The Science of Hope: The need, the challenges, and three proven strategies for successful orphan drug development

ABSTRACT

Despite the inherently small market for orphan drugs, orphan drug development has recently undergone significant growth, with global sales of over $100 billion in 2015. In 2015, more than 20 new drugs were approved by the U.S. Food and Drug Administration (FDA) and 18 new drugs were approved by the European Medicines Agency (EMA) for orphan indications. In addition to the incentives provided by the U.S. Orphan Drug Act of 1983 and similar legislation in the European Union (EU), there are several financial and competitive advantages of orphan drug development. However, there are also significant challenges in the orphan drug space, including obstacles to study execution, regulatory hurdles, and a changing reimbursement environment. With proper strategic planning, sponsors seeking orphan drug designation and approval can more skillfully navigate these clinical, regulatory, and financial challenges. This article provides an overview of the incentives, advantages, and challenges of developing therapies for rare diseases and offers three proven strategies that sponsors can employ to address obstacles on the pathway of orphan drug development.
Introduction

Enacted in 1983, the U.S. Orphan Drug Act was designed to facilitate the development and commercialization of drugs to treat rare diseases. Similar legislation in the European Union (EU) and other countries has helped to stimulate orphan drug development around the world. Over the past 10 years, the orphan drug industry has undergone impressive growth, with global sales of over $100 billion in 2015. In 2015, the FDA approved 21 new drugs and the European Medicines Agency (EMA) approved a record 18 new drugs for orphan indications. In fact, nearly one-half of the new molecular entities (NMEs) approved by the FDA in 2015 were orphan drugs.

There are an estimated 7,000 rare diseases worldwide affecting approximately 30 million patients in the U.S. and 350 million worldwide – 50 percent of whom are children. With an estimated 5 new rare diseases identified every week, orphan drug development is becoming an increasingly important component of biopharmaceutical research and development (R&D). Approximately 95 percent of rare diseases lack a single FDA-approved treatment. According to a research report by Thomson Reuters, orphan drugs are replacing the blockbuster drugs of previous decades and have the economic potential to generate as much lifetime revenue as drugs used for more common health conditions.

In recent years, large pharmaceutical companies have begun to focus their attention on orphan drug development and, in some cases, have established business units dedicated to rare diseases. Philanthropic and venture capital investment interest in orphan drug development has increased as well, resulting in increased lobbying for support of new legislation supporting FDA reform. Although orphan drugs are developed to treat a small number of patients, these therapies can...
generate significant amounts of revenue. For example, Gleevec® (Novartis Oncology), which has multiple orphan indications, had sales of $4-6 billion in 2015. The world’s second most profitable drug, Rituxan® (Genentech), which was granted orphan status for the treatment of B-cell Non-Hodgkin’s lymphoma, had sales of $7.1 billion in 2015, with expanded use in other types of cancer, as well as rheumatoid arthritis.

In order to capitalize on the regulatory and commercial incentives of orphan drug development, sponsors must be aware of the hurdles involved in studying rare diseases. This article reviews the benefits and challenges of opting to navigate the regulatory process of developing therapies for rare indications. It also provides sponsors with guidance on proven strategies to overcome obstacles in three key areas – study planning, patient recruitment, and regulatory guidance – in order to optimize the success of orphan drug studies.

Regulatory initiatives that promote orphan drug development

The U.S. Orphan Drug Act (ODA) of 1983 was enacted to stimulate research into rare diseases with significant unmet medical need. This legislation provides incentives for sponsors to develop therapies for rare conditions for which sales are unlikely to recoup R&D costs under normal circumstances. In the U.S., a rare disease or disorder is defined as one that affects fewer than 200,000 people a year, or one that affects more than 200,000 people per year but for which the costs of drug development and marketing are not expected to be recovered. The four key incentives provided by the ODA include:

- Seven years of market exclusivity
- Protocol assistance
- Tax credits of up to 50 percent of R&D costs
- FDA fee waivers and research grants

In order to receive these benefits, a sponsor must first apply for orphan drug designation and demonstrate the medical plausibility for a compound’s expected benefit in a rare disease. Since the enactment of the ODA, more than 500 orphan drugs have been approved and more than 3,200 compounds have been granted orphan designations.

Similar legislation supporting orphan drug development was introduced in the EU in 2000, as well as in countries such as Singapore, Japan, and Australia. Although the spirit of the legislation is the same as the ODA, there are some regional differences in the definition of orphan diseases and the incentives provided. For instance, the EMA considers an orphan disease to be one with a prevalence of one in 2,000 and offers the following incentives:

- Ten years of market exclusivity
- Protocol assistance at a reduced charge
- Access to the centralized authorization procedure
- EMA fee reductions
- Additional incentives for micro-, small-, and medium-sized enterprises

Advantages of orphan drug development

Currently, there are more than 450 medicines to treat or prevent rare disease under clinical trials in the U.S. alone. Developmental drivers such as government incentives, shorter development timelines, and high rates of regulatory approval are making orphan drug development as economically viable as non-orphan drug development, even though the patient pool is smaller. The time from Phase II to market is often shorter for orphan drugs due to shorter and smaller clinical trials and FDA Fast Track designation. In one analysis, the average time from Phase II to launch was 3.9 years for orphan drugs, compared with 5.4 years.
for non-orphan drugs.\textsuperscript{16} Once a compound has been granted orphan designation, the odds for approval are high (82 percent) compared to traditional drugs (35 percent).\textsuperscript{17} Of note, orphan designation for the drug in the orphan indication is maintained regardless of follow-on indications. As a result, one model for development is based on lead development of a compound with a relatively quick-to-market orphan indication, followed by consideration of expansion to other indications.

Orphan drugs also experience significant competitive advantage in being first to market. Recent research suggests that the higher pricing, increased market share, lower marketing costs, longer exclusivity period, and faster uptake of orphan drugs offset the smaller patient pool. For example, Soliris® (Alexion Pharmaceuticals), indicated for treatment of paroxysmal nocturnal hemoglobinuria (PNH), generated $541 million in sales in 2010, despite the fact that there are only an estimated 4,000-6,000 patients in the U.S. with PNH.\textsuperscript{16} The revenue-generating potential of orphan drugs is compounded in cases where drugs have multiple orphan disease indications, or go on to gain approval for larger, non-orphan disease indications. In addition, a high number of orphan drugs are biologics, which are less likely to have generic equivalents, prolonging their value to sponsors, even after patent expiration.\textsuperscript{16}

\textbf{Challenges of orphan drug development}

\textbf{Basics of the designation process}

The request process for orphan designation requires sponsors to disclose the drug, its expected orphan indication, and reasons why such therapy is needed. It also requires a discussion of the scientific rationale supporting use of the drug for the rare disease, including copies of pertinent published or unpublished papers, and a summary of the regulatory status and marketing history of the drug in the U.S. and in foreign countries.\textsuperscript{16} In order to meet the prevalence criterion for orphan drug designation in the U.S., sponsors must demonstrate that the population of patients to be treated is fewer than 200,000 people in the U.S. as the FDA will not grant orphan designation if the drug would also be effective against a very similar indication that is not rare. Sponsors may jointly apply for orphan designation of the same drug for the same use in the EU and the U.S. using a common application form (FORM FDA 3671).

Once an application has been received, it undergoes three levels of review by the Office of Orphan Products Development (OOPD), after which the sponsor is sent a letter with designation approval, a request for additional information, or a denial. In the EU, applications for orphan designation are examined by the EMA’s Committee for Orphan Medicinal Products.

\textbf{Study design and execution challenges}

Clinical trials involving therapies for rare diseases are challenging for various reasons, including poorly-understood disease processes, a lack of validated endpoints, difficulty with finding patients, and logistical problems in clinical trial organization.\textsuperscript{19} Although these obstacles are not unique to orphan drug trials, the solutions to these challenges may be more difficult to find.

When designing a rare disease study, sponsors may find it difficult or impossible to find fundamental disease information, such as disease prevalence, incidence or treatment patterns, on which to base the study protocol. In most rare diseases, there are no standardized clinical trial designs or efficacy outcome measures, leading to difficulty in selecting appropriate endpoints, outcome measures, tools, and biomarkers. The lifelong nature of rare diseases also makes it challenging to select appropriate study durations. Small patient populations limit study variation and the genetic basis or associated co-morbidities of many rare diseases can be confounding factors in study predictability.\textsuperscript{20}

Sponsors of orphan drug trials face operational challenges, such as clinical vendor or investigator selection and clinical site issues, which can contribute significantly to cost.\textsuperscript{21} A survey involving 50 biotech and pharmaceutical firms in North America and...
Europe revealed that identifying and setting up investigative sites were among the most difficult factors of conducting rare disease clinical trials. Sponsors may have difficulty finding vendors with experience in the orphan indication. Key opinion leaders (KOLs) who are the experts on the rare disease area often have limited Phase III trial experience and less experience with Good Clinical Practices (GCP) and International Conference on Harmonization (ICH) guidelines. Site selection is challenging because, for the most part, large clinical trial centers have no experience in the disease area. As study patients are often scattered over many sites around the globe, study monitors may have a fragmented relationship with the clinical sites.

**Recruitment challenges**

Recruitment for orphan drug trials is challenged by the small number of patients for each disease, low disease awareness in the general population, and an ill-defined base of treating physicians or clinics. Patient databases, typically used as a recruitment resource, are of limited utility in orphan indications because the primary inclusion criteria often consist of assessments that are not commonly recorded on medical charts. Patient recruitment may also be complicated by simultaneous studies of a rare disease, since enrollment in one trial may render a patient ineligible for another trial. Delays in patient recruitment may lead to lengthy studies, resulting in turnover of study monitors and key team members. In fact, a recent analysis of ongoing clinical trials in a subset of rare diseases revealed a trend toward increased patient numbers and lengthier study durations. This trend exacerbates the challenge of retaining patients for the full duration of a study, requiring sponsors to devote significant effort to patient follow-up and support. As a result of these operational obstacles and a lack of benchmarking data, budgeting and forecasting for orphan drug trials is particularly challenging.

**Regulatory challenges**

There are no documented differences in approval criteria for orphan drugs and drugs for common indications, and sponsors must still prove substantial evidence of the effectiveness of the drug using adequate and well-controlled investigations. Nevertheless, the FDA has publicly expressed sensitivity to applying flexibility in its approval standards to new therapies for rare disorders. Although orphan drugs may qualify for fast-track regulatory review and smaller safety data set requirements, regulatory approval may also come with laborious Risk Evaluation and Mitigation Strategies (REMS) requirements. The regulatory complexity in determining what evidence is sufficient to support FDA approval of orphan drugs is due, in part, to lack of clinical trial precedents and limited scientific understanding of rare disease processes. The creation of the position of Associate Director for Rare Diseases within Center for Drug Evaluation and Research (CDER) in February 2010 is clear acknowledgment that review of products intended for small populations requires special consideration and expertise related to appropriate research and analytic methods. The EMA also provides guidance on procedures for the granting of marketing authorization under exceptional circumstances, including indications which are encountered so rarely that comprehensive evidence cannot be provided, and orphan drugs may meet the criteria to be considered for approval under exceptional circumstances.

**Other challenges**

Other challenges associated with orphan drug development include ethical concerns and reimbursement scrutiny. A majority of rare diseases affect children, and pediatric studies require sponsors to carefully balance the ethical considerations of conducting studies in a vulnerable population with concerns about site selection, recruitment, compliance, and statistical powering. With the growing number of orphan drugs on the market, the impact on
payers is increasing and their attention towards orphan drug pricing and reimbursement is likely to increase, as well. Due to small market sizes, sponsors will need to develop a low-cost delivery model that enables specialty pharmacies to provide orphan drugs to the patients who need them.

Navigating the challenges of orphan drug development

There are various strategies that sponsors can employ to plan for, and overcome, the clinical and regulatory challenges of orphan drug development.

Study planning strategies

Sponsors should consider the proper timing for seeking orphan drug designation as the designation process is only confidential until the application has been approved, after which the designation is published in registries, including the U.S. federal register and the EU Community Register. Therefore, sponsors may want to confirm stability of formulation, validate that the formulation can be produced on a commercial scale, or file an investigational new drug (IND) application to study the product in order to protect exclusivity and limit competition. The EMA strongly encourages sponsors to request a presubmission meeting prior to filing an application since the evaluation process has a fixed duration of 90 days, which cannot be lengthened to accommodate for lack of data or other omissions. Historically, participating in a presubmission meeting has a positive impact on the success rate of the application.28

One key strategy for navigating the challenges of orphan drug development is partnering with an experienced contract research organization (CRO) with knowledge of the disease area and a track record of success in development of therapies for rare diseases. A recent survey found that 75 percent of sponsors outsourced their orphan drugs studies to a CRO.22 Since there are fewer clinical trial precedents in orphan drug trials, sponsors should build mechanisms for cross learning into the study design. Cultivating a learning mindset within the entire study team, including sites and vendors, can help to alleviate development challenges that arise. Sponsor involvement and oversight throughout the course of the trial is critical for monitoring study progress, identifying issues, and solving problems, particularly in rare disease studies. It’s important to pick the right team and focus on retaining key study personnel for the length of the trial.

KOLs may be a valuable resource for site selection, as well as site training. Sponsors should engage their KOLs and leverage their networks, and also work with KOLs to educate investigative sites that lack specific expertise in the disease area and orphan indication. Building a buffer of contingency sites can help to alleviate concerns about underperformance on recruitment. As with any other study, protocols for orphan drug trials may require adjustment during study execution. For this reason, budgeting and forecasting for the unexpected is essential in orphan drug trials. Delays or changes in scope, such as the need for additional sites and added procedures or CRO services, require sponsors to factor unforeseen costs into the study budget. Sponsors should consider visiting clinical sites to observe patient visit procedures for the first few patients. The learning gained from these observations can be applied to the development plan to improve the overall quality of the study.

Patient recruitment strategies

Sponsors who have successfully received marketing approval for orphan drugs point to the value of enlisting the trust and support of rare disease physician networks and patient advocacy groups.22 Networks such as the National Organization for Rare Disorders (NORD) are valuable resources for patient education and recruitment. In July 2012, the reauthorization of the Prescription Drug User Fee Act (PDUFA) mandated the FDA to implement ways to incorporate patient views into drug development and regulatory review. This legislation highlights the importance of patients and patient organizations in orphan drug development.
### Sponsors are advised to take advantage of free or low-cost scientific advice from the FDA and/or EMA. Frequent and open communication with the regulatory agencies for assistance in the design of clinical study protocols is essential, and sponsors are advised to document this assistance in a clear written agreement as to the nature of clinical studies to be performed.

Drug development, as illustrated by the success of the LAM Foundation in securing orphan drug designation for sirolimus, a drug to treat the rare disease lymphangioleiomyomatosis (LAM). For small rare disease populations, sponsors may have more success with clinical trial recruitment by reaching out to patients directly, rather than relying on investigators to identify qualified participants. Establishing an informational website and educational print materials targeted at patients and their caregivers may help with patient recruitment. Sponsors should also consider working with patient support and patient advocacy groups to drive clinical trial awareness to their members. Targeted advertising at the local level may be effective, as well. Disease registries and rare disease reference portals such as Orphanet are other valuable sources for both recruiting patients and improving scientific understanding of the natural history of the rare disease. From a marketing standpoint, disease registries may also be identifying and establishing distribution channels for product launch. In February 2012, the Office of Rare Diseases Research (ORDR) at the National Institutes of Health (NIH) launched a Global Rare Disease Patient Registry and Data Repository (GRDR) to collect, aggregate and share de-identified patient information in a standardized way to facilitate studies for drug development. The ORDR also encourages the establishment of specific disease registries for rare diseases.

### Regulatory strategies

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Sponsors may also benefit from communication with the OOPD, which provides assistance on gaining orphan drug designation and promotes collaboration among sponsors, professional organizations, patient organizations, and academic centers. In addition, the FDA and EMA offer official guidance on clinical trial conduct. For instance, the FDA offers industry guidance on nine different ways for a new therapy to get approved on the basis of a single adequate and well-controlled trial. The EMA offers a guideline on clinical trials in small patient populations, which outlines approaches for increasing efficiency of design and analysis for small studies.

### Conclusion

Improved scientific understanding of rare diseases is transforming the biopharmaceutical industry approach to drug therapy. Increased industry focus on the development of targeted therapies and the trend toward stratified or personalized medicine has been central to the development of many orphan drugs, as approximately 80 percent of rare diseases are related to genetic aberrations. It has been suggested that targeting these genetic defects leads to a higher likelihood of R&D success. As a result, orphan drug development shows great potential for commercialization and is an important part of the future of the global biopharmaceutical industry. In order to capitalize on the opportunity in rare diseases, sponsors must learn to navigate the regulatory and operational challenges of orphan drug development, with the ultimate goal of serving an unmet need for millions of patients around the world.
References

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