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Predictors of orphan drug approval in the European Union

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Abstract
Objective To encourage the development of drugs for rare diseases, orphan drug legislation has been introduced in the USA (1983) and in the EU (2000). Recent literature discusses factors that may influence the development of new orphan medicinal products in the EU. This study aims to identify predictors for successful marketing authorisation of potential orphan drugs in the EU.
Methods A comparison between randomly selected authorised and a matched sample of not-yet-authorised orphan drug designations has been performed. Determinants in the study included characteristics of the indication, of the product and of the sponsor. Data were collected from the public domain only.
Results Orphan drug approval was strongly associated with previous experience of the sponsor in obtaining approval for another orphan drug (OR=17.3, 95% CI=5.6–53.1). Furthermore, existing synthetic entities compared to biotechnology products tended to have a higher likelihood of reaching approval status (OR=3.9, 95% CI=0.9–16.6).
Conclusion This study showed that experience of a company in developing orphan drugs is an important predictor for subsequent authorisation of other orphan drugs. The same applies for existing (synthetic) molecules, for which much knowledge is available. Further research should be directed towards studying the quality of the clinical development program of those designated orphan medicinal products not reaching approval status.

Keywords Orphan drugs · Rare diseases · Drug development · Regulatory affairs

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Introduction

In Europe and the United States (USA) together, more than 55 million people suffer from a rare disease. It is estimated that approximately 5,000 to 7,000 rare diseases exist, and every year about 250 new ones are described [1, 2]. This is partly due to our continuously improving knowledge on disease biology and genomics, which allows more prevalent diseases to be broken down into several rare diseases. In addition to this, new symptoms, mechanisms and aetiologies are described in literature, representing more new diseases [3, 4]. As yet, for many rare diseases, no treatment is available [2, 5]. The high costs and risks of drug development, combined with difficulties in conducting clinical trials in small patient populations and the small market size, discourage the pharmaceutical industry from developing drugs for these rare diseases [2, 6]. Finding ways to bring drugs for rare diseases to patients is therefore an important public health issue [1, 7].

Consequently, several jurisdictions have put forward incentives to stimulate the development of drugs for rare diseases. Following the successful Orphan Drug Act in the

USA, the European Union (EU) introduced its Regulation on Orphan Medicinal Products in April 2000 [8–10]. The systems have much in common, although a few differences exist. In the USA, drugs indicated for a maximum of 200,000 patients (equivalent to 7 patients per 10,000 residents) are eligible for orphan drug designation. In the EU, an orphan designation will only be provided by the European Commission if the product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that affects fewer than 5 in 10,000 patients. Moreover, the sponsor should establish that there exists no satisfactory method for the diagnosis, treatment or prevention of this condition, or if such exists, that the new product will be of significant benefit for those affected by that condition [3, 10–12].

Designated potential orphan drugs in the EU are entitled to several incentives, of which a market exclusivity of 10 years upon authorisation is the most important one [12]. Other incentives are direct access to the centralised procedure for European marketing authorisation, 50% fee reductions for regulatory procedures and free scientific advice during the development process [13]. With this designation procedure, the EU aims to stimulate bottom-up initiatives to further develop possible orphan drugs.

Thus, an orphan drug designation system creates a 'pre-screen' of promising future orphan drugs. However, to be designated does not automatically mean an orphan drug will be authorised for marketing. A recent study by Joppi pointed out that in April 2004, only 7.1% of the EU designated potential orphan drugs were approved for marketing, questioning whether the incentives are sufficient to provide the European market with new orphan drugs [14]. These observations give strong impetus to the question of what determines successful development and marketing authorisation of an orphan drug. In other words: what makes an orphan designation result in an authorisation? A paper by Dear argued that the US Orphan Drug Act is so successful because of tax grants, which are not available in Europe [12]. Other factors that have been suggested as relevant in terms of influencing the likelihood of approval are the potential of the sponsor to carry out suitable clinical trials and the level of patient involvement in the development process [5]. However, beyond these suggested factors, additional characteristics may be of importance that have not been studied yet.

Since all products have to comply with the criteria of quality, safety and efficacy, we hypothesise that designated orphan medicinal products that have not (or not yet) obtained marketing approval therefore either have unfavourable characteristics or the sponsor of the product has not been able to show the favourability of the product characteristics. The latter can have multiple causes, including lack of experience or insufficient means for the clinical development program. In addition to this, the type of indication may influence the perspectives on marketing authorisation, as the risk-benefit balance may be influenced by the degree of severity of specific disease classes. The objective of this study is therefore to identify predictors of successful marketing authorisation in the EU.

Methods

Selection of candidate orphan medicinal products

The cohort of 386 designated orphan drugs and orphan drug candidates has been followed from the start of the EU Regulation on Orphan Medicinal Products in April 2000. We enrolled all designated orphan medicinal products with a marketing authorisation by the European Commission up to 1 October 2006 in our analysis and compared these to a subset of the designated, but not yet authorised, orphan drugs. To avoid potential bias due to time-related differences in the probability of getting authorisation, for each authorised product, a random sample of up to two designated products from the same time period (120 days before to 120 days after) as the designation date of the authorised product was selected. Authorised orphan drugs with multiple authorised indications (imatinib, sunitinib and dasatinib) were sampled to up to two unapproved orphan drugs for each indication.

Data collection

To test our hypothesis, we collected data for each product on the indication, the product and the sponsor. Selection of data was limited to the public domain. Indication characteristics included data on the type of disease and disease prevalence for which the product is indicated. Product characteristics included data on the type of product, proposed route of administration and previous approval or designation of the molecule in other geographic regions than the EU. Sponsor characteristics included those details of the sponsor that may be indicative for demonstrating the favourability of the product, including the size of the company, geographic region of drug development and experience of the company with drug development. A full list of these variables is shown in Table 1. If available, EMEA definitions were used for the classification of the subcategories and variables. Sources included the EMEA website (http://www.emea.europa.eu), European Public Assessment Reports (EPARs), sponsor websites, annual reports, press releases, and peer-reviewed scientific literature.

Data analysis

Characteristics of approved and unapproved orphan medicinal products were compared using a univariate analysis.

Table 1 Overview of characteristics and definitions of designated orphan medicinal products

Characteristics	Definitions
Indication characteristics	
Disease group (ATC class)	Antineoplastic and immunomodulating (L)
	Cardiovascular, blood and respiratory (C, B, R)
	Anti-infectives (J)
	Alimentary tract and metabolism (A)
	Musculoskeletal and nervous (M, N)
	Hormones (H)
	Various (V)
Prevalence group	<1/10,000
	1–3/10,000
	3–5/10,000
Inheritable	Majority of cases caused by genetic inheritance
Chronic disease	Disease duration is generally over 3 months
Childhood disease	Majority of diagnoses before age 18
Product characteristics	
Type of molecule	Biotechnological (EMEA list A, including gene therapy)
	Innovative synthetic entities (EMEA list B), NCEs, new delivery systems
	Existing synthetic entities
Pharmaceutical formulation	Parenteral
	Oral
	Other
Previously designated	Product had orphan designation for this indication elsewhere before EMEA orphan designation
Previously authorised	Product was approved for this indication elsewhere before EMEA orphan designation
Sponsor characteristics	
Type of company	Large (>250 employees or 50M turnover)
	Medium (50–249 employees or 10–50M turnover)
	Small (<50 employees or 5M turnover) and institutions
Continent of drug development	Continent of first clinical studies
	North America/Europe/Asia
Other medicinal products authorised	Sponsor has marketing authorisation for other medicinal products as of 1 Oct 2006 (anywhere in the world)
Other ODs designated	Sponsor has other designated orphan medicinal products as of 1 Oct 2006 (anywhere in the world)
Other ODs authorised	Sponsor has other authorised orphan medicinal products as of 1 Oct 2006 (anywhere in the world)

ATC Anatomical Therapeutic Chemical, *NCE* new chemical entity, *OD* orphan drug

Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each characteristic in the three categories. The outcome was defined as a successful EU marketing authorisation within the study period (April 2000-October 2006). To test whether any of the characteristics were mutually related, a multivariate model was used in which the characteristics with statistically significant crude ORs were compared using a backwards selection procedure.

Results

From the start of the EU Regulation on Orphan Medicinal Products (April 2000) up to 1 October 2006, 31 orphan medicinal products obtained marketing authorisation. One product (imatinib) has been authorised for four indications, and two other products (sunitinib and dasatinib) have been authorised for two indications, resulting in 36 approved orphan indications. A total of 60 designated (unauthorised) products were sampled to serve as controls. A small, statistically significant difference in the stage of development between the two groups was found for those products for which clinical trials were initiated, but not yet completed (P=0.02), while this was not the case for products for which experimental model studies had been initiated or completed (P=0.08), and for products for which at least one clinical trial was completed (P=0.22).

Of the 31 authorised drug products, the majority (58.3%) were designated in the first 2 years of the EU Regulation on Orphan Medicinal Products (2000–2001). Twelve were approved under exceptional circumstances, and one (sunitinib) had obtained conditional approval. Seven (22.6%) had received some form of protocol assistance or scientific advice from the EMEA. Of the 60 unauthorised designations, at least 43 (71.7%) were still in development in October 2006; of these, one had filed for market authorisation and another one had been authorised by November 2006. The development of six products could be classified as halted or on hold. For 11 products, recent data on the development status were not available.

Table 2 shows an overview of the clinical characteristics of all 31 authorised orphan drugs for 36 indications, stratified by indication category and prevalence group of the indication. Disease categories are based on ATC classes or combinations thereof that are also used by the Commission for Orphan Medicinal Products (COMP) of the EMEA [15]. The majority of the products were intended for oncologic and immunomodulatory diseases (ATC class L) (16, 44.4%) or alimentary and metabolic diseases (ATC class A) (9, 25.0%). In addition, most (24, 66.7%) authorised drugs were intended for diseases with a prevalence lower than 1 in 10,000. Of the 16 approved oncology drugs, 13 (81%) were developed by large companies, 7 (44%) originated from the USA and 5 (31%) from Switzerland. All these products were based on synthetic entities, and the majority, 12 (75%), were intended for oral use, whereas 4 (25%) were intended for systemic use.

Table 2 Summary of characteristics of authorised orphan medicinal products from April 2000 to October 2006 [21]

EU orphan designation number	INN name	Designated orphan indication	Disease group	Prevalence
EU/3/00/002	Agalsidase alpha	Treatment of Fabry disease	A	<1/10,000
EU/3/00/003	Agalsidase beta	Treatment of Fabry disease	A	<1/10,000
EU/3/00/006	Miglustat	Treatment of Gaucher disease	A	<1/10,000
EU/3/00/007	Carglumic acid	Treatment of N-acetylglutamate synthetase (NAGS) deficiency	A	<1/10,000
EU/3/00/008	Arsenic trioxide	Treatment of acute promyelocytic leukaemia	L	<1/10,000
EU/3/00/010	Anagrelide hydrochloride	Treatment of essential thrombocythaemia	L	1–3/10,000
EU/3/00/011	Busulfan	Conditioning treatment prior to hematopoietic progenitor cell transplantation	L	<1/10,000
EU/3/00/012	Nitisinone	Treatment of tyrosinaemia type I	A	<1/10,000
EU/3/00/014	Iloprost	Treatment of primary and several secondary forms of pulmonary hypertension	C, B, R	1–3/10,000
EU/3/00/018	Alglucosidase alpha	Treatment of glycogen storage disease type II (Pompe's disease)	A	<1/10,000
EU/3/01/019	Bosentan	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	C, B, R	<1/10,000
EU/3/01/020	Ibuprofen	Treatment of patent ductus arteriosus	C, B, R	1–3/10,000
EU/3/01/021	Imatinib mesilate	Treatment of chronic myeloid leukaemia	L	<1/10,000
EU/3/01/022	Laronidase	Treatment of mucopolysaccharidosis, type I	A	<1/10,000
EU/3/01/023	Pegvisomant	Treatment of acromegaly	H	<1/10,000
EU/3/01/025	Galsulfase	Treatment of mucopolysaccharidosis, type VI (Maroteaux-Lamy syndrome)	A	<1/10,000
EU/3/01/048	Ziconitide acetate	Treatment of chronic pain requiring intraspinal analgesia	M, N	1–3/10,000
EU/3/01/050	Zinc acetate dihydrate	Treatment of Wilson's disease	A	<1/10,000
EU/3/01/055	Cladribine	Treatment of hairy cell leukaemia	L	3–5/10,000
EU/3/01/059	Dexrazoxane	Treatment of anthracycline extravasations	Other	<1/10,000
EU/3/01/061	Imatinib mesilate	Treatment of gastrointestinal stromal tumours (GIST)	L	<1/10,000
EU/3/01/070	Celecoxib	Treatment of familial adenomatous polyposis	L	<1/10,000
EU/3/01/082	Clofarabine	Treatment of acute lymphoblastic leukaemia	L	<1/10,000
EU/3/02/086	Porfimer sodium	Treatment of high-grade dysplasia in Barrett's oesophagus	Other	1–3/10,000
EU/3/02/092	Deferasirox	Treatment of chronic iron overload requiring chelation therapy	Other	1–3/10,000
EU/3/02/102	Mitotane	Treatment of adrenal cortical carcinoma	L	<1/10,000
EU/3/02/131	Sodium oxybate	Treatment of narcolepsy	M, N	3–5/10,000
EU/3/03/178	Sildenafil	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	C, B, R	<1/10,000
EU/3/04/234	Sitaxentan	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	C, B, R	1–3/10,000
EU/3/05/267	Sunitinib	Treatment of malignant gastrointestinal stromal tumours	L	<1/10,000
EU/3/05/268	Sunitinib	Treatment of renal cell carcinoma	L	3–5/10,000
EU/3/05/304	Imatinib mesilate	Treatment of acute lymphoblastic leukaemia	L	<1/10,000
EU/3/05/305	Imatinib mesilate	Treatment of dermatofibrosarcoma protuberans	L	1–3/10,000
EU/3/05/338	Dasatinib	Treatment of acute lymphoblastic leukaemia	L	<1/10,000
EU/3/05/339	Dasatinib	Treatment of chronic myeloid leukaemia	L	<1/10,000
EU/3/06/364	Sorafenib	Treatment of hepatocellular carcinoma	L	3–5/10,000

The results of the univariate comparison between authorised and not-yet-authorised orphan drugs are shown in Table 3. For the categories of product characteristics and sponsor characteristics, a statistically significant association was observed for all the determinants except for the continent of drug development and for products with a previous orphan designation outside the EU. The association was strongest for those characteristics that were related to the experience of the sponsor with drug development. Previous authorisation of an orphan drug by the sponsor was associated with a 16-fold increase in the chance of authorisation compared to no previous authorisation (OR=16.2, 95% CI=5.5–47.4), whereas previous authorisation of other drugs and previous designation of another potential orphan

Table 3 Results for the comparison between authorised and not-yet-authorised orphan medicinal products

Characteristic of the orphan medicinal product	Level	Authorised indications (n=36)	Not-yet-authorised designated products (n=60)	OR (95% CI)
Indication characteristics				
Disease group (ATC class)	Antineoplastic and immunomodulating (L)	17	34	1
	Cardiovascular, blood and respiratory (C, B, R)	5	7	1.4 (0.4–5.2)
	Anti-infectives (J)	0	4	NA
	Alimentary tract and metabolism (A)	9	5	3.6 (1.0–12.4)
	Musculoskeletal and nervous (M, N)	2	7	0.6 (0.1–3.0)
	Hormones (H)	1	1	2.0 (0.1–34.0)
	Various (V)	2	2	2.0 (0.3–15.5)
Prevalence group	<1/10,000	24	26	1
	1–3/10,000	8	22	0.4 (0.2–1.0)
	>3/10,000	4	6	0.7 (0.2–2.9)
Inheritable	No	25	44	1
	Yes	11	16	1.2 (0.5–3.0)
Chronic disease	No	4	13	1
	Yes	32	47	2.2 (0.7–7.4)
Childhood disease	No	31	45	1
	Yes	5	15	0.5 (0.2–1.5)
Product characteristics				
Type of molecule	Biotechnology	6	20	1
	Innovative synthetic	15	25	2.0 (0.7–6.1)
	Existing synthetic	15	15	3.3 (1.1–10.6)
Pharmaceutical formulation	Parenteral	13	30	1
	Oral	21	12	4.0 (1.5–10.6)
	Other	1	14	0.2 (0.0–1.4)
Previously designated	No	19	41	1
	Yes	16	17	2.0 (0.9–4.9)
Previously authorised	No	27	54	1
	Yes	8	4	4.0 (1.1–14.5)
Sponsor characteristics				
Type of company	Large	27	24	1
	Medium	7	18	0.4 (0.1–1.0)
	Small and institutions	2	16	0.1 (0.0–0.5)
Continent of drug development	North America	16	22	1
	Europe	20	34	0.8 (0.4–1.9)
	Asia	0	3	NA
Other medicinal products authorised	No	3	29	1
	Yes	31	26	11.5 (3.2–42.2)
Other ODs designated	No	4	30	1
	Yes	30	28	8.0 (2.5–25.7)
Other ODs authorised	No	6	45	1
	Yes	28	13	16.2 (5.5–47.4)

OR Odds ratio, *95% CI* 95% confidence interval, *ATC* Anatomical Therapeutic Chemical, *NA* not applicable, *OD* orphan drug

drug by the sponsor yielded odds ratios (95% CI) of 11.5 (3.2–42.2) and 8.0 (2.5–25.7) respectively. Furthermore, previous authorisation outside the EU was also associated with higher chances for authorisation in the EU (OR=4.0, 95% CI=1.1–14.5). Finally, the type of product is partly associated with market authorisation. Although the association for innovative synthetic entities [e.g. new chemical entities (NCEs)] such as imatinib was not statistically significant compared to biotechnology products (OR=2.0, 95% CI=0.7–6.1), existing synthetic entities, such as arsenic trioxide and busulfan, were associated with higher chances of market authorisation (OR=3.3, 95% CI=1.1–10.6).

The results from the multivariate model, which assessed whether any of the statistically significant characteristics

Table 4 Multivariate analysis of predictors of marketing authorisation of orphan medicinal products in Europe

Predictor	Value	OR[a] (95% CI)
Other ODs approved	No	1.0
	Yes	17.3 (5.6–53.1)
Type of product	Biotechnology	1.0
	Innovative synthetic entity	1.9 (0.50–7.7)
	Existing synthetic entity	3.9 (0.9–16.6)

OR Odds ratio, *95% CI* 95% confidence interval, *OD* orphan drug
[a] Adjusted for significant variables in the univariate analysis (including other ODs approved and type of product), followed by a backwards elimination procedure. Predictors in the table are those that remained in the multivariate analysis

were related, are shown in Table 4. This model yielded two independent predictors of successful marketing authorisation, namely the experience of the sponsor having other orphan medicinal products authorised and the type of product. The association was strongest for the authorisation of other orphan products by a sponsor (OR=17.3, 95% CI= 5.6–53.1). Moreover, we found a tendency toward an association for the type of product, with an OR (95% CI) of 3.9 (0.9–16.6) for existing synthetic entities compared to biotechnology products, while no association was observed for innovative synthetic entities compared to biotechnology products (OR=1.9, 95% CI=0.5–7.7).

Discussion

This study reveals two independent characteristics of an orphan medicinal product that are associated with marketing authorisation: the experience of a company in developing drug products and the type of drug product in development.

First, we showed that experience of a company in obtaining authorisation for orphan drugs was identified as the most important predictor of market authorisation. Companies that have successfully brought an orphan drug to the market increase their odds of obtaining market authorisation for consecutive orphan drugs more than 17-fold. These results are in line with opinions expressed by many experts, however they are now supported by real data and emphasise the importance of an experienced partner in bringing a product to the market for small and medium-sized enterprises (SMEs) whose experience is often limited [5]. This observation is verified by the fact that many former SMEs with one or more approved orphan drugs have acquired the necessary experience by bringing on board experienced management at an early stage.

The EMEA has addressed this issue by offering protocol assistance and scientific advice to sponsors of designated orphan drugs. Another important recent incentive to overcome this hurdle is EMEA's dedicated SME office, which addresses the regulatory needs of SMEs [16]. These incentives seem to be good steps forward to guide smaller and relatively inexperienced companies through the regulatory maze in the development process. Although 80 procedures for protocol assistance had been completed by April 2005 [15], we found that only 4 of the products that were approved in that period had obtained scientific advice or protocol assistance from the EMEA. Furthermore, of the 31 products authorised by October 2006, only 7 (22.6%) received protocol assistance or scientific advice. In contrast, 28 (77.8%) of the 36 approved orphan indications were developed by a company that had successfully brought another orphan drug to the market in Europe or the USA. The development of imatinib is a good example of this. It was developed by a large company with extensive experience in developing and marketing medicinal products [17].

The other independent predictor that was identified was the type of product. Although not significant, it shows that the odds of authorisation for products based on existing synthetic entities may be about four times higher compared to biotechnological products. Only 6 of the 31 orphan drugs approved in the EU up to October 2006 were of biotechnological origin; of these, 5 are used for enzyme replacement therapy for metabolic disorders. This finding is not unexpected, as the development of existing synthetic entities into drug products is generally considered much more straightforward than the development of a biotech product. This group also includes orphan drugs based on existing approved therapies, such as celecoxib and sildenafil, for which development was only a matter of an indication extension. This can be one of the reasons why the relatively young European Regulation on OMPs has yielded such a high share of orphan drugs based on existing synthetic entities.

In contrast to the EU, half of the biotechnological products approved in the USA in the period 1982–2002 were designated orphan drugs [3]. The US Orphan Drug Act is therefore frequently mentioned as one of the key factors that has stimulated the US biotech industry in its growth. Several of the world's largest, US-based biotech companies have in common that their first approved product was an orphan drug [3, 18]. This is illustrated by the fact that of the six approved biotech OMPs in the EU, five were originally developed in the USA. Since the US Orphan Drug Act was initiated nearly 25 years ago, those companies have grown from SMEs to multinational companies and have since acquired much more experience in drug development than the current European biotech companies with orphan drug designations in their portfolio. On the other hand, the small number of European biotech orphan drugs is compensated for by the relatively large

number of orphan products based on existing synthetic molecules. Examples of these are the products from the French SME Orphan Europe, which are all based on existing molecules. This underlines that experience of a company is even more important for the relatively more complex biotechnological products. Since much clinical experience is already available, especially for existing synthetic molecules, this emphasises that, next to the experience of a company, experience with a drug product is also important.

Except for products indicated for alimentary tract and metabolism-related diseases (ATC class A), none of the characteristics related to the type of the indication showed a statistically significant association with market authorisation. This finding matched with our hypothesis that only the characteristics of the drug product itself or the development program of the sponsor determines the chances for market authorisation. An interesting observation here is that the number and type of products intended for oncologic indications suggest that the Regulation also provides support for the development of the more classical anticancer drugs. In fact, this is one of the most successful niches in orphan drug development in the EU so far.

Recent literature has discussed factors that influenced the development of orphan medicinal products in Europe [12, 14, 19]. One of the issues that has been raised in these papers is the absence of tax credits in the EU, compared to the USA. The reason for this is that taxation is still a national affair in the EU, which is not regulated at the Community level. Although this is compensated for by a longer period of market exclusivity in the EU and additional benefits on a national level [20], Joppi and Dear suggest that this may yield fewer orphan drugs than in the USA [12, 14]. While our analysis cannot fully produce a conclusive answer to this discussion, it gives some useful clues that the absence of tax credits alone is not the reason for the lower number of approved products in the EU. Approximately one-third of the European orphan designations were originally developed in the USA (data on file). However, in our analysis, no association was found between the continent of drug development and market authorisation. These results suggest that the absence of tax credits in the EU does not discourage companies from applying for an orphan designation in the EU.

Wästfelt described the problems of performing adequately powered RCTs in small patient populations with rare diseases, which are even more problematic in the multicultural and multilingual setting of the EU compared to the USA [5]. Moreover, the USA has a successful infrastructure for conducting trials in patient populations with rare diseases, which is coordinated by the Rare Diseases Clinical Research Network and supported by the Office of Rare Diseases of the National Institutes of Health [5]. If the small patient populations were really the key problem, we would see a larger share of orphan drugs for relatively common rare diseases in the EU, and only a very small share of orphan drugs indicated for the very rare diseases. However, in our analysis, we found no association between prevalence of the indication and market authorisation. Moreover, of the 36 indications for which an orphan medicinal product has been approved in the EU, 24 (67%) had a prevalence of less than 1 per 10,000. In addition to this, Dear stated that, although small patient numbers may hamper clinical trials for very rare diseases, it is not likely to be a problem for more prevalent rare diseases [12].

We need to consider other critical factors for the success of the development of an orphan drug. The level of patient involvement may also influence successful development and subsequent authorisation of orphan drugs [5]. Moreover, the registration dossiers of authorised orphan drugs are often of poor quality, including inappropriate study design, lack of active comparators and inadequate endpoints [14, 19]. Although this criticism is primarily directed against orphan drugs already authorised, it is very possible that these dossiers are just the ‘tip of the iceberg’. If that is the case, many orphan drugs will not reach the market because the sponsor will not be able to show evidence of favourable characteristics of the product due to the poor quality of the dossier. Since this study has been based on data from the public domain, several of these factors could not be included, which is a limitation of the study. Future research to investigate the quality of the clinical development program of designated (unauthorised) orphan drugs is needed.

Another possible limitation of the study was the risk of biased outcomes due to possible differences in the stage of development of the products between the two groups that were compared. For this reason, the controls were randomly sampled from the same calendar period as the cases, so that the chance that products would obtain approval was as equal as possible. Moreover, we compared the stage of development at the time of the application for orphan designation based on data from the available Summaries of Opinion of the EMEA. Here it was shown that, although slight differences existed, the two groups were roughly equal with regard to their stage of development at time of orphan designation.

The relatively small number of products that have so far been approved in the EU as compared to the enormous number of rare diseases emphasises that the promises of the European Regulation on OMPs have yet to be fulfilled. This paper has studied the characteristics of several of the early approved orphan drugs, the majority of them authorised within the first 2 years of the Regulation. Now that the Regulation is about to enter its ninth year of existence, the rate of orphan drug approval is gradually

increasing and more and more orphan drugs are entering the market for the seriously needed treatment of patients with rare diseases.

In conclusion, we have found that experience in the drug development process and development of already existing (small) molecules are associated with market authorisation of orphan drug designations. The EMEA addresses this with several helpful incentives to support inexperienced companies in their orphan drug development. There seems to be a steep learning curve for inexperienced companies. The incentives forthcoming from the European Regulation on Orphan Medicinal Products seem to be helpful for companies developing orphan drugs, although the industry has to 'grow' and acquire expertise on the specific peculiarities of the orphan drug development process. The differences in orphan drug approvals between the EU and the USA may therefore be best explained by the maturity of the US pharmaceutical and biotech industry compared to Europe. In addition to this factor, other characteristics related to the quality, safety and efficacy profile of a potential orphan drug certainly play a role. Especially with regard to the possibilities of sponsors to demonstrate clinical evidence of the orphan drug under development.

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References

1. Stolk P, Willemen MJC, Leufkens HGM (2006) Rare essentials: drugs for rare diseases as essential medicines. Bull World Health Organ 84:745–751
2. van Weely S, Leufkens HGM (2004) Background paper: orphan diseases. In: Kaplan W, Laing R (eds) Priority medicines for Europe and the world - a public health approach to innovation. World Health Organisation, Geneva
3. Haffner ME, Whitley J, Moses M (2002) Two decades of orphan product development. Nat Rev Drug Discov 1:821–825
4. Haffner ME (2006) Adopting orphan drugs-two dozen years of treating rare diseases. N Engl J Med 354:445–447
5. Wästfelt M, Fadeel B, Henter JI (2006) A journey of hope: lessons learned from studies on rare diseases and orphan drugs. J Intern Med 260:1–10
6. Rinaldi A (2005) Adopting an orphan. EMBO Rep 6:507–510
7. EURORDIS (2005) Rare diseases: understanding this public health priority. http://www.eurordis.org/article.php3?id_article=1296 Accessed 25 Jul 2007
8. US FDA (1983) The Orphan Drug Act, Public Law, 97–141. http://www.fda.gov/orphan/oda.htm. Accessed 12 Jul 2007
9. Benzi G, Ceci A (1997) Drugs trying to get the parents: there will be incentives for the European scientific community to develop research in the field of the orphan drugs. Pharmacol Res 35:89–93
10. Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on Orphan Medicinal Products. Official Journal of The European Communities 2000
11. Minghetti PM, Giudici EM, Montanari L (2000) A proposal to improve the supply of orphan drugs. Pharmacol Res 42:33–37
12. Dear JW, Lilitkarntakul P, Webb DJ (2006) Are rare diseases still orphans or happily adopted? The challenges of developing and using orphan medicinal products. Br J Clin Pharmacol 62:264–271
13. European Commission (2006) 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. http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/doc/orphan_en_06–2006.pdf. Accessed 25 Jul 2007
14. Joppi R, Bertele V, Garattini S (2006) Orphan drug development is progressing too slowly. Br J Clin Pharmacol 61:355–360
15. EMEA (2005) COMP report to the commission in relation to article 10 of regulation 141/2000 on orphan medicinal products. http://www.emea.europa.eu/pdfs/human/comp/3521805en.pdf. Accessed 25 Jul 2007
16. EMEA (2005) SME Office. http://www.emea.europa.eu/SME/SMEbackground.htm. Accessed 25 Jul 2007
17. Capdeville R, Buchdunger E, Zimmermann J, Matter A (2002) Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. Nat Rev Drug Discov 1:493–502
18. Haffner ME, Maher PD (2006) The impact of the Orphan Drug Act on drug discovery. Expert Opin Drug Discov 1:521–524
19. Anonymous (2007) Drugs for rare diseases: mixed assessment in Europe (2007) Prescrire Int 16:36–42
20. European Commission (2006) Inventory of community and member states' incentive measures to aid the research, marketing and development and availability of orphan medicinal products. Revision 2005. http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/doc/inventory_2006_08.pdf . Accessed 25 Jul 2007
21. European Commission (2007) Register of designated orphan medicinal products. http://ec.europa.eu/enterprise/pharmaceuticals/register/orphreg.htm. Accessed 25 Jul 2007