Determinants for successful marketing authorisation of orphan medicinal products in the EU

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In 2010, the European Regulation for Orphan Medicinal Products (OMPs) was in force for ten years. In this study we assessed possible determinants of applications for OMPs in the EU since 2000 that are associated with a successful marketing authorisation. Our analysis shows that clinical trial characteristics such as demonstrating convincing evidence of a beneficial effect on the primary endpoint, the selection of a clinically relevant endpoint, providing RCT data as pivotal study evidence and the submission of sound dose finding data are critical success factors. In addition, high medical need seems to counterweigh uncertainties about the scientific evidence in the benefit–risk assessment of OMPs.

Introduction

The European regulation of orphan medicinal products (OMPs) sets rules and provides specific incentives for sponsors of medicinal products intended for the diagnosis, prevention and/or treatment of rare diseases. In the European Union a disease is defined as rare if it occurs in five people or less per 10 000 of the population in the European Union (EU) member states and the disease is life-threatening or chronically debilitating. In addition, the regulation states that no alternative treatment should be available or that any new treatment is expected to deliver a significant additional benefit [1–3]. The number of rare diseases is estimated to be between 5000 and 8000, affecting ~30 million people in the EU [3]. For most of the rare diseases no effective treatment exists, which makes orphan drug development an important public health issue [2]. The European regulation aims to create and enhance opportunities for developing drugs for patients with rare diseases. Sponsors that develop such a medicinal product could request an orphan designation for their product in order to benefit from incentives such as direct access to the centralised marketing authorisation procedure and 10-year market exclusivity, protocol assistance during the product-development phase, financial incentives (i.e. fee reductions or exemptions) and national incentives [1].

By May 2011, a total of 855 orphan designations had been granted, whereas just 64 OMPs had been authorised for marketing in the EU since the introduction of the regulation on OMPs in 2000 (http://ec.europa.eu/health/documents/community-register/html/orphreg.htm) [4]. Since 2000 the number of submissions for marketing authorisation of OMPs has increased [5]. Arriving at a positive or negative opinion about a marketing authorisation for an OMP is subject to comprehensive evaluation of the available scientific evidence for quality, efficacy and safety of the product. The final and decisive benefit–risk assessment, the task of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), is based on the results and appropriate implementation of an extensive quality, preclinical and clinical development programme. However, other aspects including drug substance-, indication- or company-related factors such as previous experience with the drug substance or the availability of alternative pharmaceutical treatments for the disease could shape the context

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of the benefit–risk assessment for the new orphan treatments. Owing to the exceptional characteristics of orphan diseases and the patients, orphan drug development is a complex, challenging and risky enterprise, which might explain the relatively high attrition rates in the marketing authorisation procedure [6–8].

Several studies have been undertaken to learn from the successes and failures of previous marketing applications for OMPs. In previous studies by Joppi *et al*. the methodological quality of marketing application dossiers of OMPs that received marketing authorisation in the EU in the periods 2000–2004 [9] and 2000–2007 [10] has been assessed. Methodological limitations of the clinical dossiers were found during both periods. In an earlier study by our group, marketing applications for OMPs in the EU that gained marketing approval up to October 2006 were compared with a sample of designated, but not yet approved, OMPs. Substance-, indication- and company-related predictors for orphan drug approval in the EU were assessed. Previous company experience in obtaining approval for another OMP was also identified to be associated with marketing approval. Besides, existing small molecules were more likely to gain marketing approval than biotechnology products [11]. Recently, we also studied a broad range of characteristics related to failure to achieve marketing authorisation by the US Food and Drug Administration (FDA). Characteristics of the clinical trial programme, the substance, the company and interaction with the FDA were studied for non-approved and approved marketing applications for orphan drugs at the FDA, and several of them were found to be associated with marketing approval [12].

The present study aims to assess determinants of successful marketing applications for OMPs in the EU, but now with a more comprehensive and methodologically advanced approach, comparing all approved and non-approved marketing applications for OMPs in the EU since the orphan drug regulation was established in 2000.

Data of OMP dossiers from the period 2000–2006 were confidentially collected and analysed in an aggregated fashion. Data for all approved and non-approved OMPs post-2006 were collected from European Public Assessment Reports (EPARs), which are available on the EMA website (http://www.ema.europa.eu). These documents provide a summary of the complete drug development plan as submitted by the sponsor and the scientific discussion and final benefit–risk evaluation by the CHMP of the EMA.

Indication-related characteristics

From 2000 to the end of 2009, a total of 114 marketing applications for OMPs received an opinion about marketing authorisation by the CHMP or were withdrawn by the sponsor during the authorisation procedure. Of these, 97 were applications for new OMPs (including four double applications for the same indication), whereas 13 applications were for extensions of indications of previously approved drugs by the EMA. Four applications were submitted for multiple indications on the same date. Applications for multiple indications for one OMP were analysed as separate marketing applications ($n = 114$). Table 1 provides key characteristics related to the drug substance, indication, development plan, sponsor and dialogue with the EMA for the studied OMPs.

These 114 marketing applications have led to a successful authorisation of 59 OMPs for 73 indications (64%). Of those

TABLE 1

Baseline characteristics of marketing applications for orphan medicinal products in the EU

Characteristics	No. of marketing applications ($n = 114$)
Characteristics of the drug substance	
Previous approval in any country	
No	25 (21.9%)
Yes	89 (78.1%)
Small molecule	
No	29 (25.4%)[a]
Yes	85 (74.6%)
Indication characteristics	
Cardiovascular and respiratory	10 (8.8%)
Endocrinology and metabolic	17 (14.9%)
Haematology	17 (14.9%)
Immunology	8 (7.0%)
Infectious diseases	5 (4.4%)
Musculoskeletal and nervous system	10 (8.8%)
Oncology	40 (35.1%)
Other	7 (6.1%)
Lack of alternative therapy for the disease	
No	73 (64.0%)
Yes	41 (36.0%)
Prevalence in the EU	
<5 per 100 000	30 (26.3%)
5–10 per 100 000	42 (36.8%)
>10 per 100 000	42 (36.8%)
Clinical development plan characteristics	
Dose-finding studies performed?	
No	66 (57.9%)
Yes	48 (42.1%)
RCT conducted as pivotal trial	
No	48 (42.1%)
Yes	66 (57.9%)
Beneficial effect on primary endpoint according to EMA review	
No	37 (32.5%)
Yes	77 (67.5%)
Regulator concerns on the clinical development plan	
Clinically relevant endpoint used according to EMA review	
No	26 (22.8%)
Yes	88 (77.2%)
Representative target population identified according to EMA review	
No	31 (27.2%)
Yes	83 (72.8%)
Sponsor-related characteristics	
Company size	
SME	27 (23.7%)
Large	87 (76.3%)
Company experience in orphan drug development	
No	72 (63.2%)
Yes	42 (36.8%)
Regulatory dialogue with EMA	
Protocol assistance obtained from the EMA	
No	59 (51.8%)
Yes	55 (48.2%)

[a] This group consists of 28 biologicals and one advanced therapy medicinal product (ATMP).

73 approved applications, 27 (37%) were approved under exceptional circumstances and three (4.1%) were conditionally approved. Thus, 41 applications failed in the authorisation procedure. The number of approved and non-approved marketing applications for OMPs per year increased over the years. After an initial increase over the first eight years, the number of approved marketing applications has decreased during the past two years (Fig. 1). Univariate and multivariate analyses were performed to evaluate crucial determinants for success, as described in Box 1.

Most of the marketing applications for OMPs were for oncological products (35.1%; Table 1). When comparing the number of non-approved and approved marketing applications for each indication category, 28 out of 40 (70%) oncological applications and 15 out of 17 (88%) applications for metabolic diseases received marketing authorisation. By contrast, for immunological diseases or anti-infectious diseases only three out of eight (37.5%) and one out of five (20%) received marketing authorisation (Fig. 2).

Balancing uncertainties in the evidence for efficacy and safety of OMPs versus a high medical need characterises regulator dilemmas in the assessments of OMPs [13,14]. Our results suggest that European benefit–risk assessment seems to be driven by the context of medical need, as shown by the clear association between lack of an alternative therapy for the disease and a positive marketing authorisation (Adjusted odds ratio (ORadj.) 4.6, 95% CI 1.1–20.4; Table 2). Although marketing applications for orphan indications should comply with existing regulatory guidelines just as they do for other drugs, a higher degree of uncertainty about safety issues and/or efficacy results could be considered acceptable for orphan indications for which no treatment exists. Regulator responsibility to provide access to efficacious and safe products for the population is reflected by the fact that 41% of all approved marketing applications was approved under exceptional circumstances or as conditional approval. These approvals partly represent those orphan indications for which medical need was highest owing to lack of an alternative pharmacotherapeutic option.

Clinical drug development characteristics

The core of the benefit–risk assessment is the scientific discussion of the clinical drug development programme. In our case study, several characteristics of the clinical development plan were shown to influence a marketing authorisation decision.

Study endpoints: effect and clinical relevance

The strongest determinants of marketing approval were data showing a beneficial effect on the primary endpoint (when present 83.1% were approved, when absent this figure was just 24.3%) and clinically relevant endpoint used according to EMA review (when present approval was 75%, when absent it was 26.9%). Nine OMPs were approved without convincing results on the primary endpoint defined in the protocol (Table 2). This occurred when (i) survival data were requested but could not be provided or statistical significance could not be reached [e.g. Nexavar®, sorafenib tosylate for renal cell carcinoma, based on progression-free survival (PFS) it was concluded that a favourable and clinically meaningful effect had been demonstrated], (ii) when a clinical beneficial effect could not be demonstrated for the whole study population, whereas benefits were shown for a specific subgroup [e.g. Ceplene®, histamine dihydrochloride for the treatment of acute myeloid leukaemia (AML), approved as maintenance therapy for adult patients with AML in first remission concomitantly treated with interleukin (IL)-2 only] or (iii) when data were shown in a small study with limited patient numbers (e.g. Increlex®, mecasermine for the treatment of growth factor-1 deficiency, exceptionally approved). From all of the studied dossiers of OMPs, 13 were withdrawn or received a negative opinion despite a beneficial effect on the primary endpoint (Table 2). In nine of these cases, the endpoint was considered not to be clinically relevant according to regulatory review by the EMA.

The multivariate analysis confirmed that a beneficial effect on the primary endpoint (ORadj. 53.9, 95% CI 8.4–345.2) and the clinical relevance of the endpoint (ORadj. 15.0, 95% CI 2.9–77.8) according to EMA review were strongly associated with a positive

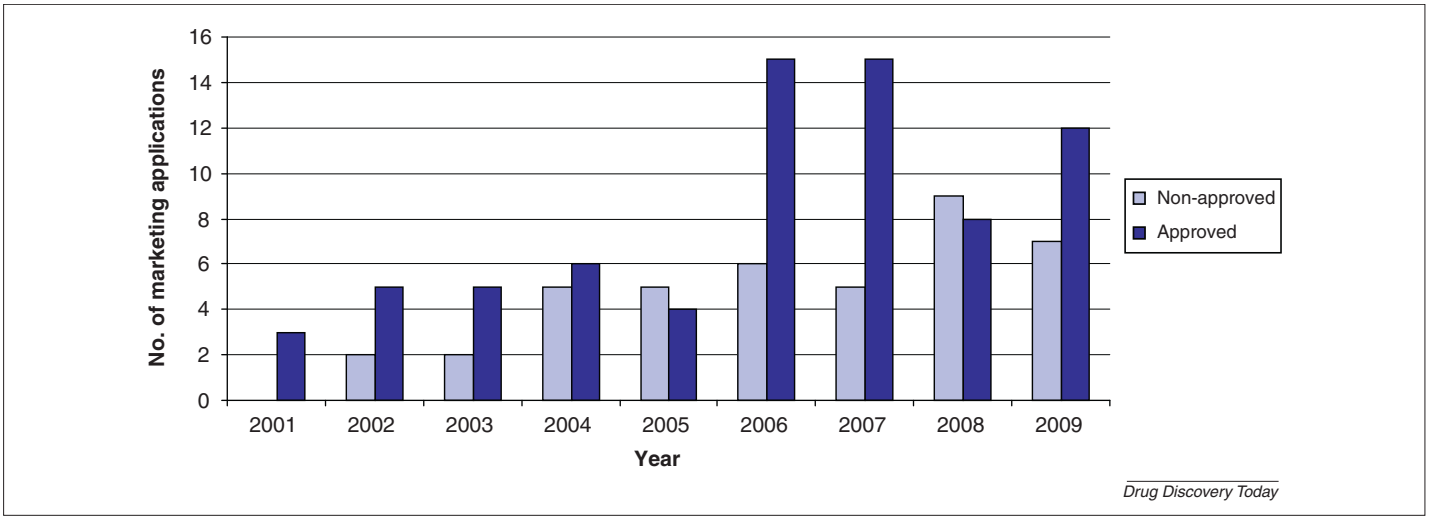

FIGURE 1

Number of approved and non-approved marketing applications for orphan medicinal products (OMPs) per year in the EU (2001–2009). Numbers of approved OMP applications per year are given in dark grey. Numbers of non-approved OMP applications per year are given in light grey. In total 73 applications were approved, whereas 41 were not approved.

BOX 1

Methodology

Potential determinants for marketing authorisation that were studied were related to drug substance, indication, clinical development plan, company and dialogue with the EMA.
Drug-related determinants included previous approval of the drug in any country irrespective of indication and whether the drug was a small molecule product or a biological or advanced therapy medicinal product. Previous approval could either mean that exactly the same product with a similar indication and formulation made by the same company was previously approved by another regulatory agency or that the same molecular substance was previously approved, but for a different indication and/or formulation and/or developed by another company. Biologicals were defined as vaccines, blood and blood components and recombinant proteins. Advanced therapy medicinal products (ATMP) were defined as tissue engineered products, cell somatic cell therapy products and gene therapy medicinal products [30]. Indication-related determinants were the prevalence of the disease in the EU according to EMA data and availability of alternative pharmaceutical therapies for the orphan disease, assessed at the time of marketing application.
Determinants used to characterise the drug development plan were the conduct of dose-finding studies, the rigor of the pivotal clinical study design [randomized clinical trial (RCT) yes or no] and the evidence of a beneficial effect on the primary endpoint. This was defined as reaching statistical significance in controlled studies or meeting predefined criteria in uncontrolled studies. In case more pivotal trials were conducted for the indication under review, the trial with the most robust study design (as defined by randomization and controlled design of the trial) and the largest number of patients was included in the analysis. We also evaluated assessment reports of the EMA looking at the suitability in terms of the clinical relevance of the studied primary endpoints and concerns or objections made related to the identification of an appropriate target population according to EMA review.
Sponsor-related determinants were company size, defined as small and medium-sized enterprise (SME) status of the company according to the SME definition of EMA [31], and company experience in OMP development. A company was considered experienced when a marketing application for an OMP had previously been submitted at EMA.
The dialogue with EMA was defined as protocol assistance obtained from the EMA.
The study outcome of interest was a positive opinion of the CHMP on the recommendation for marketing authorisation for European patients. Non-approved marketing applications were defined as applications that received a negative opinion by the CHMP or that were withdrawn from the marketing authorisation procedure between day 120 and the end of the procedure.

Data analysis

Univariate odds ratios (OR) and 95% confidence intervals (95% CI) of marketing authorisation were calculated applying logistic regression analyses. All variables with a univariate OR with a P value <0.20 were included in a multivariate logistic regression model to calculate adjusted odds ratios (ORadj.) (95% CI). All statistical analyses were conducted by using the statistical software package SPSS version 16 (SPSS Inc., Chicago, IL, USA).

marketing authorisation outcome (Table 2). A similar result was found when we assessed FDA data, where failure of the primary endpoint was related to a negative outcome of marketing authorisation (Odds ratio (OR) 25.7, 95% CI 5.3–125.1) [12]. Because the primary endpoint provides the main evidence for efficacy these results were as expected. However, the clinical relevance of the primary endpoint was not part of the FDA review process [12]. By contrast, in the EU clinical relevance of the selected endpoint according to guidelines or previous advice from regulators was strongly associated with success in the marketing authorisation procedure, next to the effect size of the efficacy results. Drug companies seem to make a trade-off between selecting a robust endpoint such as survival which demands high numbers of patients and long-term studies to demonstrate a statistical significant effect and surrogate endpoints usually requiring smaller and shorter studies, but for which translation of the findings into clinical relevance is more problematic [12–14]. Although previous studies criticised the authorised EU marketing applications for demonstrating efficacy based on surrogate endpoints [9,10], the availability of valid biomarkers and surrogate endpoints with

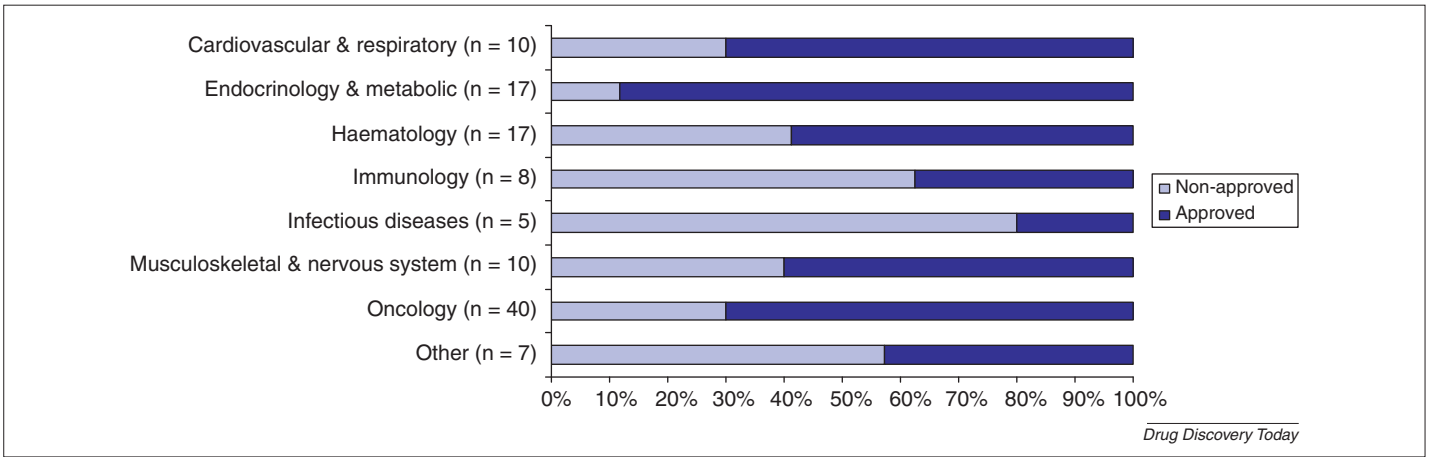

FIGURE 2

Proportion of non-approved and approved marketing applications for orphan medicinal products (OMPs) in the EU per indication category. Proportions of approved OMP applications are given in dark grey and proportions of non-approved applications are given in light grey.

TABLE 2

Association between determinants and approval of marketing applications for orphan medicinal products in the EU (univariate and multivariate logistic regression)

Variables	Total ($n = 114$)	Marketing authorisation ($n = 73$)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Characteristics of the drug substance				
Previous approval in any country				
No	25	11 (44.0%)	[1]	[1]
Yes	89	62 (69.6%)	2.9 (1.2–7.3)	1.7 (0.4–7.4)
Small molecule				
No	29[a]	14 (48.2%)	[1]	[1]
Yes	85	59 (69.4%)	2.4 (1.0–5.8)	17.1 (2.1–138.9)
Indication characteristics				
Lack of alternative therapy for the disease				
No	73	42 (57.5%)	[1]	[1]
Yes	41	31 (75.6%)	2.3 (0.98–5.4)	4.6 (1.1–20.4)
Prevalence in the EU				
> 10 per 100 000	42	26 (61.9%)	[1]	N/A[b]
5–10 per 100 000	42	25 (59.5%)	0.9 (0.4–2.2)	
< 5 per 100 000	30	22 (73.3%)	1.7 (0.6–4.7)	
Clinical development plan characteristics				
Dose-finding studies performed				
No	66	38 (57.6%)	[1]	[1]
Yes	48	35 (72.9%)	2.0 (0.9–4.4)	8.1 (1.6–41.2)
RCT as pivotal trial				
No	48	26 (54.2%)	[1]	[1]
Yes	66	47 (71.2%)	2.1 (1.0–4.6)	6.9 (1.3–36.1)
Beneficial effect on primary endpoint according to EMA review				
No	37	9 (24.3%)	[1]	[1]
Yes	77	64 (83.1%)	15.3 (5.9–40.0)	53.9 (8.4–345.2)
Regulator concerns on the clinical development plan				
Clinically relevant endpoint used according to EMA review				
No	26	7 (26.9%)	[1]	[1]
Yes	88	66 (75.0%)	8.1 (3.0–21.9)	15.0 (2.9–77.8)
Representative target population identified according to EMA review				
No	31	16 (51.6%)	[1]	[1]
Yes	83	57 (68.7%)	2.1 (1.0–4.8)	0.55 (0.12–2.5)
Sponsor-related characteristics				
Company size				
SME	27	13 (48.1%)	[1]	[1]
Large	87	60 (69.0%)	2.4 (1.0–5.8)	2.1 (0.5–9.4)
Company experience in OMP development				
No	72	39 (54.2%)	[1]	[1]
Yes	42	34 (80.9%)	3.6 (1.5–8.8)	1.9 (0.4–8.3)
Regulatory dialogue with EMA				
Protocol assistance obtained from the EMA				
No	59	38 (64.4%)	[1]	N/A[b]
Yes	55	35 (63.4%)	1.0 (0.5–2.1)	

[a] This group consists of 28 biologicals and one advanced therapy medicinal product (ATMP).
[b] N/A, not applicable (P value in univariate analysis >0.20).

demonstrated clinical relevance seems to contribute significantly to the surge in numbers of approved OMPs [15].

Rigor of the clinical trial data

Our results show that all meaningful clinical effects of OMPs should preferably be shown in an Randomized clinical trial (RCT) (ORadj. 6.9, 95% CI 1.3–36.1; Table 2). According to the CHMP, in general an application based upon one single pivotal study can suffice for a marketing authorisation if the data are compelling, the study is well designed, the outcome is positive and the data are robust in terms of efficacy and safety [16,17]. If an active comparator is available, the conduct of non-inferiority

studies can be challenging because a large sample size of patients is needed. Consequently, single-arm studies are frequently performed for OMPs ($n = 48$, 42.1%; Table 1). However, examples demonstrate that when an RCT is considered feasible it is the most preferable way to gain successful marketing authorisation. This is also described in the EMA guideline on clinical trials in small populations [17], and could be illustrated by the assessment of Vidaza® (INN-azacitidine) for the treatment of myelodysplastic syndromes. Although no authorised treatment for myelodysplastic syndromes exists yet, the CHMP requested a comparative trial with chemotherapy that had become standard of care in off-label use to demonstrate prolonged survival [18].

Dose finding

As for regular drug development, relevant dose-finding data are requested for OMPs and in this study were shown to be an independent determinant of success (ORadj. 8.1, 95% CI 1.6–41.2; Table 2). The relevance of exploratory dose-finding studies to learn about the appropriate dose regimen in confirmatory clinical studies was also previously emphasized [19]. A dose-finding study leads to an understanding of the dose–response relationship and enables selection of the optimal dose of the drug in representative patients, which might prevent unnecessary failure of confirmatory studies [19].

Drug substance and sponsor-related characteristics

Previous studies showed that experience in orphan drug development is an important predictor for subsequent marketing authorisation in the EU and the USA [11,12]. Many complexities exist in orphan drug development that make it plausible that experience in developing and marketing an OMP increases the likelihood of subsequent marketing approval. Orphan drug development by inexperienced companies can be hampered by a limited geographical outreach with poor access to patients and a lack of regulatory knowledge and experience in RCT design [11]. In the present study, experience with the molecular substance (defined as previous approval of the drug) and company experience were also associated with a positive outcome of an application, but these associations did not reach statistical significance (Table 2).

Uncertainties in benefit–risk assessment

Balancing benefits and risks of OMPs in the context of medical need is subject to an extensive scientific discussion at the level of the CHMP. This is inherent to specific issues in orphan drug development, such as lack of active comparator drugs and sufficient power to show an effect on clinically relevant endpoints, although clear cases can exist: those OMPs for diseases without alternative options, for which a clinical beneficial effect has been demonstrated in a controlled trial, are likely to receive a positive opinion by the CHMP. Similarly, OMPs for which hardly any clinical benefit was demonstrated in poorly designed studies are more likely to receive a negative opinion by the CHMP. In most cases, however, existing uncertainties are assessed in the context of available data, especially in applications without convincing evidence for clinical benefit. As described before, for some OMPs a beneficial effect, that met predefined criteria, could not be demonstrated for the whole study population. A non-pre-specified positive finding in a subgroup would normally be considered to be hypothesis-generating only [20,21], but for some OMPs the CHMP has found such results sufficient for approval. A high level of uncertainty regarding benefits and, in particular, risks also applies particularly to biological products owing to their safety issues and complex manufacturing processes of which experience is more limited compared with that for other drugs. The strong association between biological products and failure of marketing authorisation (ORadj. 17.1, 95% CI 2.1–138.9; Table 2) was driven by manufacturing, quality and safety issues, which seem to have contributed to a negative CHMP opinion. These biological products might not necessarily have deficits in the clinical development programme, which could explain some of the differences in the univariate and multivariate results.

Regulatory dialogue

The number of applications for orphan designation has increased during the past few years. This could result in more OMPs being authorised for marketing in the EU during the following ten years [5,22]. Drug developers and regulators could face new challenges in (innovative) orphan drug development that goes beyond guidelines. Increasing knowledge about disease progress, prevalence data and how to conduct a clinical trial is needed [2,23–25]. Such complex drug-development challenges need frequent and strong scientific discussions between industry and the regulatory community. Regulatory dialogue can, and should, have an essential role in safeguarding sustained knowledge exchange and increasing successful marketing authorisation. Protocol assistance is provided for OMP developers either for free (for small and medium-sized enterprises; SMEs) or with a 90% fee reduction (for non-SMEs). In previous studies with EMA and FDA dossier data it has been shown that compliance with scientific advice is associated with marketing approval [12,26]. In our study having protocol assistance or scientific advice was not associated with a successful marketing application (Table 2). Unfortunately, compliance with scientific advice could not be studied, because non-compliance was not documented in a standardized way in the study data. To increase the dialogue, the EMA and FDA have announced parallel scientific advice programmes for all products with a possible clinical significance for both agencies [27,28].

Some limitations of our case study should be reported. First, the total number (114) of non-approved and approved marketing applications has limited opportunities for analysis. Obviously, the confidence intervals of the association estimates are wide. The strength of this study reflects the fact that we included all marketing applications for OMPs in the EU since the advent of the orphan drug regulation in 2000. Second, some of the variables are correlated with each other. Specific indications might be related to the availability of an alternative therapy and therefore the availability of an active comparator, disease prevalence and difficulties with selecting appropriate endpoints. Owing to the low numbers per indication, category interaction could not be tested. Third, regulator concerns were extracted from conclusions in EPARs. Despite the fact that these are standardized documents in terms of structure and subheadings, EPARs can differ in length, completeness and amount of detail in the benefit–risk discussion. Heterogeneity in the content of EPARs might have introduced some misclassification.

Concluding remarks

In the space of ten years the marketing authorisation procedure of OMPs in Europe has evolved through trial and error, but with a clear vision on improving the health of patients with a rare disease. Our analysis of all marketing applications for OMPs in the EU aimed toward learning from ten years of regulation on OMPs has shown that demonstrating convincing evidence on the primary endpoint and the selection of a clinically relevant endpoint are crucial for success. However, other characteristics of the development plan such as an RCT as the pivotal study and sufficient learning (i.e. appropriate dose finding) have a significant role. Medical need, defined as lack of an alternative therapy for the disease, was also shown to be a relevant factor that colours the outcome of a benefit–risk assessment. These findings have a clear message to drug developers and regulators. Although orphan drugs have their inherent challenges in terms of development and assessment of benefit–risk, robust data on the real clinical benefit for the patients with a rare disease remain pivotal. Certainly, measuring with different standards as recently suggested by Kesselheim *et al.* [29] is not in the long-term interest of these patients. By contrast, taking the high medical need for drugs that target rare diseases into account remains an important factor when building and evaluating OMP dossiers.

Conflicts of interest and disclaimer

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The views expressed in this chapter are the personal views of the author(s) and must not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

References

1 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 Union*
2 Schieppati, A. *et al.* (2008) Why rare diseases are an important medical and social issue. *Lancet* 371, 2039–2041
3 Dear, J.W. *et al.* (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
4 European Medicines Agency, (2011) *Committee for Orphan Medicinal Products (COMP) Monthly report 4–5 May 2011.* EMA/COMP/135191/2011
5 (2011) Committee for Orphan Medicinal Products. European regulation on orphan medicinal products: 10 years of experience and future perspectives. *Nat. Rev. Drug Discov.* 10, 341–349
6 European Medicines Agency (2008) *Survey 2007 on the performance of EMEA scientific procedures for medicinal products for human use.* EMEA/158877/2008
7 European Medicines Agency (2009) *Survey 2008 on the performance of EMEA scientific procedures for medicinal products for human use.* EMEA/MB/30754/2009
8 European Medicines Agency (2010) *Performance of the Agency's scientific procedures: Survey 2009 for medicinal products for human use.* EMA/MB/78873/2010
9 Joppi, R. *et al.* (2006) Orphan drug development is progressing too slowly. *Br. J. Clin. Pharmacol.* 61, 355–360
10 Joppi, R. *et al.* (2009) Orphan drug development is not taking off. *Br. J. Clin. Pharmacol.* 67, 494–502
11 Heemstra, H.E. *et al.* (2008) Predictors of orphan drug approval in the European Union. *Eur. J. Clin. Pharmacol.* 64, 545–552
12 Heemstra, H.E. *et al.* (2011) Characteristics of orphan drug applications that fail to achieve marketing approval in the USA. *Drug Discov. Today* 16, 73–80
13 Buckley, B.M. (2008) Clinical trials of orphan medicines. *Lancet* 371, 2051–2055
14 Eichler, H.G. *et al.* (2008) Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. *Nat. Rev. Drug Discov.* 7, 818–826
15 Woodcock, J. and Woosley, R. (2008) The FDA critical path initiative and its influence on new drug development. *Annu. Rev. Med.* 59, 1–12
16 European Medicines Agency (2001) *Points to Consider on Application with 1. Meta-analyses 2. Use of one pivotal study.* CPMP/EWP/2330/99
17 European Medicines Agency, Committee for Medicinal Products for Human Use (2006) *Guideline on clinical trials in small populations.* CHMP/EWP/83561/2005
18 European Medicines Agency (2008) *European Public assessment report Vidaza.* EMEA/593162/2008
19 Sheiner, L.B. (1997) Learning versus confirming in clinical drug development. *Clin. Pharmacol. Ther.* 61, 275–291
20 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (1998) *ICH Harmonised tripartite guideline – statistical principles for clinical trials: E9*
21 European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) (2010) *Concept paper on the need for a Guideline on the use of Subgroup Analyses in Randomised Controlled Trials.* EMA/CHMP/EWP/117211/2010
22 European Medicines Agency (2010) *Orphan medicines in numbers: The success of ten years of orphan legislation.* EMA/279601/2010
23 European Medicines Agency (2011) *The European Medicines Agency Road Map to 2015: The Agency's Contribution to Science, Medicines, Health*
24 International Society for Pharmacoeconomics and Outcomes Research (2010) A call to make valuable innovative medicines accessible in the European Union. *Background report for the ministerial conference 23–24 September*
25 Tambuyzer, E. (2010) Rare diseases, orphan drugs and their regulation: questions and misconceptions. *Nat. Rev. Drug Discov.* 9, 921–929
26 Regnstrom, J. *et al.* (2010) Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. *Eur. J. Clin. Pharmacol.* 66, 39–48
27 European Medicines Agency (2009) *General principles EMA-FDA Parallel Scientific Advice.* EMEA/24517/2009
28 Torres, C. (2010) Rare opportunities appear on the horizon to treat rare diseases. *Nat. Med.* 16, 241
29 Kesselheim, A.S. *et al.* (2011) Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. *JAMA* 305, 2320–2326
30 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. *Official Journal of The European Union*
31 European Medicines Agency (2010) *User guide for micro, small and medium-sized enterprises (SMEs) on the administrative and procedural aspects of the provisions, laid down in Regulation (EC) No 726/2004, that are of particular relevance to SMEs.* EMA/204919/2010