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WHITE PAPER

Unlocking the Benefits of FDA Orphan Drug Designation

Maximizing Opportunities for Rare Disease Therapies

In 1983, Congress passed the Orphan Drug Act (ODA) in an attempt to counteract the economic downsides and other challenges companies faced in conducting research and developing new treatments for niche diseases with very small patient populations; so-called "orphan diseases."[1] The ODA established FDA's ability to grant Orphan Drug Designations (ODD) to products intended to treat, diagnose, or prevent a rare disease or condition. With ODD status, companies can avail themselves of the various orphan drug development incentives established by the ODA.

Passage of the ODA has helped drive development of drugs and biologics intended to treat conditions that affect fewer than 200,000 people in the United States or products that would not be able to recoup their development costs and become profitable within 7 years after approval or licensing by the FDA.[2]

Nearly 7,000 rare diseases affect approximately 30 million Americans, and only about 5% of these rare diseases have treatments approved by the FDA.[3]

There have been amendments to the ODA over the years, including the Orphan Drug Modernization Plan in 2017, which was designed to streamline the review process and established a 90-day timeline for FDA review of ODD requests. This initiative decreased wait times and increased ODD approvals[4], which elevated the impact of the ODA even further.

Obtaining an ODD for a drug or biologic is a separate process from seeking approval or licensing to market that product. A sponsor may be granted ODD status before submission of a marketing application for a product, but this does not have any impact on whether the drug or biologic will eventually be approved/licensed. Products intended to treat, diagnose, or prevent rare diseases go through the same rigorous scientific review process as any other drug or biologic submitted for approval or licensing.

> **Nonetheless, since the ODA was enacted, over 5,000 new drugs and biologics have received ODD, driving crucial and ongoing innovation and investment in biopharmaceuticals aimed at treating rare diseases.[5]**

A general understanding of the ODD process, the challenges around obtaining it, and the benefits it grants to stakeholders is key to successfully unlocking its benefits.

SOURCES

1 https://www.americangene.com/blog/benefits-of-fda-orphan-drug-designation-what-you-need-to-know/
2 https://www.fda.gov/media/83372/download
3 National Institutes of Health (NIH), Rare Disease Day at NIH (last updated 10 December 2020).
4 https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-01901-6
5 https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-01901-6

Applying for ODD

Requests for ODD are submitted to the Office of Orphan Products Development (OOPD) and must include robust data and information for consideration by the FDA. Documentation must be provided demonstrating that, 1) the product has the potential to treat, diagnose, or prevent a rare disease or condition; and 2) the prevalence of the disease or condition is less than 200,000 in the United States.[6] The disease or condition must be identified with specificity, as this affects the estimation of the population size. In some cases, a designation may be granted for an "orphan subset" of a larger population (non-orphan disease). However, the applicant must demonstrate that based on the characteristics of the drug it will only be safe and effective in the defined subset. Although orphan subsets are not commonly granted, improved diagnostic techniques, for example, have enabled applicants to match treatments with specific therapies and obtain orphan designation in certain cases.[7]

To demonstrate that the product has promise to treat, diagnose, or prevent the orphan disease, clinical efficacy data are preferred, but data from relevant animal models of the disease and/or in vitro data, along with a description of the mechanism of action of the drug and how it relates to the disease or condition may be acceptable.

Each applicant must submit their own evidence regarding prevalence of the disease or condition and cannot rely on the fact that FDA has granted orphan drug status to other drugs for the same disease or condition. Sources of information generally include published articles of epidemiology studies and/or data from disease registries.

If an ODD request is denied by OOPD, the applicant will receive a deficiency letter stating why the application was rejected. The sponsor has one year to respond to the letter unless an extension is requested.

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6 https://premierconsulting.com/resources/blog/fda-designations-for-rare-disease-products-part-2-orphan-drug-designation/

7 https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-01901-6

Benefits of ODD

ODD status makes drug developers eligible for benefits such as tax credits for the cost of conducting qualified clinical trials, exemption from paying a user fee at the time of NDA or BLA submission, and eligibility for a period of marketing exclusivity upon product approval. Although not limited to products with an ODD, OOPD provides a limited number of grants each year to support clinical trials in the rare disease space. Another benefit of ODD is that designated products are generally exempt from the provisions of the Pediatric Research Equity Act (PREA), which requires certain products be assessed in pediatric patients from birth to 17 years of age.

Tax Credits

The Orphan Drug Tax Credit (ODTC) promotes research spending by giving developers a 25% tax credit for qualified clinical testing expenses (QCTEs) for new orphan drugs.[8] Over 200 new orphan drugs have been made available to treat patients since introduction of the ODTC, including advancements in treatment for hereditary angioedema, cystic fibrosis, childhood acute lymphoblastic leukemia, and sickle cell anemia.[9] It had been estimated that without the ODTC, 33% fewer new orphan drugs would be approved over the next 10 years.[10] The ODTC encourages investment into research activities that carry greater risk and, potentially, impact short-term profits, so it remains a powerful tool to encourage development of new treatments for rare diseases.

User Fee Waiver

The current fee for submitting an NDA or BLA to the FDA for review can exceed $3,000,000. Under Section 526 of the Food, Drug, and Cosmetic Act, applicants can receive a waiver of that fee for an orphan designated product, provided the application does not also include an indication for a non-rare disease or condition.

Marketing Exclusivity

One of the most valuable benefits of ODD is obtaining 7 years of marketing exclusivity from the FDA upon product approval for the designated disease or condition. This means that for 7 years, FDA will not approve the same drug for the same orphan indication. It should be noted that an ODD and approval can be granted to a drug or biologic that is identical to an already approved product for the same orphan indication; however, the applicant of the identical drug must demonstrate that its product is clinically superior to the already approved drug. This regulation is designed to encourage innovation while ensuring patients access to already clinically proven treatments.[11]

8 https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-01901-6

9 https://rarediseases.org/assets/files/white papers/2015-06-17.nord-bio-ey-odtc.pdf

10 https://rarediseases.org/assets/files/white-papers/2015-06-17.nord-bio-ey-odtc.pdf

11 https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/frequently-asked-questions-faq-about-designating-orphan-product

Funding Opportunities

The FDA's Orphan Products Grants Program provides grants to clinical investigators and has led to the approval of more than 80 products. Since 2016, the FDA has funded studies that address the knowledge gaps in rare diseases to help support clinical trials and make the challenging nature of advancing treatments for rare diseases a little less so.[12]

12 https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/orphan-products-grants-program

Challenges to Developing Orphan Drugs

Although obtaining an ODD for a product has many advantages, there are still significant challenges to developing any treatment for an orphan indication. Obviously, the very nature of rare diseases means that the population of patients available to enroll in clinical trials is very small, and if there are other companies developing treatments for the same rare disease, competition for those patients can make things even more challenging. There can be a limited understanding of the natural history of the disease; small, heterogeneous and geographically dispersed patient populations; regulatory uncertainties and few, if any, prior clinical studies. The benefits of ODD play an essential role in incentivizing drug developers to embark on these challenging journeys.

Conclusion

Passage of the Orphan Drug Act and establishment of the Orphan Drug Designation program has accelerated the development of drugs and biologics for rare diseases over the past four decades. Between 1983 and 2019, over 5,000 drugs received ODD, and the number of drugs receiving ODD tripled between 2000 and 2020. The top three therapeutic areas have been oncology, neurology, and infectious diseases, and in the last decade designations for pediatric onset diseases increased significantly, as well.[13]

If your drug or biologic is intended to treat, diagnose or prevent a rare disease or condition (prevalence less than 200,000 in the U.S.) and you have demonstrated its promise to do so via appropriate studies, you are ready to proceed with an ODD application and unlock the benefits of this designation. Organizations such as Syner-G offer assistance to those developing and submitting applications, including strategic consulting, ensuring that applications meet all FDA requirements, and assistance in writing and submitting those applications. The use of experts can streamline the process and provide a critical cross-functional assessment of the application to ensure success.

For more information please visit: synergbiopharma.com

13 https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-01901-6