company, from a regulatory point of view? Please

(i)

(ii)

(iii)

Q13 Which, if any, initiatives by any EU Member State to encourage OMP related investment have had a significant influence for your company? Please rank 1 to 3

(i)

(ii)

(iii)