A Clinical Pharmacology-Regulatory Perspective on the Approval of Drugs for Rare Diseases

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Orphan drugs or drugs for rare diseases represents a particular regulatory conundrum. There is a desperate need for effective therapies for these patients, who have been historically underserved by the drug development community. However, there is also a need to make sure these therapies are both safe and effective. In response, the US Food and Drug Administration (FDA) has evolved new approaches to facilitate drug development in this area.

Since the implementation of the Orphan Drug Act of 1983 (ODA), a total of 522 drugs with an orphan designation have been approved. This represents approximately one-third of all new molecular entity approvals over the last 5 years and two-thirds of all therapeutic biological product approvals. Even so, there are over 7,000 indications that qualify for the orphan designation and since 1983 over 3,500 drugs have been given a designation by the FDA’s Office of Orphan Products Development (OOPD); thus, the rate of approvals is still running far behind the orphan designations (Figure 1).

While the ratio of approvals to designations is seemingly bleak, this has to be viewed in context for the standard rate of attrition for drugs entering clinical development, which, if one looks at only those compounds that transition from preclinical to phase I trials, is on the order of 1–2%. Thus, in that context, the development of drugs for orphan diseases is not doing “too bad”. However, the focus of the symposia was “Don’t Do Different Things... Do Things Differently!” In order to do things differently we must first have a context for some of the unique aspects that working in this area of the drug development space entails. From a Clinical Pharmacology perspective, we can identify a number of areas/issues that hamper drug development:

- A large heterogeneity in disease pathophysiology and treatment effects.
- Poorly understood natural histories and progression.
- Few patients are available for conducting clinical trials.
- Paucity of appropriate endpoints that predict outcomes.

These issues should not come as a surprise to anyone who works in drug development, but that they are an area of concern for the FDA as well may be a surprise to some, as the FDA is often seen as a hindrance to development. In a review of the Orphan Drug Approvals from 1983 to June 30, 2010, a report by the National Organization of Rare Diseases (NORD) found that in two-thirds of the noncancer drug orphan approvals (90 of 135) the FDA exercised either “administrative” or “case by case” flexibility. The report goes on to describe the criteria used for each of these decisions. This acknowledgment of the FDA’s willingness to use data and innovative analysis should lay to rest the image of an agency that is indifferent to the suffering of patients with rare diseases. Administrative flexibility, as defined in the paper, is related to the use of a single clinical trial for evidence of effectiveness, the use of a single trial in conjunction with “confirmatory evidence” (often Clinical Pharmacology studies or in vitro mechanistic studies), and the use of Accelerated Approval under Subpart H (21 C.F.R. Part 314). Case-by-case flexibility is by definition amorphous, but examination of the supporting table shows that the FDA is willing to consider issues related to patient factors and the severity in making approval decisions. In practice, while the authors have broken these out into separate categories, most of these approvals used a combination of both administrative and case-by-case considerations.

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In addition to showing flexibility in review, the FDA has also been proactive in providing insight and guidance to the drug development community. The FDA has issued a guidance entitled “Rare Diseases: Common Issues in Drug Development” that addresses many of the issues raised above with regard to topics such as “Natural History Studies,” “Disease Pathophysiology,” “Efficacy Endpoints,” and “Chemistry and Manufacturing Controls.” While a general guidance, FDA experience has shown that these are common areas of where orphan drug development often stalls and where additional guidance would be beneficial.

Another source of valuable information is to be found from reviewing the approval packages of other drugs. The FDA makes available at Drugs@FDA the approval packages of drugs shortly after their approval. At this website one can examine final review documents (expunged for trade secret and individually identifiable patient information). In doing so one can see the emphasis put on biomarkers and on the types of studies needed. With regard to the types of studies needed, the FDA has also published articles looking at the content of orphan drug applications. In a review of the Clinical Pharmacology sections from the 33 approved New Drug Applications (NDAs) and Biologic License Applications (BLAs) from 2006–2010 for orphan drugs, there were a total of 254 studies involving 13,468 subjects, or an average of seven studies per NDA/BLA. Of these subjects, 75% were healthy volunteers for an average of 105 patients per NDA/BLA who were evaluated in the Clinical Pharmacology programs. By sharing both the reviews and break down of the contents of these reviews, the FDA has been working to share with the industry, patient advocacy groups, and investigators real and demonstrated examples of successful development programs. These serve a very important role going forward as exemplars, as the bulk of the published literature and seminars on general drug development are focused on large-scale drug development and large multicenter trials with numbers of patients that often exceed the worldwide prevalence of a rare disease.

Beyond the writing of reports and the issuing of guidelines, the FDA is also involved in direct stakeholder engagement through a variety of mechanisms. While the most visible of these outreaches is at “widely attended meetings,” such as the ASCPT Annual Meeting, the FDA also facilitates communication through the National Institutes of Health (NIH) Therapeutics for Rare and Neglected Diseases (TRND) program and the FDA’s Centers of Excellence in Regulatory Science and Innovation (CERSI).

The TRND program is located in the NIH National Center for Advancing Translational Sciences. This program supports preclinical development of therapeutics candidates intended to treat rare or neglected disorders, with the goal of enabling an Investigational New Drug (IND) application. The FDA meets with the TRND staff to provide input and insight into the regulatory needs for a successful application through nonbinding discussion and input into development plans. One of the goals of the program is to help shepherd the drug candidate through preclinical testing such that it becomes a viable candidate for the pharmaceutical industry to take over and move into phase I testing. In doing so, some of the risk related to regulatory uncertainty can be removed from the development process.

While not focused directly on the development of drugs for rare or neglected diseases, the FDA Centers of Regulatory Excellence represent an outreach to academia. Currently there are four such centers at the University of Maryland, Georgetown University, UCSF-Stanford, and Johns Hopkins University. Through the CERSIs, the FDA offers its scientific staff a range of opportunities, including research collaborations and access to state-of-the-art science courses. These opportunities enable the FDA staff to remain engaged with the academic and medical practice community. The programs enhance the ability of the FDA staff through outreach and training, while also paying back benefits to the host universities by providing a venue to directly interact with FDA staff to obtain an insight to the regulatory process.

**CONCLUSION**

In 2010 the Institute of Medicine (IOM) released a report entitled “Rare Diseases and Orphan Products: Accelerating Research and Development.” This report was the result of a year-long evaluation of both drug development practices and legislative needs to accelerate the changes needed to improve the pace of drug development in the orphan drug / rare disease workspace. The report calls for an integrated national strategy to promote rare diseases research and product development and identifies seven key elements, a number of which directly relate to the FDA and to the science of Clinical Pharmacology. Specifically, it calls for both enhanced communication between all parties in drug development and the development of new analytic tools focused on the analysis of small populations.

In the intervening 6 years that have transpired since the publishing of this report, progress has been seen in addressing each of these seven elements. In the spirit of the workshop, the IOM report and the response to it has been a motivator to “do things...
differently” from all sides of the drug development spectrum. Because, truthfully, the development of drugs for rare and neglected disease is a group effort. It involves the patient advocates, researchers, clinicians, academia, legislators, and regulators to work together. This is often thought to be a heretical statement, but for us to advance the cause of approval of drugs for rare and neglected diseases we need to work together to advance the underlying science and understanding of orphan drug development. All parties need to share this as a common vision:

“Our situation is not comparable to anything in the past. It is impossible, therefore, to apply methods and measures which at an earlier age might have been sufficient. We must revolutionize our thinking...”^10 Albert Einstein.

Although in this context Einstein was referring to the issues of global war and peace, in a similar manner we must revitalize our thinking as well if we are to pursue safe and effective medications for these underserved populations. We must “do things differently.”

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