propharma

Taking Advantage of the Orphan Drug Act and FDA's Orphan Drug Designation (ODD)

Over the last 40 years, the Orphan Drug Act (ODA) has transformed rare disease drug development by incentivizing companies to develop therapies for conditions affecting fewer than 200,000 people in the US.

Before the ODA, treatments for these conditions were largely ignored due to high development costs and limited commercial viability. By offering tax credits, market exclusivity, research grants, and waived FDA fees, the ODA has led to the approval of hundreds of life-changing treatments, particularly in oncology and neurology. However, challenges remain, including regulatory hurdles, clinical trial complexities, and high costs. **Explore how to navigate FDA's Orphan Drug Designation pathway, maximizing the benefits and successfully bringing rare disease treatments to the market.**

History of Rare Disease Drug Development in the United States

The Orphan Drug Act (ODA), enacted in 1983, was designed to incentivize pharmaceutical companies to develop drugs for rare diseases that might otherwise be overlooked due to limited commercial profitability. Rare diseases, often referred to as orphan diseases, affect a small percentage of the population, making the development of treatments financially unfeasible under traditional market conditions. Before the ODA, treatments for rare diseases were scarce due to the high cost of research and development combined with a lack of commercial viability. Patients suffering from these conditions often had little to no treatment options available, leading to significant unmet medical needs.

The history of rare disease drug development in the US highlights the FDA's evolving role in addressing these unmet medical needs. Prior to the passage of the ODA, only a handful of drugs for rare diseases had been developed due to the significant economic risks involved. In response, advocacy groups, healthcare professionals, and patients urged the government to take action. The ODA emerged as a landmark piece of legislation, offering critical incentives that transformed the landscape of orphan drug development by providing a framework of incentives to encourage innovation and investment in these critical therapeutic areas.

Between 1983 and 2019, FDA designated 5,099 orphan drug applications, supporting the notion that the ODA has led to a significant increase in the number of treatment options available for patients suffering from rare diseases in the US.

Since its enactment, the ODA has led to the approval of hundreds of treatments for rare diseases, significantly increasing the availability of therapies and improving patient outcomes. Specifically, a publication by Miller et al. 2021 notes that the top five therapeutic areas with orphan drug designations were oncology, neurology, infectious diseases, metabolic disorders, and hematology. There have been particularly notable Increases in orphan drug designations in the areas of oncology and neurology from the time that the ODA was enacted through 2019.

The Orphan Drug Act

The ODA was established to encourage the development of treatments for rare diseases, which the Act defines as those affecting fewer than 200,000 individuals in the United States. Prior to the enactment of the ODA, pharmaceutical companies had little motivation to invest in rare disease treatments due to the limited patient populations and high development costs of these products.

The Act introduced key incentives, which include:

- **Marketing exclusivity:** Once approved, an orphan-designated drug receives seven years of exclusive market rights, preventing competitors from marketing a similar drug for the same indication.
- **Tax credits:** Companies can claim up to 25% of clinical research costs as tax credits, reducing the financial burden of development.
- **Waiver of user fees:** The FDA waives the marketing application fees, which can amount to millions of dollars, for Sponsors of orphan drugs.
- **Research grants:** The FDA's Office of Orphan Products Development (OOPD) provides funding opportunities to support the development of promising treatments.
- **Regulatory assistance:** Sponsors receive specialized guidance from FDA to streamline the approval process and navigate regulatory hurdles.

A publication by Miller et al. 2021 cites that 5,099 orphan drug applications were designated between the enactment of the ODA in 1983 through 2019. Of these, 724 (14%) designations had at least one corresponding approval. These numbers support the notion that the ODA has led to a significant increase in the number of treatment options available for patients suffering from rare diseases in the US.

Filing an Orphan Drug Designation Request

A Sponsor can submit an Orphan Drug Designation (ODD) request at any time during the drug development process. Unlike other regulatory submissions, an Investigational New Drug (IND) application is not required before an ODD application can be submitted. However, designation should ideally be sought before filing a New Drug Application (NDA) or Biologics License Application (BLA). The application process includes the following key elements:

1. A Statement of Request

The Sponsor must explicitly state that they are seeking Orphan Drug Designation for a specific rare disease or condition.

2. Sponsor's Contact Information

This includes information about the Sponsor and the Sponsor's primary contact person and/or US agent. If a Sponsor is located outside of the United States, the application must be submitted on behalf of the Sponsor by its US agent.

3. Drug Description

This includes information such as the active moiety (for small molecules), the principal molecular structural features (for macromolecules), and the physical and chemical properties of the drug.

4. Description of the Rare Disease and Medical Necessity

This should include such items as: the definition, cause, classification, symptoms and diagnosis, and treatment, keeping in mind the relation to the active moiety of the product and treating the indication.

5. Scientific Rationale for the Drug's Use

Sponsors must provide preclinical and clinical data supporting the drug's potential efficacy. This includes in vitro studies, nonclinical animal studies, and/or clinical studies in humans whether positive, negative, or inconclusive. These studies should be conducted using the drug in the rare disease or condition.

6. Evidence of Prevalence

Sponsors must demonstrate that the disease affects fewer than 200,000 individuals in the US or if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the US are fewer than 200,000 per year.

7. Justification for Medically Plausible Subsets

Where a Sponsor requests orphan designation for a drug for only a subset of persons with a particular disease or condition that otherwise affects 200,000 or more people ("orphan subset"), the Sponsor must demonstration that, due to one or more properties of the drug, the remaining persons with such disease or condition would not be appropriate candidates for use of the drug.

8. Regulatory and Marketing History of the Drug

A summary of the regulatory status of the drug in the US (open Investigational New Drug application [IND] or marketing application) as well as any other indications of the drug being investigated, other indications the drug is approved for in other countries, or other regulatory actions taken against the drug in any country.

Applications are submitted electronically via the CDER NextGen Portal or emailed to the FDA at orphan@fda.hhs.gov.

FDA Approval Criteria for Orphan Drug Designations

The FDA evaluates Orphan Drug Designation requests based on the following criteria:

- **Disease prevalence:** The rare disease must affect fewer than 200,000 people in the US. FDA maintains a database (Orphan Drug Designations and Approvals database) that can be searched by indication, displaying a comprehensive list of orphan designations for a given indication. Sponsors may wish to search this database to understand if FDA has considered the specific disease or condition to be rare for ODD requests of other Sponsors.
- **Medical plausibility:** There must be a scientifically reasonable basis for expecting the drug to be effective.
- **Clinical superiority:** When drugs with the same active moiety are competing for the same orphan indication as an approved drug, it is necessary to demonstrate that the drug offers a significant improvement in efficacy, safety, or patient care. To prove that a drug is more effective than an approved drug, a direct head-to-head comparative trial between the proposed drug and the approved drug is often required.

The FDA reviews applications and either grants a Designation Letter or issues a Deficiency Letter requesting further information or clarification. The FDA will respond to almost all Orphan Drug Designation requests within 90 days.

Orphan Drug Designation – the Good, the Bad, and the Ugly

Benefits of Orphan Drug Designation

Orphan drug status offers several advantages in the US, Including:

- **Financial incentives:** Tax credits, grants, and waived fees significantly reduce development costs.
- **Regulatory support:** FDA guidance helps Sponsors navigate the approval process efficiently.
- **Market exclusivity:** The seven-year exclusivity period protects the drug from direct competition.

These incentives have proven to be highly effective in encouraging investment in orphan drug development.

Drawbacks and Challenges

Despite its benefits, the orphan drug process presents several challenges:

- **Regulatory hurdles:** Orphan drugs still require substantial evidence of safety and efficacy, which can be difficult to obtain in small patient populations.
- **Clinical trial recruitment:** The limited number of patients makes recruiting for clinical trials challenging. In rare disease clinical trials, Sponsors may have to enroll patients at sites globally, with each site only enrolling one or few patients. This can lead to issues with standard of care.
- **High costs:** While incentives exist, developing orphan drugs remains expensive.
- **Limited market exclusivity:** Exclusivity applies only to the designated indication, meaning competitors can develop treatments for different uses of the same drug.
- **Generics and off-label use:** Once an orphan drug is approved, generic versions may enter the market and be used off-label, reducing profitability.

Additional Programs for Rare Disease Drug Development

The FDA offers additional programs to support rare disease treatment development:

- **Humanitarian Use Device (HUD) Program:** Established for medical devices benefiting populations of fewer than 8,OOO individuals per year.

- **Rare Pediatric Disease Priority Review Voucher (PRV) Program:** Provides a transferrable PRV to Sponsors of approved orphan drugs for pediatric diseases, expediting review timelines. Although this program officially expired in 2024, it was extremely successful in fostering the development of treatments for unmet medical needs in pediatric rare disease communities. From 2012 to April 2024, 53 PRVs were awarded across 39 rare pediatric diseases.
- **Global Orphan Drug Programs:** The European Medicines Agency (EMA) and Japan's regulatory agencies have their own orphan drug programs, with different criteria and incentives.

Orphan Drug Act: Advancing Rare Disease Drug Development in the US

The Orphan Drug Act has significantly advanced the development of treatments for rare diseases. By providing financial and regulatory incentives, it has encouraged pharmaceutical companies to invest in research that benefits underserved patient populations. While challenges remain, the ODA continues to drive innovation and bring new hope to patients with rare conditions. Understanding the designation process and leveraging available incentives is essential for Sponsors seeking to develop and commercialize orphan drugs in the US.

Expert FDA Consultants with Extensive Experience in Orphan Drug Development

FDA's ODD pathway is extremely beneficial in advancing the development of drugs to treat rare diseases in the US. However, obtaining orphan drug designation is challenging for even the most seasoned regulatory professionals. For more than 40 years, ProPharma's team of expert regulatory consultants has been assisting clients with the most difficult and unique FDA-related matters, including countless successful ODD submissions. Using our proprietary approach to FDA, that combines extensive scientific knowledge with extraordinary regulatory expertise, we speak with regulators in the language we all speak – science. This has allowed us to establish a unique relationship with FDA and has aided us in accomplishing thousands of successful interactions with the Agency over the years. **Contact us today to learn how we can support the development of your orphan drug.**