Proven Strategies for Rare Disease and Orphan Drug Development in the U.S.

ABSTRACT

Orphan drugs are medicinal products intended to treat diseases so rare that sponsors are reluctant to develop them under usual marketing conditions. Orphan drugs are a growing market, due in large part to tax incentives, longer periods of market exclusivity, and shorter, smaller clinical trials, as well as the premium pricing associated with many orphan drugs.

Despite increased emphasis on orphan drug development, only five percent of rare diseases currently have available treatment options. As sponsors continue to invest in rare diseases, it is important for them to understand the strategic and practical considerations of the planning and development process in order to manage the delicate balance between budget and timelines and maximize the opportunity for successful entry into the market.
Orphan drugs: a growing market

Approximately 7,000 distinct rare diseases have been identified to date affecting one in 10 Americans and an estimated 350 million people worldwide. Approximately 250 new rare diseases are identified each year, 80 percent of which are genetic in origin and 50 percent of which affect children. With advancements in genomics and precision medicine, it is expected that the number of recognized rare diseases will continue to increase.

Orphan drugs are projected to be a $178 billion market, or just over 20 percent of all prescription drug sales, by the year 2020. The market is expected to grow at an annual rate of nearly 12 percent per year through the end of the decade, compared with approximately six percent for other drugs. More than 40 orphan drugs have achieved blockbuster status, exceeding $1 billion in global sales. Most of these products have been developed by small biotechnology or specialty pharmaceutical companies, even though major pharmaceutical companies account for 70 percent of the market share.

Currently, there are an estimated 460 new medicines being studied in clinical trials for rare diseases. Before the Orphan Drug Act was passed in the U.S. in 1983, the U.S. Food and Drug Administration (FDA) had approved only 10 orphan treatments. However, in the period from 1983 to 2004, more than 325 orphan drugs were approved, representing nearly one-third of all approvals. Today, more than 3,000 compounds have received orphan drug designation, with a record 291 designations granted in 2014.
Figure 1. Pathway to development in rare disease

In order to qualify for orphan status in the U.S., a compound must either be intended for the prevention, diagnosis, or treatment of a disease affecting less than 200,000 patients per year or not expected to be profitable within seven years following FDA approval. Of note, the criteria for orphan status vary from region to region, which may impact where sponsors choose to launch their clinical trial programs. For example, the disease prevalence required to qualify for orphan designation in the EU is less than five in 10,000 people (or, less than 253,000 patients per year).

The strategy for developing an orphan drug should include the following components:

1. Knowledge of the natural history of the rare disease
2. Understanding of the product’s proposed mechanism of action, including whether it is specific to the target patient population or has applicability beyond it
3. Assurance of consistent product quality and manufacturing, especially since orphan medicinal products may necessitate novel modes of administration or specific storage requirements
4. Leveraging of pharmacology/toxicology data to support clinical program
5. Clinical evidence to establish safety and efficacy, with science-based primary endpoints
6. Benefit-risk assessment

In recent years, the FDA has implemented a more consistent process to ensure timely review of orphan drug designation applications. Beginning in the fourth quarter of 2012, the FDA began reporting and benchmarking its progress in reviewing these applications.

Figure 2. Orphan drug designation by the numbers

Roadmap for orphan drug development

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Strategic considerations for rare disease and orphan drugs

For any rare disease program, the strategy for drug development is not only critical, but also unique. Below are some strategic considerations that may be relevant to the rare disease development process.

Registries for rare diseases
Depending on the product under investigation, it may be appropriate for sponsors to consider implementing a rare disease registry. Registries are useful for identifying patients and collecting data over a long period of time, which may be critical for demonstrating the significance of the investigational product during the approval process.

Genomic models research
Genomic models research has become a key factor, especially for rare diseases that are genetic in origin. It is increasingly important for researchers to work with patients, patient advocates, or even grassroots organizations, as crowd sourcing now plays a significant role in rare disease research.

Challenges of developing for the global market
With increasing globalization, the development of novel orphan medicines can have a global impact. Sponsors must consider their entrance not only into the research space, but also into the approval and marketing space on an international scale.

Rescuing and repurposing drugs
Sponsors can work through the National Institutes of Health and other sources to identify compounds that have advanced to a certain stage and then stalled in development for the general population, but might work for a rare disease population. Sponsors may also be able to expand the indications for existing drugs by identifying potential orphan applications.

Challenge of demonstrating value
As sponsors progress in their rare disease development programs, it is critical of them to remain cognizant of the need to demonstrate value from both a patient perspective and an economic standpoint.

Amendments to orphan drug regulation
In June 2013, the FDA finalized changes to orphan drug regulation, with an emphasis on clarifying existing policies to prevent companies from utilizing the orphan drug pathway as a portal for entering the larger market. Under the new definition, the FDA explained that a subset should be taken to mean that the drug is appropriate when used in the subset, but its use in a broader population would be inappropriate due to some property or properties of the drug, such as toxicity or mechanism of action. However, even if a single drug is used to treat multiple applications that would cause it to treat more than 200,000 patients, the FDA will still consider the drug an orphan treatment for the purposes of the Orphan Drug Act as long as each patient population is under 200,000. The FDA also conceded that some new dosage forms might be clinically superior to previously-approved forms and, as such, would be eligible for their own seven-year period of orphan exclusive approval.
Practical considerations in planning rare disease studies

There are many stakeholders and elements that need to be examined in the planning and execution of rare disease trials. While each rare disease indication and trial is unique, there are certain practical considerations that are common to the planning process for every trial, such as maintaining the balance between budget and timelines. Country/site distribution, regulatory/ethics considerations, site selection, enrollment and study execution are also key components of the strategic approach to a rare disease study.

Country/site distribution

When planning country and site distribution, sponsors should consider prevalence, incidence, severity and disease progression for the indication under investigation. Sponsors will also need to understand the previous research and the standard of care, which may direct study design and endpoints, as well as disease awareness and potential investigators. Each of these factors will affect country and site distribution and help sponsors to determine whether to launch a trial globally or in a single/limited region.

Considerations for conducting a rare disease trial in a global region include:

+ Navigating country-specific regulatory agency and ethics committee approval processes. Sponsors should develop a clear strategy for implementation at the regional, country and local levels and take a proactive approach to identifying the documents that will be needed. This can have a significant impact on both the budget and the timelines.
+ Supplying the drug. For rare diseases, unpredictable or protracted enrollment may lead to issues with study drug supply. It may be advisable to utilize fewer or more centralized drug depots to deliver drugs on demand, rather than pre-loading sites and risking drug expiration or patient relocation.

Understanding nuances of insurance. Insurance is often an afterthought in study planning. There are likely to be country-specific requirements for insurance policies, so it may be helpful to work with a reputable global insurance company or local insurers early in the planning process to minimize friction in study start-up.

Handling translations. In addition to identifying what must be translated and what must be submitted in English, it is important from a quality control standpoint to ensure that documents are accurate prior to translation.

Considerations for launching a study in a single or limited region include:

+ Relocation. It is important to understand the logistics and costs of relocation, including visas, insurance, and accommodations, as well as the patient’s condition and willingness to move. Organizations such as the National Organization for Rare Diseases (NORD) or patient advocacy groups may be able to assist with relocation.
+ Enrollment. Consider subject prevalence and geographical distribution alongside the maximum workload per selected site to assess site burden.
+ Retention. The costs incurred for long-term relocation may impact study feasibility, and the travel or time commitments associated with study participation may cause subjects to lose interest. Sponsors may want to consider planning for the possibility of opening studies in other countries to mitigate against study attrition.
Applying Quality by Design to the Rare Disease Population: Special Considerations

**Regulatory and ethics considerations**

Regulatory approval timelines may be rate limiting, and must be taken into account in both the global and single/limited region clinical trial scenarios. Sponsors should be mindful that the best-case scenario for approval and study timelines is often not the reality, particularly for rare diseases. Challenges associated with timely approval include lack of familiarity with the disease, limited human data, gaps in physician expertise, and absence of a standard of care. Sponsors may be able to address and overcome these obstacles by involving a key opinion leader or lead investigator in regulatory discussions or establishing care norms.

**Site selection**

Qualified investigators and sites may be as difficult to find as patients. Key opinion leaders may have limited pivotal trial research experience, so clinical research and Good Clinical Practice (GCP) accreditation may be needed. While referral physicians and large patient encashment sites may have access to a broad patient base, they may have limited disease knowledge, requiring disease and protocol training. As standard practices may vary widely from site to site, consultation with investigators during study planning and protocol writing is essential. Understanding local site start-up processes enables sponsors to account for site-specific factors in the study budget and timeline.

**Enrollment**

For rare diseases, evidence or literature-based enrollment metrics are often unavailable and planning may need to be based on assumptions. Continual learning and re-evaluation of enrollment assumptions throughout the course of the study is critical. Since it is not uncommon for sites to only enroll a single patient, or no patients at all, it may be prudent to have back-up or extra sites to offset unpredictable enrollment. Thoughtful recruitment planning – including development of site specific data mining and outreach, collaborations with patient advocacy groups, creation of a patient registry, promotion of disease awareness, and utilization of call centers – can mean the difference between failure and success.

**Study execution**

The importance of a long-term plan for rare disease development that accounts for contingencies and interim data needs cannot be overemphasized. Sponsors are also recommended to take a proactive approach to study closeout that includes an aggressive plan for ongoing data management including clean data reviews and data transfer.

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**Figure 3. Challenges associated with country and site distribution**

1. Knowledge of disease’s natural history
2. Understanding of product’s proposed mechanism of action
3. Assurance of consistent product quality and manufacturing
4. Leveraging of pharmacology taxoloy data to support clinical program
5. Clinical evidence to establish safety and efficacy science-based primary endpoints
6. B:R assessment
Conclusion

In order to capture the financial and competitive advantages of orphan drug development, sponsors must anticipate and plan for the many challenges inherent to the study of rare diseases, including regulatory hurdles and obstacles to study startup and execution. With proper, proactive strategic planning, sponsors seeking orphan drug designation and approval can more skillfully navigate these challenges to commercialize therapies that serve critical unmet needs.

References

About Premier Research
Premier Research is a leading clinical development service provider that helps highly innovative biotech and specialty pharma companies transform breakthrough ideas into reality. The company has a wealth of experience in the execution of global, regional and local clinical development programs with a special focus on addressing unmet needs in areas such as analgesia, CNS, oncology, pediatric and rare disease. Premier Research operates in 84 countries and employs 1,000 professionals, including a strong international network of clinical monitors and project managers, regulatory, data management, statistical, scientific, and medical experts. They are focused on smart study design for advanced medicines that allow life-changing treatments.

Angi Robinson | Executive Director, Pediatrics and Rare Disease
Angi has provided executive oversight and full management support for numerous studies, including global clinical trials with a focus in pediatrics and rare diseases, as well as studies requiring the oversight of Data Safety Monitoring Boards and Data Monitoring Committees. She has also supported FDA Pre-IND meetings, IND submissions and BLA and NDA directorship, including NDA submissions for pivotal studies resulting in product approval. Her protocol experience includes multiple study designs, including PK/PD, adaptive design, and FDA Fast Track designations. Angi served as Global Project Director for Good Clinical Practice Journal’s 2008 Clinical Research Team of the Year for a pivotal clinical trial in a rare disease.