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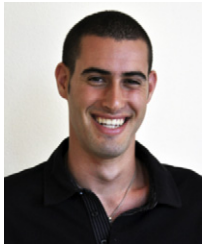
editorial

The routes to orphan drug designation – our recent experience at the FDA



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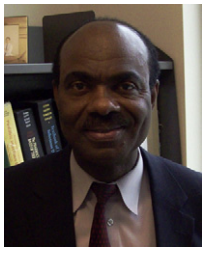

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The Orphan Drug Act (ODA) of 1983 provides incentives to advance the development of compounds that hold hope for the treatment of rare diseases [1]. Consequently, the United States (US) Food and Drug Administration (FDA)'s regulations for implementing the ODA contain two criteria which every promising compound must meet to be 'designated' as an 'orphan drug'. First, that the sponsor must demonstrate that there is a clear scientific rationale for believing that the drug has promise for treating the rare disease or condition targeted for study. Second, that the disease or condition of interest affects fewer than 200,000 persons living in the US. FDA's regulations further elaborate on the basic requirements for meeting this first criterion of scientific rationale [2]. Based on these regulations, compounds designated in 2009 were examined and categorized according to the method used for designation. The year investigated was chosen for evaluation based on data completeness and recency at the time of gathering and examining data for this editorial. From the inception of ODA to about the time of writing this paper, the 2433 products that have been orphan-designated represent a heterogeneous collection of compounds ranging from those in the very early stages of their development process to those much further along. Acceptable scientific evidence of a compound's promise for treating a rare disease or condition includes data from clinical trials (including those from the literature), animal studies or – where no animal model exists for the rare disease – *in vitro* data (together with proposed mechanism of action of the product and

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pathogenesis of the disease). Of note, proposed orphan drugs need not have active investigational new drug (IND) status at the time of orphan designation.

Owing to its compelling incentives, which include marketing exclusivity and tax credits, the ODA has been very successful, resulting in 379 FDA-approved marketed orphan drugs drawn from the pool of 2433 designated products. Indeed, according to the FDA-wide database, orphan drugs represented 31% and 37% of all FDA approved New Molecular Entity (NME) and New (first) biologic approvals (NBA) in 2008 and 2009, respectively. About 25–30 million in the US are living with rare diseases [3,4] and an estimated 7000 such diseases have been discovered thus far [4]. As biomedical sciences continue to advance in the direction of personalized therapies, and with the prospect of applying novel therapeutic approaches and gains to rare diseases, the future looks hopeful for continued expansion of the orphan drug endeavor for rare disease patients.

The scientific rationale upon which promising compounds have been designated as orphan drugs has not previously been quantitatively described. This report uses summary statistics of proprietary FDA-held data to describe the basis upon which designated products fulfilled the scientific rationale criterion. These data, we believe, provide information that may be useful to sponsors of future orphan drugs.

The applications and FDA reviews of all 160 orphan designations granted in calendar year 2009 were examined. The means by which the scientific rationale criterion was satisfied were hierarchically classified into clinical experience, animal studies, or *in vitro* studies. There were non-overlapping categories based on the most advanced evidence submitted in the application. Clinical experience included all human testing; for these products, data were collected on sponsor-reported trial phase, the number of trial enrollees, and whether there was an active IND at the time of the request for orphan designation. Moreover, applications reporting clinical experience included a subset with no trial phase information. However, these applications contained clinical experience reports that served as evidence of product potential efficacy. For designation requests that included animal model studies as the most advanced level of evidence, we further subclassified studies as primate, large mammal, or rodent studies. Additionally, all products were categorized by broad therapeutic indications and by product class (small molecule drugs and biological products).

Of the160 orphan designations granted in 2009, 115 (72%) were small molecule drugs and 45 (28%) were biological products. Oncologic therapies were the most represented (67, 42%), followed by products designated for rare inborn errors of metabolism (14, 9%), neurological diseases (13, 8%) and infectious diseases (12, 8%). The remainder (54, 34%) comprised a heterogeneous collection of other disease indications.

Table 1 shows that the scientific rationale for designation was most frequently clinical experience (106, 66%) followed by animal models (51, 32%) and finally *in vitro* studies (3, 2%). There were 87 designations based on clinical experience for which sponsors reported a phase of study. Most were reported to be in phase II (47, 44%), followed by phase III (21, 20%) and the remaining designations were in phases I (19, 18%). For their designations, some applications (19, 18%) used the clinical experience option for which no study phase was reported. Among the 51 designations granted based on animal studies, rodent studies were overwhelmingly the most commonly submitted evidence (38, 76%).

TABLE 1

Scientific rationale presented by sponsors for orphan product designations in 2009

Scientific rationale	Number of designations (%)
Clinical experience	
Phase I	19 (17.92%)
Phase II	47 (44.34%)
Phase III	21 (19.81%)
Phase of study not reported or specified	19 (17.60%)
Total	106 (66.25%)
Animal study	
Primate	6 (12.24%)
Large mammal	7 (14.29%)
Rodent	38 (74.51%)
Total	51 (31.88%)
***In vitro* study**	
Total	3 (1.88%)
Total designations	160

Of the 106 designations granted based on clinical evidence, the number of study participants was not stated for three designations. The three were excluded from Fig. 1. The median number of enrollees was 46 study subjects. At the time of orphan status designation, 56 of the 106 (53%) had an active IND.

The review shows that, despite the animal model option for demonstrating scientific evidence in support of orphan designation, sponsors often apply only after gathering data from clinical experience. For some sponsors, there may be marketplace advantages to avoiding an early self-revealing public disclosure that results from an early orphan drug designation. For other sponsors, however, there may be greater advantages to receiving orphan designation earlier in the process of product development. This, of course, only applies to companies (or other entities) that pay tax in the US. For others, the ability to recoup clinical trial costs through ODA-stipulated tax credits cannot be maximized if a designation request is filed after the initiation of clinical trials. Less tangibly, the interest generated by orphan drug status may lead to new sources of investment capital for small biotechnology companies struggling to advance their products. Finally, the facilitative services of FDA's Office of Orphan Products Development are most easily secured when therapeutics are formally designated as orphan drugs.

Given the number of years that ODA has been in place, this study could be viewed as a 'snapshot' review. As indicated above, we chose 2009 due to data completeness and recency. By our experience, what is being reported is probably comparable to the year immediately prior to, and the period since, 2009.

This editorial provides the first quantitative description of the scientific rationale proffered by sponsors granted FDA orphan

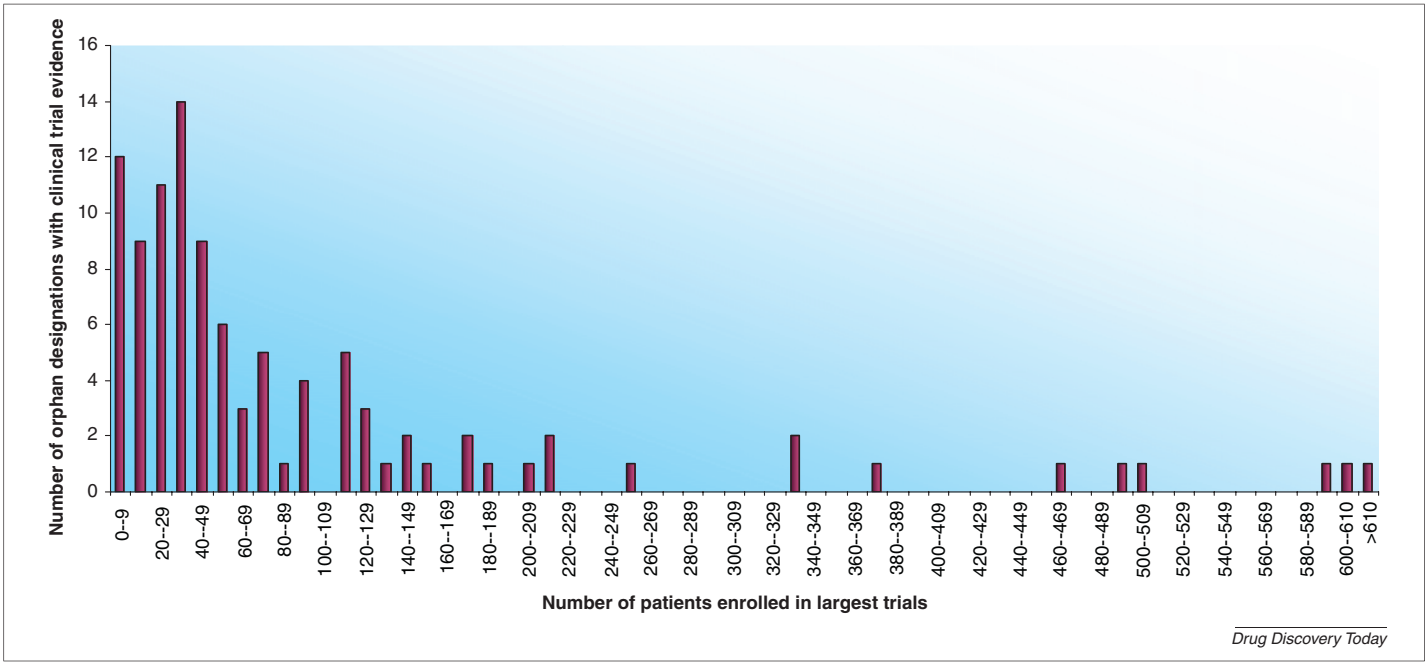

FIGURE 1

Orphan product designations based on clinical experience – 2009. This figure presents the frequency distribution of orphan designations by the number of patients enrolled in sponsors' largest trails upon which the designations were based. In 2009, there were 106 orphan product designations that were granted based on clinical experience of using the product in patients. The number of study participants was not reported in three designations, which were not included in this figure. Bars represent the number of orphan product designations.

status designation. The data indicate that most designations granted in the year evaluated were based on clinical experience. In addition, despite the option of submitting an orphan drug designation application early in development, a large proportion of drug sponsors elected to request orphan status later in the product development process. We do acknowledge that sponsors may have different business-related reasons for picking the specific time to apply for orphan designation when they do so. That notwithstanding, we believe that it is probably still worthwhile to make sponsors generally aware that a greater benefit may be derived from the ODA-stipulated tax-credit incentive for sponsors who submit their requests for designation in the earlier rather than the later steps of the drug development process.

Acknowledgments

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2 21 CFR Part 316: Orphan Drug Regulations; Proposed Rule, 56 Federal Register 19 (29 January 1991), p. 3340
3 Braun Miles, 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
4 National Institutes of Health, Office of Rare Disease Research. Rare Disease Information (http://www.rarediseases.info.nih.gov/Default.aspx)

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