Orphan drug development across Europe: bottlenecks and opportunities

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With the assignment of the 500th European Union orphan drug designation in 2007, the Regulation on Orphan Medicinal Products truly begins to show its potential for delivering new medicines to patients with rare diseases. Here, we analysed European orphan drug development at a national level and unveil a strong relationship between orphan drug development and pharmaceutical innovation performance in Europe. Moreover, we identify gaps in transition from science into orphan drug development as important bottlenecks that exist in several European countries. Our findings underline the importance of innovation-based policies to enhance the development of orphan drugs in Europe.

Seven years after coming into force, the European Union (EU) Regulation on Orphan Medicinal Products has yielded over 500 orphan designations and, more importantly, nearly 45 orphan medicinal products have been approved for marketing [1–4]. Similar to its United States (US) counterpart, the EU Regulation contains several economic and regulatory incentives to stimulate the development of drugs for rare diseases (Box 1) [4,5]. The US Orphan Drug Act, which came into force in 1983, is highly appreciated for its role in delivering new medicines to patients with rare diseases and claims have even been made that introduction was responsible for fostering the birth of the US pharmaceutical biotechnology industry [6–8]. A recent report on the impact of the EU Regulation revealed that 53% of EU orphan designations concern novel or innovative products. In addition, many of the other EU orphan designations are innovative uses of already existing molecules [3]. A good example in this respect is the use of arsenic trioxide, which was compounded already in the 19th century [9], and was recently approved as an orphan drug in the US and in the EU for the treatment of acute promyelocytic leukaemia. Despite the positive impact of the Regulation on orphan drug development, it has also been suggested that orphan drug development is progressing too slowly [10]. This may have been true during the first years of the Regulation; however, the incremental annual growth in the number of orphan designations and orphan drug approvals during the years 2006 and 2007 now convey a different message (see http://www.ec.europa.eu/enterprise/pharmaceuticals/register/index.htm).

Approximately 85% of the orphan designations applications originate from small- and medium-sized enterprises (SMEs) (Torrent-Farnell, ICORD 2005, see http://www.icord.cc/stockholm_2005.php?p=speaker_presentations). For these companies, the EU Regulation provides an important opportunity to demonstrate the potential of their new technology platforms and drug products. Promising products may subsequently be licensed or sold to other companies for further development or may be developed by SMEs under their own steam [11–13]. Although previous research has shown that successful European orphan drug development was mostly associated with experienced companies and known compounds [14], the EU Regulation is starting to play an important part in stimulating innovation in the area of life sciences in Europe, just like the US Orphan Drug Act did in the US [6]. This is emphasised by the fact that the nearly 50 approved orphan drugs represent a considerable part of the overall number

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BOX 1

Orphan drug legislation in Europe

Since April 2000, sponsors of a potential orphan drug in the EU can apply at the EMEA for orphan drug designation. If the Committee for Orphan Medicinal Products (COMP) judges that the potential orphan drug is indicated for the prevention, treatment or diagnosis of a life-threatening or chronically debilitating disease with a maximum prevalence of 5 patients in 10,000 inhabitants and that it will be of significant benefit for those affected by that condition, an orphan designation can be awarded [4]. Designated potential orphan drugs are entitled to several incentives, of which a market exclusivity of ten years upon authorisation is the most important one [44]. Other incentives are direct access to the centralised procedure for European marketing authorisation, fee reductions for regulatory procedures, free scientific advice and protocol assistance during the development process [3]. In contrast to the US, tax incentives are not provided in the EU at community level [45]. With this designation procedure, the EU aims to stimulate bottom-up initiatives to further enhance the development of innovative new treatments for patients with rare diseases.

of drugs approved through the EU centralised procedure since 2000 [3,15].

To assess the effect of the EU Regulation on the development of orphan drugs at a national level, we categorised the European orphan designations between April 2000 and December 2007 per country of origin. Our results show that the origin of designated orphan products is not homogenously distributed across the European countries. Since innovation plays an important role in orphan drug development, and a widespread difference in innovation performance between European countries also exists, we investigated whether the level of orphan drug development was associated with the level of innovation performance of the individual country. Our findings unveil a strong relationship between orphan drug development and pharmaceutical innovation performance in Europe and underline the importance of innovation-based policies to enhance the development of orphan drugs in Europe.

Orphan drug development in Europe

From the start of the EU Regulation on Orphan Medicinal Products in April 2000 up to 31 December 2007, 521 medicinal products have obtained an orphan designation and are recorded in the Community Register for Orphan Medicinal Products (see http://www.ec.europa.eu/enterprise/pharmaceuticals/register/index.htm). In the EU an orphan designation can be applied for at any stage in the development process, provided that the sponsor can establish that the product fulfils the criteria for designation (Box 1). Furthermore, the application for an orphan designation should take place before the application for market authorisation. Review of the summaries of opinion of the EU orphan designations reveals that the stage of development at the time of application varies from preclinical to clinical development (see http://www.emea.europa.eu/htms/human/orphans/opinions.htm). An orphan designation could thus be regarded as the first proof that studies are being conducted with the aim to develop an orphan medicinal product for a specific, rare, indication. Therefore, in our opinion, the number of orphan designations provides a good indicator for the level of orphan drug development in each member state. However, only sponsors residing in the European Economic Area (EEA) can submit applications at the European Medicines Agency (EMEA) and consequently a considerable number of designations from companies or institutions outside the EEA have been submitted by EEA-based subsidiaries or consultancy firms. Moreover, to provide a trustworthy comparison between the various countries, the stage of development of each orphan designation should be standardised. In drug R&D successful execution of each stage, from discovery to market authorisation application, is essential to obtain market authorisation. Although pharmaceutical innovation includes drug discovery and drug development, in this study we defined country of origin as the country in which the company or institution was located that was leading the step from preclinical work to initial clinical development of the particular product for the designated indication (Fig. 1). The rationale behind this definition is that the transition from preclinical to clinical development is generally accepted as a central, but also in many ways challenging, step in drug development. Furthermore, the move of a drug product into the clinical testing stage represents the first step of a company or institution to show real commitment towards developing an orphan medicinal product.

Absolute orphan drug output across Europe

Out of the 521 orphan designations, a total of 300 (58%) were originally developed by European companies or institutions, while the remainder of the designations originated from outside Europe, predominantly from the US (177 out of 521, 34%). The number of countries of origin of the European orphan designations was limited to 12 EU member states, Switzerland and Norway (Fig. 1a). In particular France and Germany, being the larger European countries, accounted for a large fraction of the 300 European orphan designations. For 12 of the remaining 15 EU member states, the lack of orphan designations can partly be explained by the fact that drug discovery and development is a lengthy process, and that, before joining the EU in 2004 or 2006, companies or institutions from these Eastern European countries did not have access to the incentives stated in the EU Regulation. By contrast, several countries from outside the EEA, particularly Switzerland and the US, accounted for a considerable number of orphan designations, while these countries did not have access to the EU incentives. Moreover, three of the EU-15 countries (Luxembourg, Portugal, Ireland) had access to the incentives stated in the EU Regulation from the start of 2000, but did not account for any orphan designation. Our findings show that the wide heterogeneity across the countries of Europe with regard to the level of orphan drug development cannot be entirely explained by differences in (direct) access to the incentives provided by the EU orphan drug legislation.

Relative orphan drug output across Europe

Larger European countries are more likely to produce larger numbers of orphan designations, because these countries will probably harbour more companies and may have larger R&D expenditures than smaller European countries. To come to a more fair comparison, we therefore adjusted for size differences between countries, via standardisation by population size. The results, depicted in Fig. 1b, show that European orphan drug development is primarily

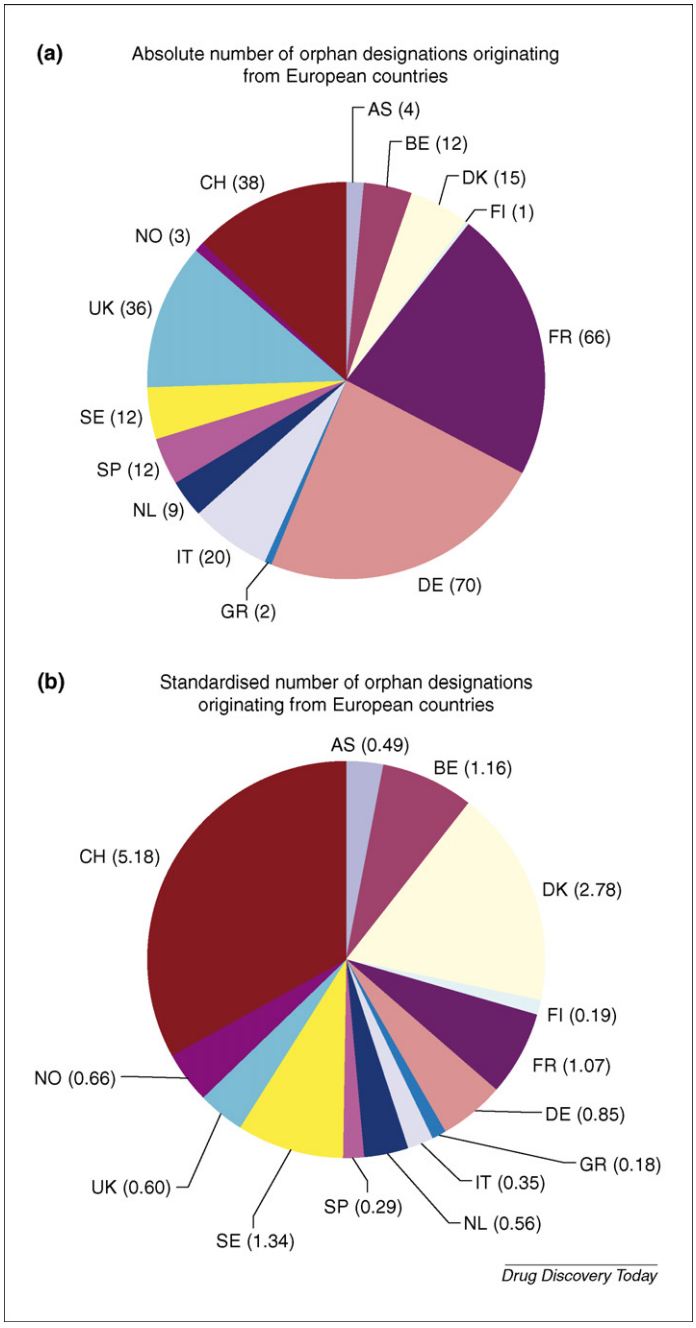

FIGURE 1

Absolute **(a)** and standardised **(b)** number of orphan designations (n = 300) originating from European countries. The country of origin of a designated orphan medicinal product was defined as the country in which the company or institution was located that was leading the step from preclinical work to initial clinical development of the particular product for the designated indication (typically Phase I or Phase I/IIa clinical trials or proof-of-concept). For products not yet in clinical development, the country of origin was determined as the country in which the company or institution was located that was leading the latest preclinical development program for the designated indication. For multinational companies the country of origin was defined as the country of the headquarters of the company. Publicly available sources (e.g. PubMed, company websites, patent databases, press releases) were used to determine the country of origin. Data in (b) were standardised per million of population (2000–2007). AS, Austria; BE, Belgium; DK, Denmark; FI, Finland; FR, France; DE, Germany; GR, Greece; IT, Italy; NL, The Netherlands; SP, Spain; SE, Sweden; UK, United Kingdom; NO, Norway; CH, Switzerland.

centred in Northwestern Europe, with Switzerland and Denmark as frontrunners. Countries outside the EU-15 that produced at least one orphan designation were also included in the study. The number of designations per million, for the countries included in the study, ranged from 0.18 (Greece) to 5.18 (Switzerland). Adjustment for size differences between countries by gross domestic product (GDP) instead of population size resulted in a comparable distribution.

In this study, we aimed to find an explanation for the observed heterogeneity in orphan drug development across Europe. Since innovation plays an important part in orphan drug development, we hypothesised that the level of innovation performance of the individual European countries is related to orphan drug output, and thus provides an explanation for the heterogeneous distribution of orphan drug development across Europe. A recent report from the US that focussed on the development of orphan drugs supports our hypothesis [16]. In this report it was suggested that the increase in orphan drug development in the US is mainly caused by advances in science and expenditures on pharmaceutical R&D over the past years. Moreover, a recent publication reveals that Switzerland's innovation performance was one of the key factors driving its success in the growth of its biotechnology industry [17].

Pharmaceutical innovation performance in Europe

General innovation performance

Innovation is generally characterised as the process of diffusion, integration and exploitation of knowledge to create economic and social value [18]. As part of the Lisbon Strategy, which aims to make the EU the most dynamic and competitive economy in the world by 2010 [19,20], the EU assesses the innovation performance of its member countries in an annual European Innovation Scoreboard (EIS) (see http://www.proinno-europe.eu/index.cfm?fuseaction=page.display&topicID=248&parentID=51). Consequently, the EIS may be used as an instrument to compare the innovation performance of European countries to the actual output of orphan designations. Switzerland, Denmark and Sweden, frontrunners in orphan drug development in Europe, are also the top ranking countries in innovation performance in the EIS during 2002–2006. This observation clearly supports our assumption that innovation performance plays a part in orphan drug development across Europe. However, the indicators included in the EIS cover all sectors of science and industry and consequently the EIS is probably too general to be predictive for orphan drug development in Europe. This is best exemplified by Finland, which ranks high in innovation performance in the EIS, but only one orphan designation was found to originate from this country. Evidently, a set of innovation indicators more specific for the pharmaceutical sector is required to really substantiate the impact of innovation performance on orphan drug development.

Pharmaceutical innovation performance

Pharmaceuticals provide the largest share in the European trade balance in high technology and R&D and consequently play an important part in innovation in Europe [21]. Pharmaceutical innovation is the focus of many recent publications, especially in conjunction with the Lisbon Strategy [19]. Most of these publications deal with addressing the halted productivity of the pharmaceutical industry [22–24], the innovation gap between

Europe and the US [25–27], and the European paradox [28,29]. To reach the goals of the Lisbon Strategy, this innovation gap needed to be addressed and, consequently, specific action measures have been implemented all over the EU, including in the field of drug development. The European Commission focuses on facilitating innovation and research in the EMEA Roadmap to 2010 [30] and apart from the Regulation on Orphan Medicinal Products [4], policy implications in this field include the recently implemented Paediatric Regulation [31] and the Innovative Medicines Initiative (see http://www.imi.europa.eu). Moreover, the World Health Organisation's 'Priority Medicines for Europe and the World' report is a good example of how science is driving agenda setting in public and private research expenditures [32]. Among these initiatives, the EU Regulation on Orphan Medicinal Products has been found to be a valuable incentive system for stimulating the transition from the highly ranked European science towards real innovations that benefit the European economy as well as patients with rare diseases.

An important question that arises from these observations is how pharmaceutical innovation performance at the country level influences orphan drug discovery and development throughout Europe. Well-known indicators of pharmaceutical innovation performance include scientific output, number of pharmaceutical patent applications, pharmaceutical R&D expenditure and the output of the pharmaceutical industry in terms of new chemical entities (NCEs) or top selling drugs [18,33–37]. An algorithm to assess drug innovation has also been described recently [38]. Similar to general innovation performance, each of these indicators alone is not considered the optimal metric for pharmaceutical innovation performance of a country [33,34] and consequently in this study we focus on three sequential stages within the drug development process. The first stage is that of biomedical scientific output, the start of every attempt to develop a therapy for a (rare) disease. The second stage is that of the innovation in pharmaceutical development, measured in terms of R&D expenditure, pharmaceutical patent applications and the number of SMEs active within the pharmaceutical sector. Finally, the third stage is the pharmaceutical output in terms of orphan designations. We collected data on indicators for each of these three stages of orphan drug development, taking a time delay between the stages into account (Table 1). Linear regression analyses between the selected indicators that describe innovation in pharmaceutical development and the number of orphan designations per million inhabitants revealed a strong correlation. The correlation coefficients (R^2) for pharmaceutical R&D expenditure, the number of pharmaceutical patents and for SMEs active in the pharmaceutical sector were 0.90, 0.88 and 0.71, respectively. Statistical data on pharmaceutical SMEs at a national level were limited to class DG24.4

TABLE 1

Pharmaceutical innovation scores in Europe on a national level

Country	Biomedical scientific output (1994–2004)	Innovation in pharmaceutical development (1998–2004)			Pharmaceutical output (2000–2007)
	Citations in biomedical sciences[a] (no./1000 population)	Expenditures on pharmaceutical R&D[b] (€/million population)	Patents[c] (no./million population)	SMEs[d] (no./million population)	Orphan designations (no./million population)
Austria	46.5	23.2	8.7	9.7	0.49
Belgium	58.4	103.5	14.9	8.6	1.16
Denmark	93.7	115.6	25.1	13.4	2.78
Finland	92.6	35.6	8.5	5.3	0.19
France	39.5	53.9	13.9	8.6	1.07
Germany	39.0	41.0	15.1	5.5	0.85
Greece	10.3	3.3	0.8	3.6	0.18
Ireland	32.5	16.6	7.2	12.3	0
Italy	26.7	15.0	4.7	11.2	0.35
Luxembourg	10.7	N/A	2.6	1.0	0
Netherlands	79.3	23.0	10.0	7.3	0.56
Portugal	6.4	N/A	0.7	9.7	0
Spain	17.2	11.4	2.3	8.0	0.29
Sweden	117.6	119.8	20.0	13.3	1.34
United Kingdom	79.5	78.5	14.2	7.4	0.60
Norway	N/A	21.2	8.0	3.0	0.66
Switzerland	146.9	286.7	38.1	29.4	5.18

Data on indicators were extracted from publicly available resources and standardised by population size. To eliminate possible time-related biases as a result of the lengthy development process, data on biomedical scientific output were obtained from the period 1994 to 2004, while that of the innovation in pharmaceutical development (pharmaceutical private R&D expenditure, patent applications and SMEs) was obtained from 1998 to 2004 and that of the output of European orphan designations from 2000 to 2007.

[a] From Soteriades and Falagas [46] and completed with data from the Institute for Scientific Information (see http://www.in-cites.com).
[b] From reports by the European Federation of Pharmaceutical Industries and Associations [47].
[c] International patent class A61K, preparations for medical, dental or toilet purposes, from the European Patent Office (http://www.espacenet.com/index.en.htm).
[d] NACE class DG24.4, manufacturers of pharmaceuticals, medicinal chemicals and botanical products, from Eurostat (http://epp.eurostat.ec.europa.eu/portal/page?_pageid=0,1136195,0_45572097&_dad=portal&_schema=PORTAL) and completed with calculated data from the Swiss Bureau for Statistics (data for 1998 and 2001 for all [48]).

according to the classification of economic activities in the European Community (NACE). NACE DG24.4 is the overall pharmaceutical manufacturing class, which will include highly R&D focussed SMEs as well as more basic manufacturing SMEs. Consequently, typical manufacturing countries, in particular Ireland and Portugal [39], also score well in number of pharmaceutical SMEs, which may explain the observed lower correlation between orphan designations and SMEs. The correlation between biomedical scientific output, as measured by the number of citations in biomedical sciences per population, and orphan designations per population was weaker however ($R^2 = 0.57$). The overall results showed a high level of robustness because the overall picture did not change when other comparators (GDP, absolute data) were used for the standardisation of the data (data not shown).

The weak correlation between scientific output and orphan drug development as compared to the strong correlation between the second stage of pharmaceutical innovation and orphan drug development suggests that this second stage is more important for orphan drug development than the first stage. To investigate this further, we determined relative rankings of countries for these stages of the drug development process and plotted them in a graph (Fig. 2). The size of the 'bubbles' in Fig. 2 represents the standardised number of orphan designations per country. Here, it can be observed that Denmark and Switzerland are in the top three for biomedical scientific output, innovation in pharmaceutical development and pharmaceutical output in terms of orphan designations. Sweden is also in the top three in all stages; however, it lags behind the other two countries in terms of orphan designations. This finding indicates that Sweden has difficulties translating innovation into pharmaceutical output, which has previously been described as the 'Swedish Paradox' [40]. The results of the other countries reveal that their rank for biomedical scientific output is not always equal to their rank for innovation in pharmaceutical development. Finland, The Netherlands and, to a lesser extent, the UK, can be identified as countries that score very well in terms of scientific output, but have not (yet) been able to translate their scientific output into innovations in pharmaceutical development and subsequently into pharmaceutical output. This observation has also been noted in a broader perspective by others [41,42], but is in contrast to findings by McMillan *et al.*, who emphasise the important role of public science in the biotech industry [37]. For this reason, biotech companies tend to concentrate around centres of knowledge, such as highly ranked universities [36]. However, McMillan's study is from a US perspective, while in Europe differences exist regarding how countries have responded to the growth in biotechnological science. The European Commission addressed this 'European Paradox' in its 2003 report on science and technology indicators [29]. Not all countries have been able to translate the growth in biotechnological science into real innovations, as measured in patents for that purpose. This is especially the case for several smaller and medium-sized countries, as these countries often lacked the amount of industry capacity necessary to translate the inventions in science into products. Recent initiatives have been implemented in The Netherlands (Top Institute Pharma, see http://www.tipharma.nl) and Belgium (Institute for the Promotion of Innovation by Science and

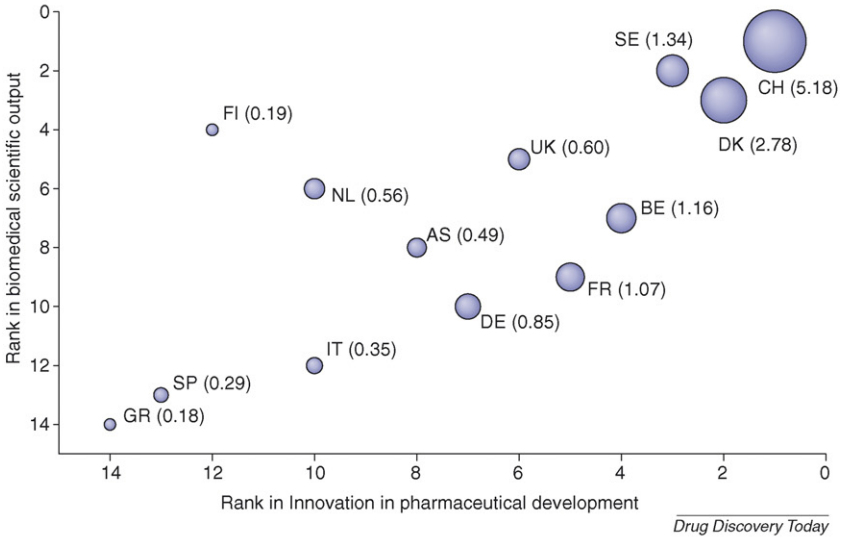

FIGURE 2

Biomedical scientific output, innovation in pharmaceutical development and orphan designations in Europe. Rankings on pharmaceutical innovation performance are calculated from the integer of the combined ranking of expenditures on pharmaceutical R&D, pharmaceutical patents and pharmaceutical SMEs. Rankings for biomedical scientific output are based on the number of citations in biomedical sciences. Only countries for which data were available on all indicators have been included in the graph. 'Bubble' size corresponds to the standardised number of orphan designations for each country (in brackets). Countries corresponding with the 'bubbles' in the top right-hand corner of the graph (Switzerland, Denmark, Sweden) rank highest in pharmaceutical development and scientific output. The number of orphan designations from Sweden is lower than expected based on its position in the graph. The group of countries corresponding with the 'bubbles' in the middle of the graph develop average numbers of orphan designations. The two 'bubbles' above this group represent countries (Finland and The Netherlands) that have a lower ranking for innovation in pharmaceutical development than for scientific output. AS, Austria; BE, Belgium; DK, Denmark; FI, Finland; FR, France; DE, Germany; GR, Greece; IT, Italy; NL, The Netherlands; SP, Spain; SE, Sweden; UK, United Kingdom; NO, Norway; CH, Switzerland.

Technology in Flanders, see http://www.iwt.be) that should lead to a more optimal translation of science into pharmaceutical innovation and eventually pharmaceutical output.

All the aforementioned findings thus provide support for this hypothesis of the European Paradox and it is our conclusion that not only is the quality of the biomedical scientific output of importance for orphan drug development in Europe but also that the performance in innovation in pharmaceutical development is even more important. Here, we have identified a bottleneck in the drug discovery and development process for several European countries. Our findings therefore support policies that foster investments in general drug development to promote the development of medicines for rare diseases. Indeed, a recent paper by Kola [43] supports these findings by stating that innovation in drug development is of crucial importance for increasing success rates in drug development.

Concluding remarks

In conclusion, four main findings originate from this study. First, we have shown that the European Orphan Drug Designations originate for about 58% from European companies or institutions. This underlines that the incentives from the European Regulation also encourage sponsors from outside the EU to develop orphan medicinal products for the European Market. Second, we have found that a wide heterogeneity in the level of orphan drug development exists across Europe. Third, we have shown that orphan drug development is strongly related to the performance of innovation in pharmaceutical development of the individual countries. Those countries that harbour large amounts of pharmaceutical SMEs, and the countries in which companies spend larger amounts on pharmaceutical R&D and apply for more patents, do develop more orphan drugs. National policies to stimulate the development of orphan drugs should therefore be aimed at stimulating innovation in the pharmaceutical sector. Fourth, we have determined that scientific output in biomedical sciences plays a part in stimulating the development of orphan drugs as well, although not as large as innovation in pharmaceutical development. This finding identifies the bottleneck in the development of orphan drugs. The quality of the science originating from a country alone appears to be of less importance than the performance in innovation in pharmaceutical development. It is therefore essential for countries not only to stimulate the quality of their universities and schools, but also to invest in a favourable climate that fosters innovation in pharmaceutical development. The same applies for the devotion of additional resources specifically aimed at orphan drugs; these should be devoted to drug discovery as well as drug development. Only a combination of these policies will bring more of the seriously needed treatments for many patients with a rare disease to the market.

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