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Characteristics of orphan drug applications that fail to achieve marketing approval in the USA

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The US Orphan Drug Act has fostered the development of drugs for patients with rare diseases by granting 'orphan designations', although several orphan drugs for which a marketing application has been submitted to the FDA have failed to obtain approval. This study identified the clinical trial design, the level of experience of the sponsor and the level of interaction with the FDA to be associated with non-approval. Sponsors, therefore, should engage in dialogue with the FDA and thoughtfully design pivotal clinical trials in accordance with FDA guidance documents.

The development of medicinal products for the treatment of rare diseases is widely seen as an important public health issue [1–3]. Drugs for rare diseases face heightened challenges in achieving regulatory approval [1]. By law, introducing a new drug in the USA normally requires overcoming several hurdles: first, the drug is studied in animals and then humans (ultimately, via clinical trials), under the aegis of an Investigational New Drug (IND) permit. Second, an application is made to market the drug, in the form of a New Drug Application (NDA), which subsumes the data gathered under the IND and attempts to establish that the drug is safe and effective for its proposed use, that associated product labeling is accurate and that the drug is produced using sound manufacturing methods. Conducting a clinical trial for a rare disease is hampered by many practical limitations, including statistical design challenges and the enrolment of a sufficient number of participants [4]. Commercial drug developers might be discouraged further by the small size of the potential market for such a drug [5]. Consequently, the USA and the EU, as well as several other jurisdictions, have put into force specific legislation to stimulate the development of drugs, biological products and (in the USA) devices intended for the treatment, diagnosis or prevention of rare diseases [6,7]. The US Orphan Drug Act, enacted in 1983 and later amended, defines a rare disease as one affecting 200 000 or fewer individuals within the USA. Granting orphan product status requires that a drug be associated with a scientifically plausible rationale for efficacy (a much lower standard than required by a successful NDA) and does not convey marketing approval – an orphan product must undergo the same rigorous IND and NDA process that any other drug must follow. Orphan product status does provide a sponsor with attractive benefits, however: a waiver of the FDA user fees for NDA review ($1.4 million in 2009), free scientific advice, tax credits for clinical trials and seven years of market exclusivity after NDA approval [6,8]. As of May 2009, 2002 orphan designations had been granted in the USA, of which 338 were approved for marketing (http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm. July 10, 2009) [8]. As shown in Fig. 1, the number of new orphan designations per year ranged from 62 to 141 between 1998 and 2007, and the number of orphan marketing approvals was between 6 and 22.

Like the USA, the EU has dedicated legislation that provides incentives for companies and institutions developing an orphan drug, enacted in 2000. In a previous study, aiming to determine predictors of successful approval of orphan drugs in the EU, we found that a company's prior experience in developing orphan drugs was important [9]; in addition, an orphan drug based on a molecule that had been approved previously for another indication had a higher probability of approval [9]. A study by Joppi *et al.* [10] reported that in the EU, only a small percentage (7.1%) of orphan designations had been approved by December 2004,

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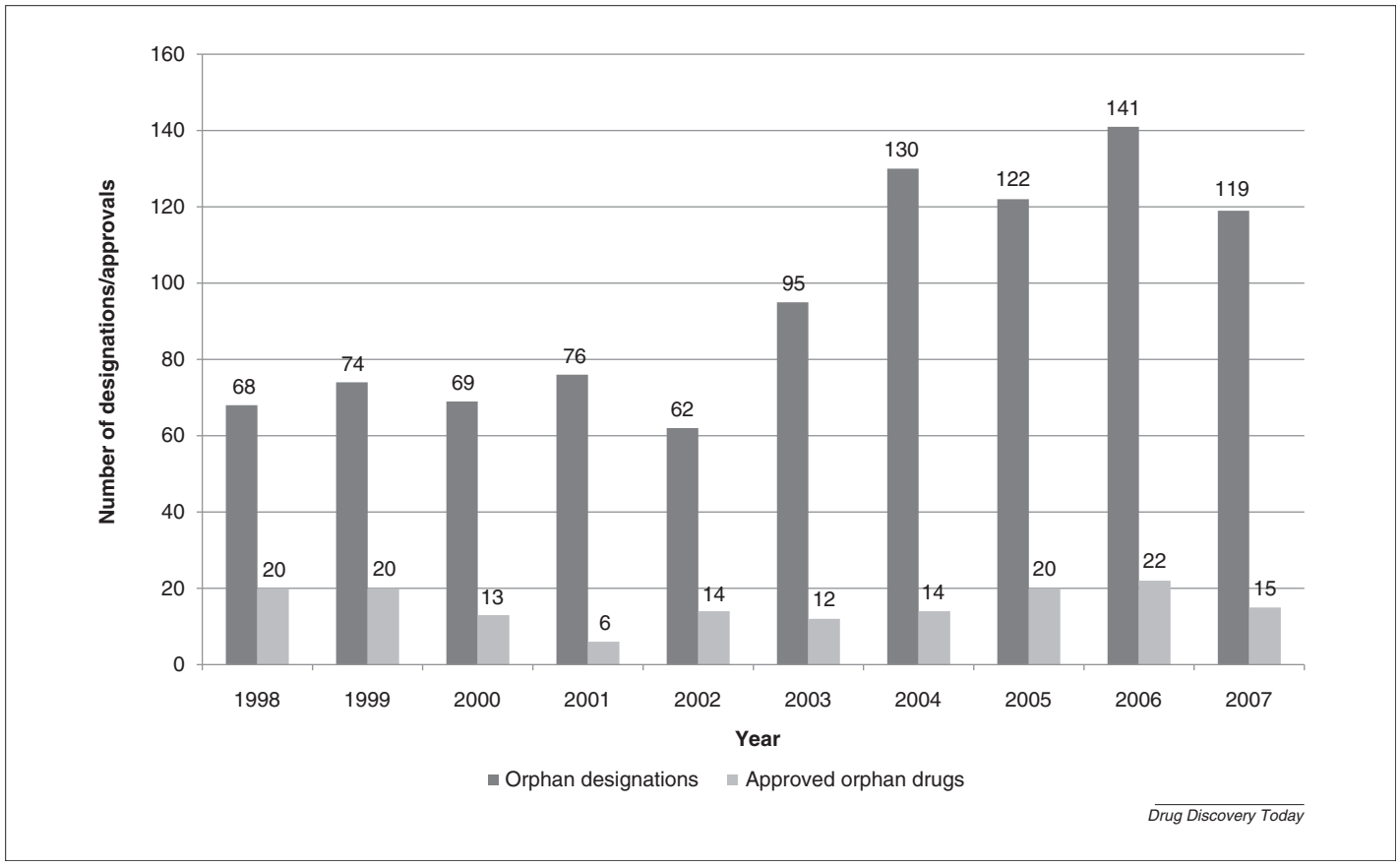

FIGURE 1

Orphan designations and orphan approvals in the USA (1998–2007). The number of drugs, biologics and devices that have obtained an orphan designation (dark gray) or a marketing approval (both NDA and BLA; light gray) from the FDA (http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm. May 10, 2010). A large majority of the designations are for drugs. Between 1998 and 2007, 140 orphan NDAs were approved and 23 were not approved, of which 15 (65%) had electronically available reviews and were included in this study.

although the short follow-up time in that publication suggests that the percentages will rise as additional approvals accrue over time. These figures nonetheless suggest that development of many designated orphan drugs was discontinued in the pre-clinical or clinical stages, for commercial or medical reasons. Substantial attrition has also been observed for non-orphan drugs, for the same reasons [11]. Joppi *et al.* [10] commented that the low approval rates for European orphan drugs might be due to the poor documentation underpinning the applications and that many orphan drugs were approved under exceptional circumstances, without comprehensive data on the safety and efficacy of the product [12]. Deficiencies included the use of clinically irrelevant surrogate endpoints, a low number of study subjects, inappropriate use of a comparator and the absence of adequately conducted randomized controlled trials [12].

Joppi's critique was also directed toward the effectiveness of the EU orphan drug incentives and noted the consequently low number of orphan drugs that achieve marketing approval in the EU. This article aims to determine the crucial factors related to failure to achieve marketing approval in the USA. Knowledge of these crucial factors will help orphan drug developers (both industry and academic institutions) and regulators to increase the efficiency of the application process, thereby stimulating innovation, promoting the regulatory goal of assuring drug safety and efficacy [13,14], and, it is hoped, helping to speed the availability of much-needed therapies for life-threatening and/or chronically debilitating rare disorders.

Characteristics of the clinical trial program

For the period from January 1998 to December 2007, we identified and obtained 15 FDA-non-approved marketing applications (NDAs) for orphan drugs and 41 approved marketing applications for orphan drugs to serve as controls (Fig. 2). Of the 15 non-approved NDAs, two were withdrawn by the sponsor before an FDA decision was made; two received an 'Approvable' letter (in 2004 and 2006), indicating that the NDA could not be approved until additional issues were resolved; and 11 received a 'Non-Approvable' letter from the FDA. A univariate analysis, as described in Box 1, has been performed to determine factors associated with non-approval of orphan drug applications in the USA. Table 1 displays the results of the univariate analysis of the characteristics of these applications.

Endpoint

A crucial variable associated with the outcome of the FDA review was the outcome of the primary endpoint of the pivotal clinical trial, which accords with a prior study of factors that contribute to a first-cycle approval for non-orphan NDAs [15]. If efficacy of the drug with respect to the primary endpoint cannot be established in a pivotal trial, the odds for non-approval are very high

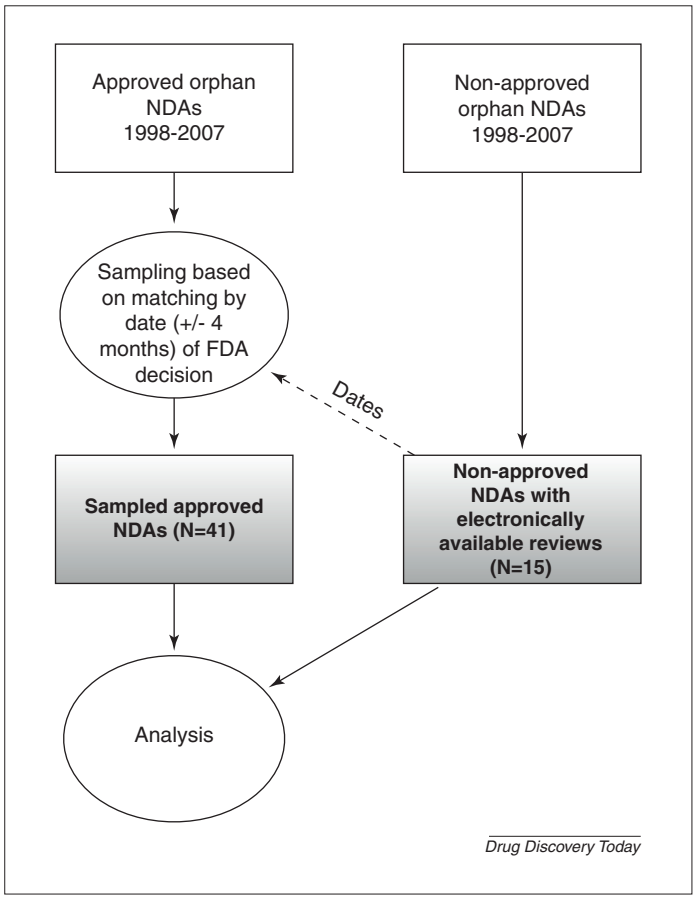

FIGURE 2

Graphical depiction of sampling of the cases and controls. Up to three approved NDAs were sampled for each non-approved NDA based on the decision date of each of the 15 non-approved NDAs (http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm. May 10, 2010 and http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. April 10, 2009). We defined a 'non-approved' new drug application (NDA) as one that suffered one of these fates: (i) it was withdrawn; (ii) it received a 'Not Approvable' letter from the FDA; or (iii) the FDA indicated that the NDA could not be approved until additional issues were resolved. We identified designated orphan drug applications that were non-approved during the period January 1998 to December 2007 and for which FDA review information was readily available in electronic form (we excluded non-approved device and biologic license applications, or BLAs, which appear in much smaller numbers). All identified non-approved drug applications were compared to a sample of orphan drugs with approved NDAs. For each non-approved application, we randomly selected up to three orphan NDAs that were approved within the time span of four months before or after the decision date for the non-approved application.

(OR = 25.67; 95%CI = 5.3–125.1), an association that increased over time from an OR of 16.00 (95%CI = 2.1–120.7) for the first eight non-approved NDAs to an OR of 47.50 (95%CI = 3.6–636.2) for the final seven consecutively non-approved NDAs.

The outcome of the primary endpoint depends heavily upon the nature of that endpoint. If a more clinical primary endpoint (such as overall survival) is chosen, the limited duration or small sample size of a trial might not provide adequate power to demonstrate statistical significance [16]; it might be easier to demonstrate an effect upon a biomarker, but such a surrogate endpoint might not be a demonstrably valid substitute for a clinical endpoint [17] and consequently not be acceptable to the FDA or EMEA [14]. Some applications of the non-approved orphan drugs studied here do demonstrate statistically significant results in association with secondary endpoints or when studied in subgroups of the target population. These studies are powered upon the primary endpoint, however, and according to the guidelines of the International Conference on Harmonization, such analyses are considered exploratory and do not provide sufficient evidence for approval [18]. Consequently, the choice of a primary endpoint must be based on balancing the feasibility of a specific drug study against regulatory requirements. The results of previous (earlier phase) studies and of studies for similar drugs should guide this decision [19]. This is illustrated by the example of pulmonary arterial hypertension (PAH), a rare disease associated with a high level of drug development [20]. For this multifactorial complex disease, a six minute

BOX 1

Methodology Data collection Each of the selected (approved and non-approved) NDAs were characterized according to the properties of the drug and its indication, the properties of the clinical trial program, the properties of the drug's sponsor and the properties of the sponsor's interactions with the FDA, as defined in Table 1. Data for non-approved NDAs were obtained from the FDA in accord with the *Statement of Authority and Confidentiality Commitment from the Netherlands Medicines Evaluation Board not to publicly disclose non-public information shared by the US Food and Drug Administration* [37]. Data for approved NDAs were obtained from the FDA's publicly available database Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. April 10, 2009).

Characteristics of the drug included: whether it was a 'New Molecular Entity' (NME, a drug for which no active moiety has previously received marketing approval) and whether it had a history of prior marketing approval or previous (non-approved) use in clinical practice. Data associated with the indication included the disease category into which the indication falls, the number of patients with the disease in the USA and the availability of other approved drugs for the disorder. The clinical trial program was evaluated according to the rigor of its design (as indicated by the use of randomization and controls), the total number of patients exposed to the studied drug, the number of patients in the pivotal clinical trials, the age and sex of study participants in the pivotal trial, the nature and achievement of the endpoint, and the identification of an appropriate target population. If the FDA indicated that multiple pivotal trials had been conducted, the most rigorous clinical trial was included in our study, as defined by greatest number of the following four criteria: randomization, use of controls, double blinding and use of multiple centers. If two trials were equivalent, both were included in the analysis. The characteristics of the sponsor included sponsor size and location and its history of prior experience with orphan drugs.

Characteristics of the sponsor's interactions with the FDA included consideration of whether the NDA had been previously reviewed, whether pre-NDA meetings were held, whether FDA advice was followed and the FDA's judgment concerning the sponsor's data quality and integrity.

Data analysis

Characteristics of approved and non-approved applications were compared using univariate logistic regression analysis using SPSS version 16.0 for Mac (SPSS, Chicago, Illinois). Odds ratios (ORs) and their corresponding 95% confidence intervals (95%CIs) were calculated for each characteristic in the five categories.

TABLE 1

Characteristics of products in the study.

Variable in the study	Non-approved NDAs[a] (%) [*N* = 15][b]	Approved NDAs[a] (%) [*N* = 41][b]	OR (95%CI)
Characteristics of the drug			
Type of drug			
Existing molecule	1 (7)	15 (37)	1 [Reference][c]
New formulation of existing molecule	3 (20)	7 (17)	6.43 (0.6-73.4)
New Molecular Entity (NME)	11 (73)	19 (46)	8.68 (1.0-75.0)
Previous clinical use: has this molecule been used previously in clinical practice (including off-label use, other indication, other region)?			
Yes	8 (53)	29 (71)	1 [Reference]
No	7 (47)	12 (29)	2.12 (0.6-7.1)
Previous approval: has this molecule been approved previously (in the past, or in another country or region)?			
Yes	8 (53)	23 (56)	1 [Reference]
No	7 (47)	18 (44)	1.12 (0.3-3.7)
Characteristics of the indication			
Indication category			
Cancer	10 (67)	18 (44)	1 [Reference]
Infectious diseases	1 (7)	5 (12)	0.36 (0.0-3.5)
Metabolic diseases	0 (0)	5 (12)	–
Neurologic diseases	0 (0)	3 (7)	–
Poisoning	1 (7)	4 (10)	0.45 (0.0-4.6)
Pulmonary diseases	1 (7)	2 (5)	0.90 (0.1-11.2)
Other diseases	2 (13)	4 (10)	0.90 (0.1-5.8)
Number of affected individuals in the US: total population for which the orphan drug is indicated in the US			
Fewer than 4999	2 (13)	6 (15)	1 [Reference]
Between 5000 and 49 999	4 (27)	17 (42)	0.71 (0.1-4.9)
Between 50 000 and 200 000	9 (60)	18 (44)	1.50 (0.3-9.0)
Currently available therapy: is another drug currently approved for the proposed indication?			
Available	11 (73)	27 (66)	1 [Reference]
Unavailable	4 (27)	7 (17)	1.40 (0.3-5.8)
Characteristics of the clinical trial program			
Rigor of pivotal clinical trial design			
Randomized, double blinded, controlled trial(s)	3 (20)	12 (29)	1 [Reference]
Other controlled trial(s)	6 (40)	11 (27)	2.18 (0.4-10.9)
Uncontrolled trial(s)	6 (40)	15 (37)	1.60 (0.3-7.8)
Total exposed population: number of subjects who have been exposed to at least one dose of the study product in all clinical trials			
0–299	4 (27)	10 (24)	1 [Reference]
300–799	5 (33)	15 (37)	0.83 (0.2-3.9)
800 or more	5 (33)	13 (32)	0.96 (0.2-4.5)
Total number of patients in pivotal clinical trials (all trial arms)			
0–149	5 (33)	19 (46)	1 [Reference]
150–299	4 (27)	7 (17)	2.17 (0.5-10.5)
300 or more	5 (33)	13 (32)	1.46 (0.4-6.1)
Primary endpoint used in pivotal clinical trial			
Overall survival, cure	6 (40)	9 (22)	1 [Reference]
Progression-free survival, symptomatic relief	1 (7)	8 (20)	0.19 (0.0-1.9)
Other (biomarkers, surrogate endpoints, quality of life, etc.)	8 (53)	23 (56)	0.52 (0.1-1.9)
Primary endpoint outcome: did a pivotal trial yield positive results with respect to the primary endpoint, as judged by the FDA reviewer?			
Success	3 (20)	35 (85)	1 [Reference]
Failure	11 (73)	5 (12)	25.67 (5.3-125.1)
Correct target population: was the most appropriate target population identified for the drug, according to the FDA review?			
Identified	10 (67)	40 (98)	1 [Reference]
Not identified	5 (33)	1 (2)	20.00 (2.1-190.9)
Sex of study participants in pivotal clinical trial: percentage of male subjects in pivotal study			
0%–25%	4 (27)	7 (17)	1 [Reference]
26%–74%	9 (60)	22 (54)	0.72 (0.2-3.1)
75%–100%	1 (7)	3 (7)	0.58 (0.0-7.7)
Trials conducted in special age groups: has a pivotal trial been conducted in patient groups with an average age below 18 or above 65?			
Yes	1 (7)	11 (27)	1 [Reference]
No	13 (87)	23 (56)	6.22 (0.7-53.8)
Characteristics of the sponsor			
Company size			
Large company (more than 250 employees)	2 (13)	24 (59)	1 [Reference]
Small or medium enterprise	13 (87)	11 (27)	14.18 (2.7-73.9)
Prior experience with orphan drugs: has the sponsor previously developed and marketed an orphan drug?			
Yes	5 (33)	26 (63)	1 [Reference]

TABLE 1 (*Continued*)

Variable in the study	Non-approved NDAs[a] (%) [*N* = 15][b]	Approved NDAs[a] (%) [*N* = 41][b]	OR (95%CI)
No	10 (67)	14 (34)	3.71 (1.1-13.0)
Location of sponsor: geographic location of the headquarters of the sponsor			
USA	14 (93)	32 (78)	1 [Reference]
Other region	1 (7)	9 (22)	3.94 (0.5-34.1)
Characteristics of interactions with the FDA			
Prior FDA review: has this NDA been previously been reviewed by the FDA, resulting in a non-approvable or approvable decision?			
First review	12 (80)	29 (71)	1 [Reference]
Multiple reviews	3 (20)	11 (27)	0.66 (0.2-2.8)
Pre-NDA meeting: was a pre-NDA meeting conducted between sponsor and FDA?			
Yes	6 (40)	30 (73)	1 [Reference]
No	5 (33)	3 (7)	8.33 (1.6-44.6)
Sponsor followed FDA advice: did the sponsor follow FDA advice with respect to the design and conduct of the pivotal trials?			
Yes	9 (60)	37 (90)	1 [Reference]
No	5 (33)	1 (2)	20.56 (2.1-198.4)
Data quality and integrity: did the FDA judge that the quality and integrity of the sponsor's data were insufficient?			
Sufficient	10 (67)	36 (88)	[Reference]
Insufficient	5 (33)	1 (2)	OR = 18.0 (1.9-172.2)

[a] NDA: New drug application.
[b] Percentages in each cell do not add up to 100% because the unavailability of data on some of the characteristics resulted in several missing values for both cases and controls. As a result of rounding, some of the percentages add up to 101%.
[c] Reference category for univariate logistic regression.

walking distance test has been studied as a surrogate endpoint for improvement in the quality of life and survival of PAH patients [21,22]. Although this surrogate parameter is not perfect [23], regulators have accepted the 6-min walking distance as a primary endpoint in the marketing applications of several drugs for the treatment of PAH [21]. For other diseases, however, suitable endpoints are much harder to define. This is illustrated by cystic fibrosis (CF) [24]. Because of the erratic nature of this disease, clinical trials for CF have been hampered by the lack of validated and reproducible endpoints for the primary chronic lung disease [25]. The result is that more than 50 US orphan designations are aimed at the treatment of CF – but only a handful of agents have been approved in the USA, and these drugs treat only secondary manifestations of CF, rather than the primary chronic lung disease [24]. Progress in the past decade regarding the pathophysiology of CF has now led to the introduction of new primary endpoints, both clinical and surrogate, that can be used for clinical trials [25]. This continuing search for new and valid biomarkers for drug efficacy and safety is compliant with the FDA's Critical Path Initiative [26].

Finally, Richey *et al.* [27] have discussed the benefits of accelerated approval for oncologic drugs, including many with an orphan indication, and found that most drugs approved via an accelerated procedure have shown a confirmed therapeutic benefit and did not seem to have a higher risk for serious adverse drug reactions once the drug was on the market. According to Richey *et al.* [27], accelerated approval with phase II trial data might thus facilitate the successful clinical development of oncological orphan drugs. Although not included in the analysis of this article because of the absence of information on accelerated approval for several of the non-approved orphan drugs, 10 out of the 41 approved orphan drugs included in this study had accelerated FDA approval [27].

Target population

The results also emphasize the importance of clearly defining the target population for an orphan drug. For 5 of the 15 non-approved orphan drug applications, the FDA review indicated that the sponsor had not yet identified the most appropriate patient population for the drug, which possibly resulted in an underestimation of the potential effect of the drug in the pivotal trial. The probability of non-approval of these NDAs was considerably higher than for NDAs for which the appropriate patient population had been identified (OR = 20.00; 95%CI = 2.1–190.9).

The smaller patient populations associated with orphan drug clinical trials can result in reduced statistical power, requiring a larger drug effect to achieve a given level of statistical significance than would be required when using a larger study population [28]. The patients available for a pivotal trial can exhibit substantial heterogeneity with regard to diagnosis, disease stage and disease subtype [4]. Evolving knowledge in genetics and pathogenesis might result in further subdivision of a disease into multiple subtypes [14,29], and a new drug might be highly efficacious for one of these subtypes and demonstrate lesser efficacy for others. Consequently, the patient population for a clinical trial should be matched to the disease subtype that is expected to show optimal efficacy, to maximize the probability of a positive outcome and subsequent approval for the population in which the product is efficacious. Eichler *et al.* [14] illustrated this stepwise approval for imatinib (Gleevec®) and bevacizumab (Herceptin®) in the EU, both of which were initially approved for an indication with a relatively small patient population that has now been broadened to include other subpopulations and additional disease conditions. After successful approval for the first indication, consecutive subtypes can be explored in additional trials.

Characteristics related to the sponsor

Characteristics describing the sponsor showed a clear association with non-approval: small and medium enterprises (OR = 14.18; 95%CI = 2.7–73.9) and companies or institutions without prior experience with orphan drug development (OR = 3.71; 95%CI = 1.1–13.0) have considerably higher probabilities for non-approval of their FDA applications. Our results demonstrate that applications

from larger and more experienced companies have a higher proportion of approved orphan drugs. Prior success in developing orphan drugs was also positively associated with approval in our previous study of orphan drug development in the EU [9]. According to a prior report, sponsors with previously approved drugs were more likely to get their subsequent NDAs approved within one FDA review cycle [15]. A study by Seoane-Vazquez demonstrated that companies with multiple orphan designations had higher chances for approval of their NDAs [30]. In addition, previous studies indicated that while university medical centers or small and medium enterprises initiated early development of the majority of EU orphan designations, larger or more experienced companies brought many of these to the market [13,31]. These findings support our other findings that revealed the importance of a well-founded decision on the choice of primary endpoints and target population.

Interactions with the FDA

Our study suggests that interaction and dialogue with the FDA is important. Applications for which a pre-NDA meeting with the FDA was not held have a more than eightfold (OR = 8.33; 95%CI = 1.6–44.6) increase in the probability of rejection. For six NDAs, the FDA medical review or decision letter indicated that the sponsor had not adhered to FDA advice regarding the design or conduct of the clinical trial program; the probability of non-approval was statistically higher for these NDAs, compared to those of sponsors that followed FDA's advice (OR = 20.56; 95%CI = 2.1–198.4). Finally, for several of the non-approved NDAs, the quality and integrity of the data submitted to the FDA were insufficient. FDA reviews of five NDAs (33%) indicated that case report forms were missing, statistical analyses were done improperly, or other issues cast doubt upon the reliability of the studies (OR = 18.0; 95%CI = 1.9–172.2).

Obtaining FDA advice in pre-NDA meetings and adhering to regulatory advice from the FDA in designing and conducting the pivotal clinical trials are both associated with approval. Many orphan designations are based on innovative biotechnological molecules, new molecular entities (NMEs), or innovative formulations [28,32,33]. Obtaining advice from the FDA may be especially important for sponsors of these drugs. The FDA was the first drug regulatory agency to implement dialogue with applicants, starting in the early 1980s [14], coinciding with the enactment of the Orphan Drug Act (1983). Redmond has suggested that this might be one factor behind the low rate of non-approval for orphan drugs in the USA [34]. The long history of regulatory dialogue between sponsor and FDA has already provided developers of US orphan drugs with considerable experience. According to Haffner, the Orphan Drug Act might have stimulated the creation and growth of several biotechnology companies, such as Genzyme and Amgen, as well as firms dedicated to the development of orphan drugs, such as Orphan Medical [31,35]. Moreover, this study emphasizes the importance of trial data of good quality, in line with the requirements for good manufacturing practice.

Product and indication

Compared to drugs based on previously approved molecules, NMEs have an eightfold higher chance of non-approval (OR = 8.68; 95%CI = 1.0–75.0), although no statistically significant association was found between non-approval of an NDA and the type of indication, the prevalence of the indication or the availability of other drugs for the indication. Because of the small number of cases, however, the sample sizes in this study are particularly small at the indication level. Moreover, two recent papers present evidence that the approval rates for NDAs in general do vary by therapeutic category [8,36]. The absence of a statistically significant association between non-approval of an NDA and the type of indication, therefore, might not mean that no such an association exists.

This study is based on the concept that one can learn from unsuccessful attempts to obtain marketing approval for an orphan drug. Although the academic side of orphan drug development is also of great importance for successfully developing an orphan drug, this study focused on obtaining regulatory approval for orphan drugs in the USA. Our results demonstrate that approval of an NDA is correlated with characteristics of the drug, the sponsor, the clinical trial plan, and the interactions and dialogue the sponsor has with the FDA. No correlation with non-approval was observed for the characteristics of the indication of a drug.

We restricted this study to all non-approved orphan NDAs for which electronically available records were readily available, which limited us to the year 1998 onward. Therefore, our results only represent a sample (15 out of 23) of those orphan drugs that failed to receive market approval since 1998. The resulting small sample size of the study leads to broader 95%CIs than would have been encountered if using a larger sample size and might have led to selection bias in favor of recent products. To minimize this bias, we have sampled controls based on the time of the FDA review decision, such that the included cases and controls are temporally proximate. The fact that this small study has nevertheless yielded several statistically significant characteristics associated with the outcome of the FDA review process is, therefore, illustrative of the strength of these associations. Although a multivariate logistic regression analysis would have been preferred for this analysis, the limited sample size made it impossible to implement this approach. The results presented in this study might, therefore, be different owing to correlations with other statistically significant variables in this study. Finally, we were limited by the incompleteness of data regarding some of the characteristics, resulting – for some study variables – in missing values for both cases and controls. The results of this study, therefore, should be considered hypothesis generating rather than hypothesis confirming. Further studies with well-matched controls are needed to establish the characteristics that are found to be associated with orphan drug approval.

Concluding remarks

In conclusion, this study pinpoints two crucial characteristics of successful orphan drug applications in the USA (graphically summarized in Fig. 3). First, the choice of the primary endpoint and target population of a pivotal clinical trial for an orphan drug might affect the outcomes of the main clinical trial and consequently its probability of successful marketing (NDA) approval. To increase the flow of new drugs to patients with rare diseases, selection of these trial variables must be made carefully. Second, inexperienced companies (and companies developing innovative orphan drugs based on NMEs) might face extra challenges when designing and conducting these clinical trials, and these companies might benefit from active participation in dialogue with the

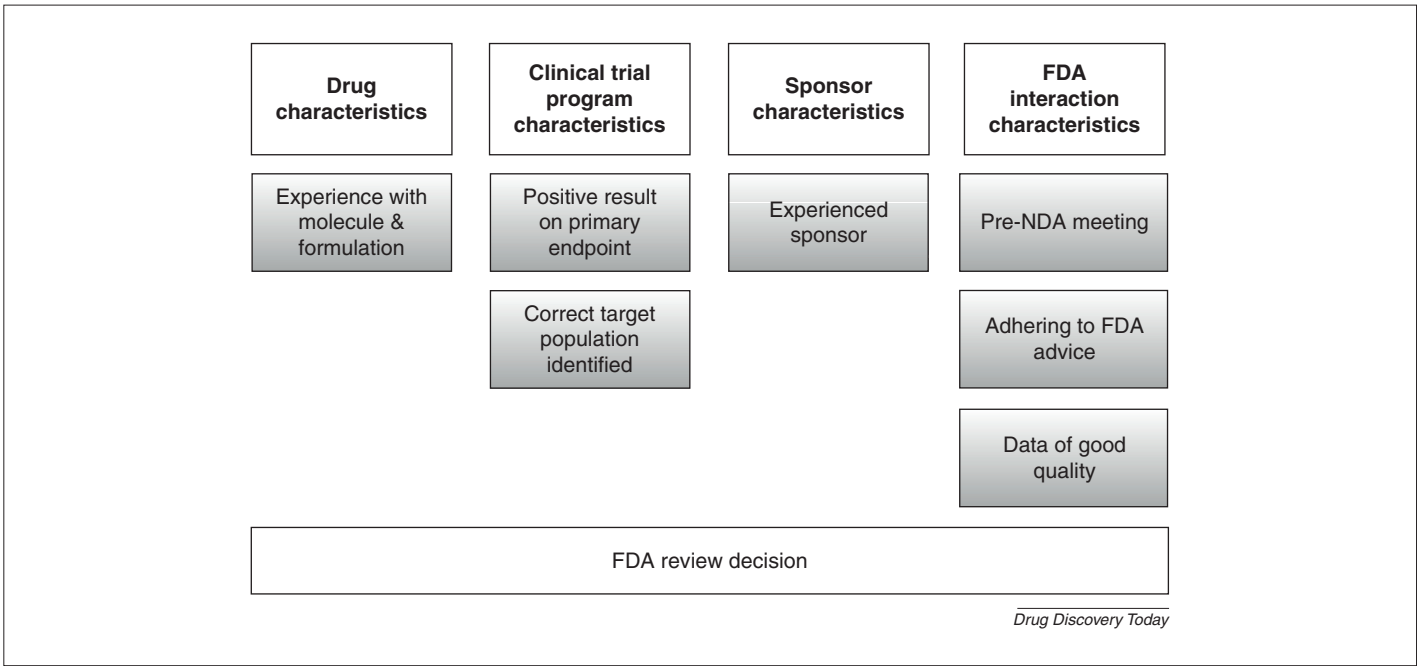

FIGURE 3

Characteristics associated with orphan drug approval in the USA.

regulatory authorities and utilizing the special incentives for regulatory assistance and advice that are offered by the FDA.

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References

1 Van Weely, S. and Leufkens, H. (2004) Background paper: orphan diseases. *Priority Medicines for Europe and the World* World Health Organization
2 Schieppati, A. *et al.* (2008) Why rare diseases are an important medical and social issue. *Lancet* 371, 2039–2041
3 Stolk, P. *et al.* (2006) Rare essentials: drugs for rare diseases as essential medicines. *Bull. World Health Organ.* 84, 745–751
4 Buckley, B.M. (2008) Clinical trials of orphan medicines. *Lancet* 371, 2051–2055
5 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
6 The Orphan Drug Act (1983) United States Public Law No. 97-414
7 Anonymous, (1999) Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 November 1999 on orphan medicinal products. *Off. J. Eur. Commun.* 18, 1–5
8 Braun, M.M. *et al.* (2010) Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. *Nat. Rev. Drug Discov.* 9, 519–522
9 Heemstra, H.E. *et al.* (2008) Predictors of orphan drug approval in the European Union. *Eur. J. Clin. Pharmacol.* 64, 545–552
10 Joppi, R. *et al.* (2006) Orphan drug development is progressing too slowly. *Br. J. Clin. Pharmacol.* 61, 355–360
11 Dimasi, J.A. (2001) Risks in new drug development: approval success rates for investigational drugs. *Clin. Pharmacol. Ther.* 69, 297–307
12 Joppi, R. *et al.* (2009) Orphan drug development is not taking off. *Br. J. Clin. Pharmacol.* 67, 494–502
13 Heemstra, H.E. *et al.* (2008) Orphan drug development across Europe: bottlenecks and opportunities. *Drug Discov. Today* 13, 670–676
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 Anonymous, (2006) *Independent Evaluation of FDA's First Cycle Review Performance – Retrospective Analysis Final Report.* Booz Allen Hamilton
16 Ruberg, S. and Cairns, V. (1998) Providing evidence of efficacy for a new drug. *Stat. Med.* 17, 1813–1823
17 Wagner, J.A. (2002) Overview of biomarkers and surrogate endpoints in drug development. *Dis. Markers* 18, 41–46
18 Anonymous, (1998) ICH Harmonised tripartite guideline – statistical principles for clinical trials: E9. *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*
19 Hanson, B. (2008) The art of choosing sound study endpoints. *Injury* 39, 656–658
20 Humbert, M. (2008) Update in pulmonary arterial hypertension 2007. *Am. J. Respir. Crit. Care Med.* 177, 574–579
21 Groepenhoff, H. *et al.* (2008) Exercise testing to estimate survival in pulmonary hypertension. *Med. Sci. Sports Exerc.* 40, 1725–1732
22 Strange, G. *et al.* (2008) Bosentan therapy in patients with pulmonary arterial hypertension: the relationship between improvements in 6 minute walk distance and quality of life. *Respirology* 13, 674–682
23 Puhan, M.A. *et al.* (2008) Interpretation of treatment changes in 6-minute walk distance in patients with COPD. *Eur. Respir. J.* 32, 637–643
24 Mayer-Hamblett, N. *et al.* (2007) Advancing outcome measures for the new era of drug development in cystic fibrosis. *Proc. Am. Thorac. Soc.* 4, 370–377
25 Davis, S.D. *et al.* (2007) Endpoints for clinical trials in young children with cystic fibrosis. *Proc. Am. Thorac. Soc.* 4, 418–430
26 Woodcock, J. and Woosley, R. (2008) The FDA critical path initiative and its influence on new drug development. *Annu. Rev. Med.* 59, 1–12
27 Richey, E.A. *et al.* (2009) Accelerated approval of cancer drugs: improved access to therapeutic breakthroughs or early release of unsafe and ineffective drugs? *J. Clin. Oncol.* 27, 4398–4405
28 Wastfelt, M. *et al.* (2006) A journey of hope: lessons learned from studies on rare diseases and orphan drugs. *J. Intern. Med.* 260, 1–10

29 Kebriaei, P. *et al.* (2002) Acute lymphoblastic leukaemia: diagnosis and classification. *Best Pract. Res. Clin. Haematol.* 15, 597–621
30 Seoane-Vazquez, E. *et al.* (2008) Incentives for orphan drug research and development in the United States. *Orphanet J. Rare Dis.* 3, 33
31 Haffner, M.E. *et al.* (2002) Two decades of orphan product development. *Nat. Rev. Drug Discov.* 1, 821–825
32 Haffner, M.E. (2006) Adopting orphan drugs – two dozen years of treating rare diseases. *N. Engl. J. Med.* 354, 445–447
33 Grabowski, H.G. and Moe, J.L. (2008) Impact of economic, regulatory, and patent policies on innovation in cancer chemoprevention. *Cancer Prev. Res.* 1, 84–90
34 Redmond, K. (2004) The US and European regulatory systems: a comparison. *J. Ambul. Care Manage.* 27, 105–114
35 Haffner, M.E. and Maher, P.D. (2006) The impact of the orphan drug act on drug discovery. *Expert Opin. Drug Discov.* 1, 821–825
36 DiMasi, J.A. *et al.* (2010) Trends in risk associated with new drug development: success rates for investigational drugs. *Clin. Pharmacol. Ther.* 87, 272–277
37 Netherlands Medicines Evaluations Board, (2009) *Statement of Authority and Confidentiality Commitment from the Netherlands Medicines Evaluations Board.* http://www.fda.gov/InternationalPrograms/Agreements/ConfidentialityCommitments/ucm095356.htm