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 Europe.
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:

- 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 will not be profitable within 7 years following approval by the FDA

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.
ORPHAN DRUG & RARE DISEASE DEVELOPMENT
Understanding the U.S. and European Regulatory Landscape

Productive partnerships and proper, proactive regulatory planning can significantly reduce development time and budget, while increasing development success.

As compared with standard drugs, orphan drugs typically require shorter clinical development times, spend fewer months in regulatory review and are more likely to be approved by the FDA. The expedited development pathway and higher likelihood of FDA approval highlight the impact firms can have in the area of orphan drugs and rare diseases. Productive partnerships and proper, proactive regulatory planning can 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 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 is comprised of two main steps:

1. Request to the Office of Orphan Products Development (OOPD) to grant orphan designation to a drug or biological product
2. Send 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

Both of these steps are influenced by FDA incentives, which can be applied and implemented at any time during the development lifecycle. These incentives include:

**FDA Incentives for Orphan Drugs**
- Grant Program / Tax Credits
- Market Exclusivity
- Rare Pediatric Disease Priority Review Vouchers

**Related Strategic Options to Accelerate Development**
- GAIN Act
- Breakthrough Therapy Designation

**FDA Incentives for Orphan Drugs**

**Grant Program / Tax Credits**

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 can cover up to 50% of the clinical trial costs, and user fees, which are often a hindrance to orphan drug development, may be waived. In 2014, more than $2 million in user fees were waived for sponsors investigating potential rare disease therapies.

**Market Exclusivity**

If an orphan drug designation is based on a plausible hypothesis of clinical superiority based on a Major Contribution to Patient Care (MC-PC), the product is eligible for Orphan Drug Exclusivity, which offers seven years of exclusivity following FDA market approval and significant lead time against competitive threats to gain market traction.
There must be preliminary clinical evidence that the product may demonstrate substantial improvement on one or more clinically-significant endpoints compared with available therapies.

**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 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 [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 to Accelerate 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.

**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 conditions 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 1, so it involves more intensive regulatory scrutiny on planning. Sponsors are also required to demonstrate an organizational commitment involving senior management.

**EU Orphan Landscape**

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 nor 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 granting marketing authorization.

**Figure 4. Orphan Designations vs. Approvals: EU and U.S.**

The success of orphan incentives in driving drug development is reflected in the steady growth in orphan designations in the EU, with 136 designations granted in 2013 and 187 designations (a nearly 40% 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 product development public knowledge.

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
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 – 5 in 10,000 in the EU vs. ~7.5 in 10,000 in the U.S.
- Period of market exclusivity – 10 years in the EU vs. 7 years in the U.S.
- Review of exclusivity – After 5 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.

### Figure 6. EMA Scientific Advice Fees

<table>
<thead>
<tr>
<th>Scientific advice</th>
<th>Fee</th>
</tr>
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<tbody>
<tr>
<td>Small and Medium sized Enterprise (SME)</td>
<td>90% reduction</td>
</tr>
<tr>
<td>SME + orphan</td>
<td>100% reduction</td>
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<tr>
<td>Orphan</td>
<td>75% reduction</td>
</tr>
<tr>
<td>Advanced Therapy MP (ATMP)</td>
<td>65% reduction</td>
</tr>
<tr>
<td>ATMP + SME</td>
<td>90% reduction</td>
</tr>
<tr>
<td>ATMP + orphan</td>
<td>bd</td>
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<tr>
<td>Normal product</td>
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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.

### Figure 7. Orphan Drug Development in EU vs. U.S.

<table>
<thead>
<tr>
<th></th>
<th>EU</th>
<th>US</th>
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</thead>
<tbody>
<tr>
<td>Legal basis</td>
<td>Reg EC/141/2000</td>
<td>Orphan drug act 1983</td>
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<tr>
<td>Prevalence</td>
<td>5 in 10,000</td>
<td>Approx 7.5 in 10,000</td>
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<tr>
<td>Incentives</td>
<td>10 years market exclusivity</td>
<td>7 years market exclusivity</td>
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<tr>
<td>Exclusivity review</td>
<td>After 5 years if prevalence changes</td>
<td>No change</td>
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<tr>
<td>Timeline</td>
<td>90 d (COMP) + 30 d (EC)</td>
<td>No timelines (1-3 months)</td>
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<tr>
<td>Procedural</td>
<td>Centralised procedure and EU wide approval</td>
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</tbody>
</table>

### 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.
About Premier Research

With more than 1,000 employees and operations in 50 countries, Premier Research is a contract research organization (CRO) serving highly innovative biotechnology, pharmaceutical and medical device companies. Premier Research has a wealth of experience in rare disease and pediatric research, having managed 100 projects in each area in the last five years alone.

About Nach Dave | Director, Regulatory Affairs

Nach has worked for and consulted to the pharmaceutical and medical device industry for 15 years. He began his career in Data Management with Sandoz Pharmaceuticals and has since worked in senior positions in clinical operations and regulatory affairs for companies such as Merck, Bristol Meyers Squibb and, most recently, Maxx Orthopedics. In addition to his industry appointments, Nach was previously an adjunct professor in the Drug Regulatory Program at Long Island University.

About Carol Huntington | Associate Director, Regulatory Affairs Europe

Carol joined Premier Research in December 2014 with nearly 20 years of drug development experience gained in small, medium and large pharmaceutical companies working in Germany, the UK and France. She provides regulatory strategic and procedural advice. Carol has worked as a regulatory project manager and also has experience in regulatory writing, including MAA submissions and briefing documents for regulatory agency meetings.

References

1. Food and Drug Administration.
2. Evaluate Pharma. 27 October 2014.