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Characteristics of rare disease marketing applications associated with FDA product approvals 2006–2010

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New drug and biologic product marketing applications submitted to FDA's Center for Drug Evaluation and Research (CDER) between 2006 and 2010 were analyzed to identify rare disease application characteristics associated with higher approval rates. The results show that approval rates were similar for rare and common disease applications. Larger company size, prior regulatory experience and priority review designation were associated with higher approval rates. The study findings show that rare disease product development is feasible, and increased interactions between product developers and FDA in early investigational phases can facilitate product development.

Introduction

The development of drug and biological products to treat rare diseases is an important and often challenging area of clinical research. In addition to having small numbers of patients available for inclusion in clinical trials, the natural histories of the diseases are often poorly understood, there can sometimes be few practitioners experienced in caring for patients with rare diseases and rare diseases can lack disease-specific endpoints and assessment measures [1,2]. Thus, designing scientifically rigorous clinical trials that adequately assess the efficacy and safety of rare disease products can be difficult.

Rare diseases, which are disorders affecting less than 200,000 persons in the USA, also have considerable unmet medical needs. There are an estimated 7000 different rare diseases, most of which are serious conditions with no approved products available for their treatment [3]. Recently, rapid advances in molecular biology and targeted pharmacologic research have led to a substantial increase in rare disease investigational agents entering clinical development, some of which will be submitted to regulatory authorities for evaluation for marketing approval [4]. The Orphan Drug Act (ODA) provides incentives intended to make the development of products that will be used by small numbers of patients financially viable [5], but it does not alter the statutory standard for the approval of orphan products from the one used for common disorders; both require substantial evidence of effectiveness from adequate and well-controlled studies to support approval. However, US law recognizes that there are many kinds of drugs that are used for a wide range of indications and enables flexibility in applying the statutory standard to marketing applications. FDA exercises this flexibility and its scientific judgment to determine the type and quantity of data needed to meet statutory requirements for approval [6]. Since the ODA was enacted in 1983, approximately 390 orphan products have been approved by FDA [7], many of which have relied upon non-traditional clinical development programs to support approval, such as a single adequate and well-controlled study [8–12]. FDA's Center for Drug Evaluation and Research (CDER) approved ~90% of these orphan products [7]. The remaining 10% were approved by FDA's Center for Biologics Evaluation and Research (CBER) – mainly blood-derived products such as coagulation factors.

For the purpose of supporting rare disease product development, we undertook an evaluation of CDER's rare disease marketing application history, focusing on a recent five-year period (2006–2010). The goal of this assessment was to identify factors associated with product approvals that could inform the development of guidance, advice and other reasonable approaches to

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successful rare disease product development. Shortly after beginning this evaluation, the Institute of Medicine (IOM) published a report on the results of a two-year examination of the current state of research on healthcare for rare diseases [1], which included a recommendation to conduct a similar assessment [13]. In this article we present the findings of this analysis, which, consistent with the IOM recommendation, are intended to identify factors correlating with rare disease product approvals that could inform future development programs, and to identify areas where additional resources might be directed.

Data sources

All of CDER's New Drug Applications (NDAs) and Biologics License Applications (BLAs) for new molecular entities (NMEs) and new therapeutic biologic products (biologics) for which a regulatory action was taken between 1 January 2006 and 31 December 2010 were analyzed. Only NMEs and new biologics were included, because they represent pharmaceutical innovation best. An NME is defined as a drug for which the active ingredient has not been previously approved by FDA in any other application [14]. Therapeutic biologics include biotechnology-derived products (e.g. monoclonal antibodies), but exclude products derived from blood, human tissues and cell products, gene therapies, vaccines and xenotransplantation products, which are regulated by CBER. Applications were identified from FDA's internal drugs, biologics and orphan products databases. Applications were categorized by whether they underwent a standard (ten-month) or priority (six-month) review. Regulatory actions include approvals (AP) and non-approvals (NA), including various actions that did not result in an approved marketing application. These actions include the FDA regulatory terms of 'complete response' (CR), 'not approvable' and 'approvable' decisions, all of which mean the products were not approved [15,16]. Regulatory actions were also assessed by whether they were first-review-cycle APs or other actions (AP in greater than one cycle or NA action). Applications that received a refusal to file (RTF) decision or were withdrawn by the applicant were also assessed. The filing of an application means that FDA 'has made a threshold determination that the application is sufficiently complete to permit a substantive review' [17]. To ensure data completeness and accuracy, data were abstracted and reviewed by three of the authors (L.J.B., L.A.T and A.R.P.) [7]. Agreement on data content and completeness was reached by consensus, and 100% consensus was reached for all data included in the analysis.

The analysis period from 2006 until the end of 2010 was selected for two reasons. First, in September 2005 FDA completed a major reorganization transferring most of the therapeutic biologics that were previously regulated in CBER to CDER. The year 2006 was the first complete calendar year after this reorganization. Second, because science is continually evolving, a review of applications within this recent period was thought to represent current medical and regulatory practices best, and would therefore inform future advice and development programs most effectively.

Application characteristics

Applications were counted as AP or NA by the last regulatory decision made in the time period from 2006 to 2010. Applications that underwent multiple review cycles during this five-year period were counted once per indication (i.e. specific disease for which the product was evaluated, such as chronic myelogenous leukemia), and only the last decision was counted. For example, if an application was submitted and received an NA decision, and was then re-submitted and approved (two review cycles), an approval decision was assigned to this product. However, if a new product was submitted and reviewed for more than one indication (e.g. treatment for two different diseases or populations, such as sunitinib for gastrointestinal stromal tumors and advanced renal cell carcinoma [18]), during one review cycle, each indication was counted separately and, therefore, a new product could be counted more than once as long as a separate evaluation (i.e. independent assessment of the product's safety and effectiveness) was performed for each indication. This approach was thought to be reasonable, because the product developer would have had to invest additional resources for each indication.

We also evaluated the following variables:

- Company size (determined from publically available sources) was defined as small (<250 employees), medium (250–14,999 employees) and large (≥15,000 employees). These cut-off points were selected by grouping companies into tertiles by number of employees. The small company cut-off of <250 employees is also similar to that used in a previous analysis [19]. If a smaller company became part of a larger company before the marketing application submission the company was categorized as large because larger company resources probably would have contributed to the product's clinical development.
- Rare disease prevalence in the USA was assessed using all available data including the product's orphan designation application to FDA, National Institutes of Health databases and other sources (e.g. literature, Centers for Disease Control and Prevention estimates). Because prevalence estimates can be limited by incomplete information, our figures are estimates based on best available data [1]. Whenever possible, the disease's estimated prevalence assessed at the time when clinical development began was used, because this would have affected product development considerations [20].
- Prior regulatory experience was defined as the company developing the product having had at least one FDA-approved product in its portfolio before submission of the new product application.
- Disease-specific regulatory experience was defined as there being at least one FDA-approved product commercially available in the USA for the disease, even if clinical endpoints and trial design from prior approvals differed from those in the new application.
- Regulatory communication was defined as an end-of-Phase II (EOP2) meeting between FDA and the product developer having occurred during pre-marketing clinical development. EOP2 meetings are generally held to discuss the planning of the Phase III investigations and protocols [21]. EOP2 meeting correlation with a first-review-cycle approval was also assessed because products undergoing multiple review cycles would probably have had additional opportunities for interactions between the product developer and FDA, and the effect of an EOP2 meeting on the clinical development program after the first-review cycle would be expected to diminish.

Statistical analysis

This was a descriptive, retrospective study primarily designed to identify factors correlating to rare disease product approvals and did not include a prespecified hypothesis. Overall, and for the rare disease applications, exact odd ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated to look for associations between regulatory action (AP versus NA), the main study outcome of interest and application characteristics including: indication type (rare versus common disease), application type (biologic versus NME), review type (priority versus standard), company size (small, medium and large, included as a continuous explanatory variable where small = 1, medium = 2 and large = 3), company prior regulatory experience (Y/N), disease-specific regulatory experience (Y/N), first-review-cycle approval (Y/N) and EOP2 meeting (Y/N). All characteristics with a univariate OR with a P value <0.2 were included in a multivariable logistic regression model of all study data to estimate adjusted ORs (aORs) and respective 95% CIs. Among the rare disease applications, approval rates were assessed by disease prevalence categories of 0–25, 25–50, 50–75, 75–100, 100–125, 125–150 and 150–175 (in thousands) of persons in the USA with the disorder. All analyses were performed using SAS® version 9.1 (SAS®, NC, USA; http://www.sas.com/) without adjustments for multiplicity. All reported P values are two-sided.

Overall findings

Between 1 January 2006 and 31 December 2010 there were 177 new product NDA and BLA submissions to CDER; 128 for common (72%) and 49 for rare (28%) disease indications. Of these 177 applications, four received an RTF decision (one was for a rare disease) and 11 were withdrawn during the review cycle by the applicant (including one rare disease application). The remaining 162 submissions underwent full regulatory review leading to an action; 118 AP (73%) and 44 NA (27%) actions. Among the 162 submissions for which a full FDA review was completed, 47 (29%) were for rare disease indications, of which 33 were NMEs and 14 were biologics. For common disease indication applications (n = 115; 71%), 103 were NMEs and 12 were biologics.

Regulatory characteristics

The overall analysis found no significant association between approval rates and indication type for rare (77%) versus common (71%) diseases [OR = 1.3; 95% CI (0.6; 3.2)]. Additional analyses by application characteristics among all 162 applications are summarized in Table 1.

There was an association between approval rates and product type, with 25 out of 26 (96%) biologics receiving approval decisions compared with 93 out of 136 (68%) NMEs [aOR = 6.8; 95% CI (0.9; 54.6)]. Review type was also associated with a higher probability of approval, with 87% of priority reviews receiving approval decisions versus 65% of standard reviews [aOR = 2.7; 95% CI (1.1; 6.9)].

Company size was associated with approval rate overall. Small companies had the lowest approval rate (50%) compared with the large (79%) and medium-sized (81%) companies. Additional

TABLE 1

Characteristics of new molecular entities and new biological product applications

Characteristic	Approval no. (%)	Non-approval no. (%)	OR (95% CI)[a]	aOR (95% CI)[b]
All applications n = 162				
Indication				
Rare disease	36 (77)	11 (23)	1.3 (0.6; 3.2)	NI
Common disease	82 (71)	33 (29)		
Application type				
Biologic	25 (96)	1 (4)	11.6 (1.8; 485.4)	6.8 (0.9; 54.6)
NME	93 (68)	43 (32)		
Review type				
Priority	48 (87)	7 (13)	3.7 (1.4; 10.4)	2.7 (1.1; 6.9)
Standard	70 (65)	37 (35)		
Company size[c]				
Large	45 (79)	12 (21)	2.0 (1.2; 3.2)	1.2 (0.6; 2.7)
Medium	54 (81)	13 (19)		
Small	19 (50)	19 (50)		
Prior regulatory experience				
Yes	101 (81)	24 (19)	5.0 (2.1; 11.7)	3.1 (1.0; 9.6)
No	17 (46)	20 (54)		
EOP2 meeting				
Yes	102 (76)	33 (24)	2.1 (0.8; 5.4)	1.8 (0.7; 4.7)
No	16 (59)	11 (41)		
Prior disease experience				
Yes	106 (73)	39 (27)	1.1 (0.3; 3.7)	NI
No	12 (71)	5 (29)		

Abbreviations: NME, new molecular entity; EOP2, end-of-Phase II; aOR, adjusted odds ratio.

[a] Exact test.

[b] NI = variable not included in multivariable logistic regression model (univariate P value <0.2).

[c] Defined per number of employees (large ≥15,000; medium 250–14,999; small <250), variable modeled as a continuous predictor in the models, where small = 1, medium = 2 and large = 3.

analyses of characteristics by company size showed some notable trends (Table 2).

- When compared with small companies, large and medium-sized companies were more likely to have prior regulatory experience (large 100% and medium 87% versus small 26%). Large companies were more likely than medium-sized and small companies to submit applications for which there was prior disease experience (large 96%, medium 87% and small 84%), and were more likely to have submitted applications that received priority review (large 43%, medium 31% and small 26%).
- Small and medium-sized companies were more likely than large companies to submit rare disease indication applications (small 34% and medium 36% versus large 18%). Medium-sized companies were more likely to have submitted biologics applications than large or small companies (large 9%, medium 25% and small 11%).

The overall proportion of submissions from applicants with prior regulatory experience was 77% ($n = 125$), which was associated with a greater probability of approval (81%) compared with submissions from companies without prior regulatory experience (46%) [aOR = 3.1; 95% CI (1.0; 6.9)]. This association was probably confounded by company size, which was strongly associated with prior regulatory experience. The occurrence of an EOP2 meeting during clinical development ($n = 135$ applications; 83%) was positively associated with approval [aOR = 1.8; 95% CI (0.7; 4.7)]. We also noted that, for the four applications that were not filed by CDER, three (75%) were not discussed at an EOP2 meeting. Prior disease experience, a characteristic for the majority of reviewed applications ($n = 145$; 90%), was not associated with approval rate [OR = 1.1; 95% CI (0.3; 3.7)].

TABLE 2

Application characteristics by company size

Characteristic	No. (%) Company size		
	Large ($n = 57$)	Medium ($n = 67$)	Small ($n = 38$)
Indication			
Rare	10 (18)	24 (36)	13 (34)
Common	47 (82)	43 (64)	25 (66)
Type of application			
NME	52 (91)	50 (75)	34 (89)
Biologic	5 (9)	17 (25)	4 (11)
Prior disease experience			
Yes	55 (96)	58 (87)	32 (84)
No	2 (4)	9 (13)	6 (16)
EOP2 meeting			
Yes	48 (84)	57 (85)	30 (79)
No	9 (16)	10 (15)	8 (21)
Review type			
Priority	24 (43)	21 (31)	10 (26)
Standard	33 (57)	46 (69)	28 (74)
Prior regulatory experience			
Yes	57 (100)	58 (87)	10 (26)
No	0 (0)	9 (13)	28 (74)

Abbreviations: NME, new molecular entity; EOP2, end-of-Phase II.
Company size defined per number of employees (large ≥15,000; medium 250–14,999; small <250).

Rare disease applications

Assessment of the 47 rare disease indications submissions that underwent a full review found that product type, review type, company size and prior regulatory experience were associated with approval rates (Table 3). Notably, BLA applications had higher approval rates (100%) than those for NMEs (67%). By review type, 88% of priority reviews received approval decisions versus 53% of standard reviews [OR = 6.1; 95% CI (1.2; 34.9)].

Owing to the small numbers of rare disease applications, we collapsed the medium-sized and large companies into one group for comparison against the small companies. The proportion of approvals among the large and/or medium-sized companies was 88% compared with 46% among the small companies [OR = 8.8; 95% CI (1.5; 52.4)]. The approval rate among submissions for which the applicant already had a marketed product was 89% (32 out of 36) compared with 36% of submissions from applicants without prior regulatory experience [OR = 14.0; 95% CI (2.2; 94.5)]. There was a trend, although not statistically significant, toward a higher approval rate among applications that were discussed at an EOP2 meeting (i.e. 83% approval versus 58% approval among those not discussed). Multivariable logistical regression models were not performed in this subset of applications. No association was found between prior disease experience and approval rates among the rare disease applications.

An analysis of approval rates using the disease prevalence categories of 0–25, 25–50, 50–75, 75–100, 100–125, 125–150 and 150–175 (in thousands) of persons in the USA with the disorder found a strong trend toward higher approval rates for the lower prevalence categories (50,000 patients or fewer; Fig. 1).

First-review-cycle approvals

Review type was most strongly associated with a first-review-cycle AP; priority reviews ($n = 55$) had a first-review-cycle approval rate

TABLE 3

Characteristics of rare disease applications ($n = 47$)

Characteristic	No. (%)		
	Approval	Non-approval	OR (95% CI)[a]
Application type			
Biologic	14 (100)	0 (0)	Cannot be estimated
NME	22 (67)	11 (33)	
Review type			
Priority	28 (88)	4 (12)	6.1 (1.2; 34.9)
Standard	8 (53)	7 (47)	
Company size[b]			
Large/medium	30 (88)	4 (12)	8.8 (1.5; 52.4)
Small	6 (46)	7 (54)	
Prior regulatory experience			
Yes	32 (89)	4 (11)	14.0 (2.2; 94.5)
No	4 (36)	7 (64)	
EOP2 meeting			
Yes	29 (83)	6 (17)	3.5 (0.6; 18.2)
No	7 (58)	5 (42)	
Prior disease experience			
Yes	27 (75)	9 (25)	0.7 (0.1; 4.2)
No	9 (82)	2 (18)	

Abbreviations: NME, new molecular entity; EOP2, end-of-Phase II.
[a] Exact test.
[b] Defined per number of employees (large ≥15,000; medium 250–14,999; small <250).

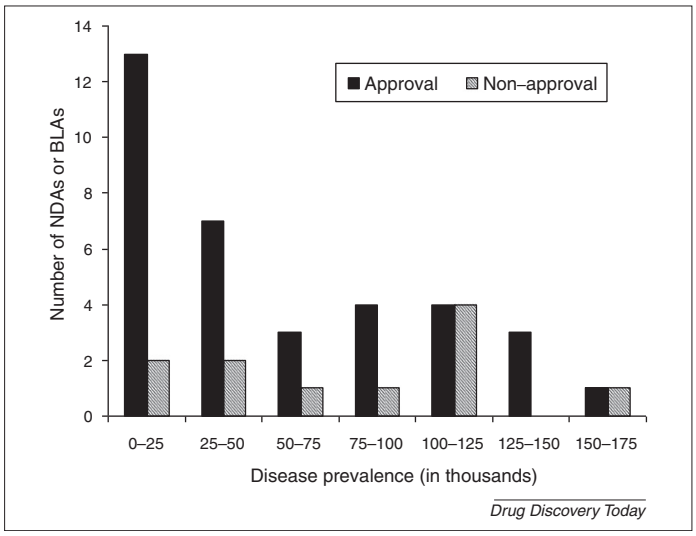

FIGURE 1

Marketing applications for rare disease indications presented as numbers of approvals and non-approvals by disease prevalence (in thousands) of persons in the USA with the disorder. Numbers of rare disease product approvals are represented by solid black bars. Numbers of rare disease non-approvals are represented by hatched black bars. Overall there were a total of 47 applications: 36 approvals and 11 non-approvals, with the largest numbers of approvals in the lowest prevalence categories (0–25,000 and 25,000–50,000) from 2006 to 2010.

of 78% versus 37% for standard reviews (n = 107) [OR = 6.0; 95% CI (2.7; 12.7)] (Table 4). This association was also shown for rare and common disease indications when evaluated separately. We also found a trend favoring higher first-review-cycle AP rates for applications for which an EOP2 meeting was held for common and rare disease applications, although the result was not significant. Prior regulatory and disease experience were not associated with first-review-cycle approval rates.

Discussion

The primary goals of this study were to identify characteristics associated with marketing approvals and to identify how resources or other interventions could be targeted to support rare disease product development. Similar studies have been performed that assessed subsets of orphan product applications in the USA and European Union (EU), or where Orphan products were assessed by therapeutic area, such as oncology or neurology [4,9,10,19,22–25]. Our study differs from these previous studies in that it included all CDER-approved and -non-approved marketing applications for NMEs and new biologics in all therapeutic areas from 2006 to 2010, and compared the approval rates of applications for rare disease indications to those for common diseases.

TABLE 4

First-review cycle approval rate by review type and EOP2 meeting status

	Priority	Standard	OR (95% CI)[a]
Review type			
All applications	43/55 (78)	40/107 (37)	6.0 (2.7; 12.7)
Common disease	18/23 (78)	35/92 (38)	5.9 (1.9; 21.7)
Rare disease	25/32 (78)	5/15 (33)	7.1 (1.5; 35.1)
	Yes	**No**	**OR (95% CI)[a]**
EOP2 meeting held			
All applications	71/135 (53)	12/27 (44)	1.4 (0.6; 3.5)
Common disease	48/100 (48)	5/15 (33)	1.8 (0.5; 7.4)
Rare disease	23/35 (66)	7/12 (58)	1.4 (0.3; 6.3)

Abbreviation: EOP2, end-of-Phase II.
[a] Exact test.

NMEs and new biologics for rare diseases comprise ~30% of all marketing applications reviewed and approved by CDER during the study period. Notably, more than half of the 26 new biologics applications submitted to CDER were for rare disease indications. We found that approval rates for marketing applications for rare and common disease indications were similar. Rare disease prevalence was not associated with approval rate, and there was a trend toward more applications submitted – and more approvals – for treatments intended for the lowest prevalence rare diseases (50,000 persons or fewer in the USA). Exploration of additional factors correlating with approval rates for lower versus higher prevalence rare diseases was not performed in our analysis. Because most rare disorders are genetic disorders with low prevalence in the population, the finding of more applications and approvals for lower prevalence disorders could merely reflect this fact [26]. However, whether or not there are other factors leading to more approvals in lower prevalence rare diseases, such as a better understanding of the underlying disease defect and pathophysiology (e.g. because of single gene mutations), or some other factors, warrants further exploration.

High approval rates overall (87%) and for first-review-cycle approvals (88%) were associated with priority review application designations. Products are eligible for priority review if they are considered to address unmet needs – that is, provide a 'significant improvement compared to marketed products in the treatment, diagnosis or prevention of a disease' and priority designation is intended to direct overall attention and resources to the evaluation of applications for products with this potential [27,28]. The finding of high approval rates for priority review applications is consistent with the priority designation program goals. We additionally note, not surprisingly because rare disease products are largely intended to address unmet medical needs, that many rare disease applications (68%) received priority review designation.

Company size was found to be an important characteristic associated with approval rate, with applications submitted by large and medium-sized companies having higher approval rates than those submitted by small companies. This could be the result of larger companies having more drug development and regulatory experience and greater resources (i.e. financial support and experienced personnel) to devote to their development programs. Larger companies were also more likely to have prior regulatory experience (93% of large and medium-sized companies) than small companies (26%), and would, therefore, be expected to have a greater understanding of the clinical development programs necessary to meet regulatory requirements.

We found it interesting that small companies were more likely to pursue 'novel' clinical development programs – that is, they were more likely to pursue development of products for diseases without an existing approved product (16% of applications) compared with larger companies (4%). Smaller companies were also more likely to pursue rare disease indications compared with large

companies. About one-third (34%) of the reviewed rare disease applications were submitted by small companies even though applications from small companies accounted for only 23% of reviewed applications overall. Thus, novel products for rare disease indications were developed disproportionately by small and medium-sized companies, which had fewer resources available to pursue clinical development. Another notable finding was that overall, as well as by rare and common diseases applications separately, approval rates for products for which there is no prior disease experience (71%) were similar to those for products with prior experience (73%), suggesting that prior disease-specific regulatory experience did not affect approvals rates.

Our study results have important implications for those considering the development of products to address unmet medical needs. First, our results show that approval rates for rare disease marketing applications are high, and there is a strong trend toward higher numbers of approvals for rare disease products intended for the treatment of less prevalent disorders. Second, because prior disease-specific regulatory experience was not associated with approval rate, we encourage product developers to consider this finding when deciding whether to pursue product development for a novel indication. Third, there was a trend toward higher approval rates in applications that were discussed at EOP2 meetings. This suggests that communication with regulatory authorities during product development is important, and could be of particular importance for small companies lacking regulatory experience.

Findings in this analysis are largely consistent with the results of similar analyses conducted by others for orphan drug applications in the EU and the USA. Notably, larger company size and prior experience in orphan drug development was associated with marketing approval in the EU and USA [19,22,24,25]. Interestingly, however, in an analysis of regulatory scientific advice (SA) in drug development for rare and common disease products in the EU, regulatory interaction alone was not associated with approval but rather whether drug developers complied with SA given by the European regulatory authorities [25]. Additional analysis also showed that content of SA differed with company size, with larger companies asking more questions overall and notably more clinical drug development questions than smaller companies [29]. A detailed assessment of the content of meetings between FDA and drug developers has not been performed, but is likely to be informative as to specific information exchanges that occurred during these interactions and areas that could be of most benefit, and at which timepoints or milestones, during drug development. We also note that the correlation of first-review-cycle approval and EOP2 meetings in our analysis was smaller than the association between EOP2 meetings and all approvals. This finding was unexpected, the reasons for which are unknown, and will additionally require further analysis.

There is one major limitation to this study. We only evaluated applications that progressed through clinical development to marketing application submission, and did not evaluate products discontinued in earlier phases. We acknowledge that many investigational agents do not enter into or continue through clinical development for various reasons, such as efficacy and safety concerns or a lack of resources [30–32]. From the data analyzed in this study, it was not possible to assess whether rare disease product development is more adversely affected by these factors than common disease product development. The results do suggest, however, that, because approval rates for rare disease applications are high (especially for priority reviews), targeting increased efforts toward the marketing application review process is unlikely to increase substantially the number of new rare disease products becoming available to patients. We recommend instead that more attention be focused toward earlier phases of development, including basic scientific, translational, preclinical and early clinical phase biomedical research and regulatory scientific development. We additionally recommend that increased resources be directed toward identifying the specific factors impeding rare disease product development in these earlier phases. The identification of these factors is beyond the scope of this analysis and will be an area for future study.

Concluding remarks

Rare disease products represented a significant proportion of NME and new biologic product applications submitted to and approved by CDER from 2006 to 2010; and, importantly, clinical development programs capable of supporting marketing approvals for rare disease products are feasible. A particularly noteworthy finding for rare disease applications was that prevalence was not associated with approval rates overall; however, there was a strong trend toward higher numbers of approvals for products to treat lower prevalence disorders ($\leq$50,000 patients). Small and medium-sized companies are developing most of the novel products intended for unmet medical needs, and for a substantial percentage of rare disease products. However, applications submitted by small companies have lower approval rates than those submitted by larger companies, and this might represent an area where additional attention could be directed. Because prior regulatory experience was associated with higher marketing application approval rates, it is probable that small companies and companies developing products for rare diseases and unmet needs would benefit from more interaction with regulatory agencies.

Despite the success of the ODA, substantial unmet needs for the rare disease community remain [4]. Only ~250 rare diseases have approved treatments and, even when considering the additional ~400 products in development [33], not all of which will result in marketing approvals, the overwhelming majority of rare diseases lack products available or under investigation. The clinical development of products capable of supporting marketing approvals requires the development of comprehensive scientific evidence of product quality, effectiveness and safety, and a favorable benefit:risk assessment for the treatment of the disease. This evidence will be subject to careful assessment by regulatory authorities, and is the most important determinant of approval for individual product applications. Given the continuing medical needs for most rare diseases, additional work to identify the specific factors impeding rare disease product development, and the targeting of resources toward biomedical and regulatory science, particularly for earlier phases in product development, are strongly recommended.

Conflict of interest

All authors declare no conflict of interest relevant to the subject matter discussed in the manuscript.

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References

1 Field, M.J. and Boat, T.F., eds) (2010) *Rare Diseases and Orphan Products: Accelerating Research and Development*, The National Academies Press
2 Haffner, M.E. *et al*. (2002) Two decades of orphan product development. *Nat. Rev. Drug Discov.* 1, 821–825
3 Griggs, R.C. *et al*. (2009) For the rare diseases clinical research network. Clinical research for rare disease: opportunities, challenges, and solutions. *Mol. Genet. Metab.* 96, 20–26
4 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
5 Orphan Drug Act, Pub. L. 97-414. 96 Stat. 2049 (1983). Amended in 1984 by Pub. L. 98-551 to add a numeric prevalence threshold to the definition of rare diseases
6 US Food and Drug Administration, (2011) *Code of Federal Regulations Title 21: Approval of an Application and an Abbreviated Application. Pt314.105*. US Government Printing Office
7 US Food and Drug Administration (2011). Search orphan drug designation and approvals. (Accessed, 25 April, 2012, at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm)
8 Haffner, M.E. (2006) Adopting orphan drugs – two dozen years of treating rare diseases. *N. Engl. J. Med.* 354, 445–447
9 Kesselheim, A.S. *et al*. (2011) Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. *JAMA* 305, 2320–2326
10 Mitsumoto, J. *et al*. (2009) Pivotal studies of orphan drugs approved for neurological diseases. *Ann. Neurol.* 66, 184–190
11 Sasinowski, F.J. (2011) Quantum of Effectiveness in FDA's Approval of Orphan Drugs. Cataloguing FDA's Flexibility in Regulating Therapies for Persons with Rare Disorders. (Accessed, 25 April, 2012, at: http://www.rarediseases.org/docs/policy/NORDstudyofFDAapprovaloforphandrugs.pdf)
12 US Food and Drug Administration, (1998) *Guidance for Industry. Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.
13 Institute of Medicine Committee on Accelerating Rare Diseases Research and Orphan Product Development, Board on Health Sciences Policy, (2010) Regulatory framework for drugs for rare diseases. In *Rare Diseases and Orphan Products: Accelerating Research and Development,* (Field, M.J. and Boat, T.F., eds), pp. 73–110, The National Academies Press
14 Federal Food, Drug, and Cosmetic Act (FD&C Act), Section 505(b) [21 USC §355]. New Drugs. As amended through December 31, 2004
15 US Food and Drug Administration. News and Events, July 9, 2008. (Accessed, 25 April, 2012, at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116920.htm)
16 US Food and Drug Administration. Complete Response Letter Final Rule, July 9, 2008. (Accessed, 25 April, 2012, at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084138.htm)
17 US Food and Drug Administration, (2011) *Code of Federal Regulations Title 21: Filing an Application and Receiving an Abbreviated New Drug Application. Pt314.101*. US Government Printing Office
18 Dagher, R. and Justice, R. (2006) Summary review of NDA, 21938 gastrointestinal stromal tumors (GIST), 21968 renal cell cancer (RCC). Search US Food and Drug Administration Drugs@FDA. (Accessed, 25 April, 2012, at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm ['sunitinib'])
19 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
20 US Food and Drug Administration. Search internal orphan drug designation and approvals (not publically accessible). (Accessed January through July, 2011)
21 US Food and Drug Administration, (2011) *Code of Federal Regulations Title 21: Meetings. Pt 312.47*. US Government Printing Office
22 Heemstra, H.E. *et al*. (2008) Predictors of orphan drug approval in the European Union. *Eur. J. Clin. Pharmacol.* 64, 545–552
23 Talele, S.S. *et al*. (2010) Therapies for inborn errors of metabolism: what has the Orphan Drug Act delivered? *Pediatrics* 126, 101–106
24 Putzeist, M. *et al*. (2012) Determinants for successful marketing authorization of orphan medicinal products in the ER. *Drug Discov. Today* 17, 352–358
25 Regnstrom, J. *et al*. (2010) Factors associated with success of market authorization applications for pharmaceutical drugs submitted to the European Medicines Agency. *Eur. J. Clin. Pharmacol.* 66, 39–48
26 Melnikova, I. (2012) Rare diseases and orphan drugs. *Nat. Rev. Drug Discov.* 11, 267–268
27 US Food and Drug Administration (1992). Prescription Drug User Fee Act (PDUFA). Standard Review and Priority Review. (Accessed, 25 April, 2012, at: http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm)
28 FDA, CDER Manual of Policies and Procedures (MAPP) 6020.3, Priority Review, July 16, 2007. (Accessed, 25 April, 2012, at: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082000.pdf)
29 Putzeist, M. *et al*. (2011) Regulatory scientific advice in drug development: does company size make a difference? *Eur. J. Clin. Pharmacol.* 67, 157–164
30 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
31 Stolk, P. *et al*. (2006) ''Rare essentials'': drugs for rare diseases as essential medicines. *Bull. World Health Organ.* 84, 745–751
32 Dickson, P.I. *et al*. (2010) Research challenges in central nervous system manifestations of inborn errors of metabolism. *Mol. Genet. Metab.* 102, 326–338
33 Castellani, J.J. (2011) Report. Orphan Drugs in Development for Rare Diseases. More than 400 Medicines in Development to Treat or Prevent Rare Diseases. (Accessed, 25 April, 2012, at: http://www.phrma.org/sites/default/files/878/rarediseases2011.pdf)