Orphan Drug & Rare Disease Development: Understanding the U.S. and European regulatory landscape

ABSTRACT

Today, more than ever, researchers are focused on providing care for the approximately 7,000 rare diseases that may have been overlooked in the past due to the challenges of conducting clinical trials in small populations and limited commercialization potential. The orphan drug arena focuses on identifying and studying potential treatments to serve the significant unmet needs of patients living with rare diseases, and the current landscape offers a variety of incentives, government support and regulatory agency assistance to encourage orphan drug development.

In this white paper, we will discuss key strategic considerations – for both the U.S. and the EU – that may be employed to accelerate your orphan drug and rare disease development program. We will focus on the regulatory aspects of bringing therapies for rare diseases to market, with specific emphasis on the similarities and differences between the regulatory pathways in the U.S. and the EU.
US orphan drug and rare disease landscape

In the U.S., a rare disease is defined as a condition that affects fewer than 200,000 people and an orphan drug is either:1

+ A drug or biological product used for the prevention, diagnosis or treatment of a rare disease in the U.S., or
+ A drug or biological product that is not expected to recover the costs of development and marketing

Since 2003, there has been a dramatic increase in the number of orphan drug designations, particularly in the U.S., as sponsors better understand the incentives associated with orphan drug development and the strategies that can be leveraged to streamline development efforts. There has also been more financial commitment and a deliberate effort by both established firms and up-and-coming companies to invest more time and resources to developing more compounds and products in the orphan drug arena.
Despite the consistent growth in orphan drug development over the past 10+ years, there is still significant work to be done. We have only begun to scratch the surface of the approximately 7,000 rare diseases, many of which are genetic, and the majority of patients with rare diseases remain underserved.

As compared with standard drugs, orphan drugs typically involve smaller Phase III trial sizes, spend fewer months in regulatory review, and are more likely to be approved by the FDA since these therapies often represent significant therapeutic advances. The expedited development pathways and higher likelihood of FDA approval highlight the impact firms can have in the area of orphan drugs and rare diseases, keeping in mind that orphan drugs are subject to the same regulatory requirements and marketing approval process as standard drugs. Productive partnerships and proper, proactive regulatory planning can potentially significantly reduce development time and budget, while increasing development success.

**Strategic considerations for U.S. development**

Despite broad awareness of the existence of incentives for orphan drug development, many sponsors still remain uncertain about how to take advantage of these incentives. A top-line
The typical grant provides $200,000 to $400,000 per year for three to four years, followed by a re-compete process, which is more likely to be successful when sponsors are able to show some data that the product is viable from a therapeutic and safety perspective. Any domestic or foreign, public or private, for-profit or nonprofit entities may apply for the grant program.

consideration when undertaking orphan drug development is to partner early and partner often with regulators to bring therapies for rare diseases forward.

The pathway to orphan drug development begins with a request to the Office of Orphan Products Development (OOPD) to grant orphan designation to a drug or biological product and ends with submission of an NDA or BLA to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) to market an orphan drug or biological product. The process typically involves frequent interactions with the FDA to discuss and agree upon the clinical development program requirements needed to support product registration. Of note, meetings with the OOPD are also available prior to submitting an application for orphan designation and the process of orphan drug development.

The FDA offers a variety of incentives, both during development and following approval, to support sponsors of orphan drugs. These incentives include:

**FDA incentives for orphan drugs**

- **Grant program**
- **Tax credits**
- **Market exclusivity**
- **Rare pediatric disease priority review vouchers**

**Related strategic options for expedited development programs**

- **GAIN Act**
- **Fast track designation**
- **Breakthrough therapy designation**
- **Accelerated approval**
- **Priority review**

**FDA incentives for orphan drugs**

**Grant program**

Approximately $14 million are provided per year to sponsor companies through the orphan drug grant program, which is applicable to drugs, biologics, medical devices, or even medical foods. While this amount may seem small for traditional drugs, it has a significant impact in the orphan drug arena, where trials are typically smaller and shorter in duration. The typical grant provides $200,000 - $400,000 per year for three to four years, followed by a re-compete process, which is more likely to be successful when sponsors are able to show some data that the product is viable from a therapeutic and safety perspective. Any domestic or foreign, public or private, for-profit or nonprofit entities may apply for the grant program.

**Tax credits**

Tax credits can cover up to 50 percent of the clinical trial costs and are available for qualifying costs incurred between the date orphan drug designation is granted and the date of FDA approval. In 2014, more than $2 million in user fees were waived for sponsors investigating potential rare disease therapies.

**Market exclusivity**

Orphan Drug Exclusivity offers seven years of exclusivity following FDA market approval and significant lead time against competitive threats to gain market traction.

**Rare pediatric disease vouchers**

The Rare Pediatric Disease Priority Review Voucher Program was created under the FDA Safety and Innovations Act (FDASIA) to encourage development of drugs and biologics for rare pediatric diseases. Products that undergo priority review are generally given an approval decision – positive or negative – within six months after the filing date, rather than the usual 10 months. The premise of the program is that sponsors who receive approval of a rare pediatric disease product application for a
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rare pediatric disease are eligible to receive a priority review voucher (PRV) which can be redeemed, transferred, or sold to another sponsor, to obtain priority review a subsequent application for a different product that would otherwise be ineligible for priority review. The FDA has published a Rare Pediatric Disease Priority Review Vouchers Draft Guidance for Industry to assist sponsors in navigating this program, which requires a sponsor to notify the FDA of its intention to redeem a voucher at least 90 days prior to redemption.

Related strategic options for expedited development

GAIN Act
The GAIN (Generating Antibiotic Incentives Now) Act created under FDASIA aims to encourage development of antibacterial and antifungal drugs for the treatment of serious or life-threatening infections. Eligible products are granted a Qualified Infectious Diseases Product (QIDP) designation. Products with a QIDP designation are eligible for priority review of marketing applications and fast track designation, as well as an additional five years of exclusivity at the time of FDA approval.

Fast track designation
Fast track designation applies to drugs with the potential to address unmet needs. This pathway accelerates new drug development and review by increasing FDA communication and enabling rolling review. The key distinguishing factor of this expedited development program is that fast track designation may be based on results from non-clinical studies indicating that the product may represent a significant therapeutic advantage. Sponsors should request fast track designation no later than the pre-submission meeting, if possible. Of note, the designation may be rescinded if the drug no longer meets qualifying criteria.

Breakthrough therapy designation
Also created under FDASIA, the Breakthrough Therapy Designation is designed to expedite development and review of breakthrough therapies. To qualify as a breakthrough therapy, a product must be intended to treat a serious or life-threatening condition and there must be preliminary clinical evidence that the product may demonstrate substantial improvement on one or more clinically-significant endpoints compared with available therapies. Of note, approval may be based on an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict a drug’s clinical benefit and the designation may be withdrawn if the product no longer meets qualifying criteria. Sponsor should be aware that breakthrough therapy designation carries with it intensive guidance on efficient drug development during the Investigational New Drug (IND) phase, beginning as early as Phase I, so it involves more intensive regulatory scrutiny on planning.

Accelerated approval
This pathway allows early approval of a drug that offers a benefit over current treatments based on a surrogate endpoint or other clinical measure that is reasonably likely to predict a clinical benefit. After accelerated approval is granted, the drug must still undergo additional confirmatory studies to establish benefit.

Priority review
Priority review calls for review within six months instead of the standard 10 months. This pathway is reserved for situations in which the Center for Drug Evaluation and Research has determined that the investigational drug could potentially provide a significant advance in medical care. Priority review is typically requested with the original biologics license application (BLA), new drug application (NDA), or efficacy supplement.
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Orphan Drug Legislation in the EU

Orphan drug legislation was introduced in the EU in 2000. These regulations stipulate that patients with rare diseases deserve the same quality, safety, and efficacy standards for medicinal products as other patients and that, in order to make these products available to all patients in the EU, orphan drugs are required to obtain a Community Authorisation through the centralized marketing authorization procedure.

To qualify for orphan designation in the EU, a product must:

- Be intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition that affects no more than five in 10,000 people in the EU
- Be unlikely to be marketed without incentives

In addition, there should exist no satisfactory method of diagnosis, prevention, or treatment of the condition in question that has been authorized in the EU or, if such method exists, the product will be of significant benefit to those affected by that condition. The Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA) is responsible for determining whether all orphan designation criteria have been met, and the Committee for Medicinal Products for Human Use (CHMP) is responsible for providing a scientific opinion on the application merits for marketing authorization.

The success of orphan incentives in driving drug development is reflected in the steady growth of orphan designations in the EU, with 124 designations granted in 2013 and 201 designations (more than 60 percent increase) granted in 2014. While the actual percentages vary from year to year, more than half of the medicines that receive a positive opinion for orphan designation from the EMA concern medical conditions affecting children.
Strategic considerations for EU development

An application for orphan designation in the EU can be made at any stage of development prior to submission of the application for marketing authorization. It is recommended to apply as early as possible during the development lifecycle in order to maximize the benefits from available incentives, but it is worth noting that all products receiving orphan designation are published on the EMA website, making orphan designation status public knowledge. Pre-submission meetings with the Committee for Orphan Medicinal Products (COMP) are also encouraged.

Incentives
In addition to the competitive, development and pricing advantages that may be associated with orphan drugs, incentives for development of orphan medicinal products in the EU include:

+ Protocol assistance (scientific advice) which is provided free of charge for orphan drugs for pediatric studies and at a 75% discount for other studies
+ 10 years of market exclusivity
+ Fee reductions for marketing authorization applications and maintenance
+ EU incentives in the form of grants
+ National incentives in the form of grants and tax reductions

Related strategic options to accelerate development
Expeditied review programs offered by the EMA include:

+ Accelerated assessment, which applies when a medicinal product is expected to be of major health interest. This pathway can reduce review time from 210 days to 150 days exclusive of clock stops. Accelerated assessment should be requested at least two to three months before submitting the marketing authorization application. In addition, the EMA strongly recommends that sponsors request a pre-submission meeting six to seven months before submission.
Conditional marketing approval applies to medicinal products that address seriously debilitating or life-threatening diseases, emergency threats, or orphan indications. This pathway can be used when the benefit of immediate availability to public health outweighs the risk that additional data is still required. Conditional marketing approval is only valid for a year at a time and must be renewed annually until full approval is granted.

Exceptional circumstances apply when applicants are unable to provide comprehensive clinical data due to the rarity of the disease, the present state of scientific knowledge, and/or ethical constraints. Of note, orphan drugs must still meet the additional criteria for orphan designation to be granted this status.

As of March 2016, the EMA has introduced the PRIority MEdicines (PRIME) program, which applies to medicinal products that either offer a significant therapeutic advantage over existing therapies or benefit patients without treatment options. To be eligible for PRIME, a medicine must show potential to benefit patients with unmet medical needs based on early clinical data. Like accelerated assessment, PRIME can reduce review time.

Notably, the European Commission is currently reviewing the orphan medicinal product guideline with regard to the definition of “significant benefit” and the provisions for market exclusivity, with new guidance expected in 2016.

**EMA/FDA harmonization**

For sponsors who are investigating products for use in both the EU and the U.S., there are points of commonality between the development and approval process for the EMA and FDA. Many companies will submit a joint EMA/FDA application when seeking orphan drug designation, and following designation, a joint annual report summarizing the status of product development.

Key differences between orphan drug development in the EU and the U.S. include:

- Prevalence criteria to qualify as a rare disease – five in 10,000 in the EU vs. fewer than 200,000 in the U.S.
- Period of market exclusivity – 10 years in the EU vs. seven years in the U.S.
- Review of exclusivity – After five years if prevalence changes in the EU and no review in the U.S.

Of note, in the EU, sponsors may apply for orphan designation for an already-approved medicinal product provided the orphan designation concerns a not-yet-approved therapeutic indication. This requires a separate marketing authorization that only covers the orphan indication.

**Conclusion**

Wide-ranging incentives that include grants, tax credits, waivers of user fees, and longer periods of market exclusivity are fueling the growth in orphan designations and orphan drug approvals. These incentives help to lower development costs, shorten review times, and facilitate earlier and more frequent communication with regulatory agencies, all of which accelerate the time to market for drugs and biologics that have the potential to transform the lives of people suffering with rare diseases.
References

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Dr. Lisa Pitt is Premier Research’s premier regulatory official, and provides strategic guidance and oversees the company’s regulatory affairs service offerings. Dr. Pitt has more than two decades of experience in the pharmaceutical and contract research industries and extensive expertise in small-molecule and biologic pharmaceutical product development, from early phase through registration and post-marketing. She oversaw regulatory activity for global product development teams at MedImmune as Director of Regulatory Affairs and served as Director and Principal Regulatory Affairs Consultant at PAREXEL. She also held regulatory positions at Novartis Pharmaceuticals, and immediately prior to joining Premier Research, was a senior regulatory project manager at the U.S. Food and Drug Administration, responsible for drugs and biologic products intended for the treatment of inherited metabolism disorders.

Dr. Pitt holds a doctorate in pharmacy from the University of Maryland School of Pharmacy, a Master of Science and Jurisprudence from Seton Hall Law School, and a bachelor’s degree in biological sciences from the University of Delaware.

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.