

The U.S. FDA Orphan Drug Product Program

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1 INTRODUCTION AND OVERVIEW

The U.S. Orphan Drug Act was signed into law in 1983 and for the first time, provided incentives for the pharmaceutical industry to develop drugs that otherwise had minimal commercial return on investment, but which are necessary, and often life-saving, for patients with rare diseases. The Orphan Drug Act is codified in 21 CFR Part 316.

There are approximately 6000 rare disorders affecting approximately 25 million Americans. More importantly, of these rare disorders, approximately 85 are life-threatening and 50 are specific to pediatric populations. From 1983 to the end of 2005, 1463 drugs received orphan drug designation. Of those, 289 (225 drugs/64 biologics) have received marketing approval and represent approximately 14 million patients treated annually. It is estimated that one new orphan drug saves approximately 211 lives per year.

The Office of Orphan Products Development (OOPD) was created within the Office of the Commissioner for two purposes. First, this office evaluates requests for orphan drug designation, and once a drug is designated, acts as an internal FDA advocate to interface with the FDA review division to help facilitate progress. The OOPD is separate from the FDA therapeutic review divisions. The review divisions are still responsible for evaluating data in terms of risk-versus-benefit considerations and approving drugs for marketing. Second, the OOPD is responsible for evaluating, awarding, and monitoring the progress of orphan drug grants. Currently, the OOPD has 21 employees overseeing approximately 100 active orphan drug grants. The office is located in the Park Lawn Building in Rockville, MD, but will be moving soon to the new FDA campus in White Oak, MD.

This document provides a brief overview of the regulatory legal history of the Orphan Drug Product Program followed by a description of the orphan drug designation process and orphan drug grant program.

2 REGULATORY LEGAL HISTORY

Since 1983, Congress has amended the Orphan Drug Act several times.

- The 1984 amendment redefined “rare disease or condition” as any disease or condition that affects less than 200,000 persons in the United States or for which there is no reasonable expectation of recovering development costs through U.S. sales.¹
- The 1985 amendment extended the marketing exclusivity to patentable as well as nonpatentable drugs and allowed for Federal grants for the clinical evaluation of orphan-designated drugs.²
- The 1988 amendment required industry sponsors to apply for orphan designation prior to submission of a marketing application for marketing approval.³

- The Orphan Drug Final Regulations were published in the *Federal Register* on December 29, 1992, and became effective 30 days later.⁴
- The FDA Modernization Act of 1997 included a provision that exempted designated orphan drug products from paying new drug application fees (\$774,000 in 2006). It also included a provision for orphan product sponsors to seek waivers for postapproval annual establishment and product fees on a case-by-case, year-by-year basis.⁵
- A further amendment to the Orphan Drug Act is being prepared by the FDA to provide clarification on the issue of appropriate medically plausible subsets of patients. It should be issued in the next few months.

The Orphan Drug Act provides a number of specific incentives for sponsors of orphan-designated drugs. These include:

- Seven years of exclusive marketing rights to the sponsor of a designated orphan drug product for the designated indication once it receives approval to market from the FDA.
- A credit against tax owed for up to 50% of qualified clinical research expenses incurred in developing a designated orphan product.⁶ This tax credit has a carry-back/carry-forward provision, which allows the sponsor to carry the excess credit back one tax year if they are unable to use part or all of the credit because of tax liability limits, and to then carry any additional unused credit forward for up to 20 tax years after the year of the credit. This later provision is important to start-up companies that may not make any profits until the drug in question is on the market. The Internal Revenue Service administers the tax credit provisions of the Orphan Drug Act. For further details, an appropriate tax attorney should be contacted.
- Eligibility to apply for orphan drug grants. In recent years, the OOPD has encouraged (through higher funding priority scores) the formation of Orphan Drug Networks for specific rare diseases.

3 ORPHAN DRUG DESIGNATION PROCESS

A sponsor may request orphan drug designation for:

- A previously unapproved drug.
- A new indication for an already marketed drug. The drug product may be a new formulation and the requisite information for a new drug product required by International Conference on Harmonisation (ICH)/FDA would need to be provided in a marketing application.
- A drug that already has orphan drug status—if the sponsor is able to provide valid evidence that their drug may be clinically superior to the first drug.

In either of the above scenarios, the sponsor would need to include patent certification in the marketing application that demonstrates that there are no patent infringement issues.

If a valid request (per the process below) for orphan designation is made, the OOPD can award an orphan drug designation for the same drug for the same rare disease or condition to more than one sponsor.

The orphan drug process is essentially a twofold process. A company or an individual can apply for orphan drug designation as described in this section without having an active clinical program. If orphan drug designation is received from the FDA, the sponsor can conduct investigative clinical studies in the United States to support the proposed designation (and thereby be eligible for the U.S. tax credits [if the NDA is eventually approved] and FDA support as designated below). However, the sponsor is not required to do all or any of the clinical development program in the United States as long as the clinical studies generally meet ICH standards and FDA expectations. A drug is not given Orphan Drug Status until an NDA marketing application is approved by the FDA Therapeutic Area Review Division (the second part of the twofold process). Once this marketing approval is obtained, the OOPD certifies the sponsor with regard to tax credits and exclusivity. Thus, from a competitive perspective, the first sponsor to obtain an approved NDA for an orphan designated product and indication obtains the postmarketing tax credits and 7 years of marketing exclusivity.

There is no formal application for an orphan drug designation. However, the regulations identify what needs to be included in a complete signed and dated document.⁷ Essentially, it is a five- to ten-page document with appropriate literature references appended (to support the incidence statements and can increase the total size of the submission to approximately one volume) and generally includes:

The specific rare disease or condition for which orphan drug designation is being requested.

- Sponsor contact, drug names, and sources.
- A description of the rare disease or condition with a medically plausible rationale for any patient subset type of approach.
- A description of the drug and the scientific rationale for the use of the drug for the rare disease or condition.
- A summary of the regulatory status and marketing history of the drug.
- Documentation (for a treatment indication for the disease or condition) that the drug will affect fewer than 200,000 people in the United States (prevalence).
- Documentation (for a prevention indication [or a vaccine or diagnostic drug] for the disease or condition) that the drug will affect fewer than 200,000 people in the United States per year (incidence).
- Alternatively, a rationale may be provided for why there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States.

Once the request for designation has been received (OOPD will send an acknowledgment of receipt letter), a formal response will take between 1 to 3 months. On notification of granting of an orphan drug designation, the name of the sponsor and the proposed rare disease or condition will be published in the *Federal Register* as part of the public record. After marketing approval, a

copy of the orphan drug application is available in the public domain under the Freedom of Information Act.

Once an orphan drug designation has been granted by the FDA, it can only be revoked if the application is found to contain false data or if there is insufficient drug to supply the market needs. Of note is that the designation cannot be revoked even if the population postdesignation exceeds the original 200,000 patient prevalence estimates. Finally, the sponsor of an orphan designated drug must provide annual updates that contain a brief summary of any ongoing or completed nonclinical or clinical studies; a description of the investigational plan for the coming year; any anticipated difficulties in development, testing, and marketing; and a brief discussion of any changes that may affect the orphan drug status of the product.

Outside of providing appropriate documentation for disease or condition prevalence estimates, the major issue in orphan drug designations becomes obtaining agreement from the OOPD on the medical plausibility of a patient population subset. Thus, if a disease or disorder that is being applied for is predicated on only a subpopulation of the entire population with the disease without a medically or scientifically/pharmacologically plausible argument, the designation is generally not granted. For example, a drug to treat muscle wasting in only one type of cancer when it also occurs in other types of cancer would not be acceptable because the condition applies to a larger patient population and mechanistically, there are no data to suggest that it differs in different cancer subpopulations.

The above medical plausibility issue has arisen from the earlier history of orphan drug designation. Currently, 3 of the top 20 best-selling drugs in the United States were initially approved for at least one orphan indication. In a related statistic, the top five drugs with orphan indications have >\$1 billion in annual sales each.

4 ORPHAN GRANT PROGRAM

Section 5 of the Orphan Drug Act authorizes appropriations for grants or contracts to assist eligible entities in defraying the costs of qualified clinical research expenses.⁸ Congress will generally allocate between \$10 and \$13.5 million to the program on an annual basis. To date, approximately 40 approved products have been primarily funded through the orphan drug grant program.

Clinical trials in any phase of development are eligible, but they need to be conducted under an active U.S. IND with the appropriate FDA therapeutic division. Phase I trials are eligible for up to \$200,000 per year for a maximum of 3 years. Phase II or III trials are eligible for up to \$350,000 per year for a maximum of 3 years. Assuming adequate enrollment progress, the OOPD preferentially renews existing grants over new ones.

Once a year, a Request for Applications is announced in the *Federal Register*. The OOPD performs an administrative review, and if acceptable, then a scientific review of the grant application. A second level review is performed by a National Advisory Council, and a priority score (similar to academic grants) is assigned. Grants are awarded by decreasing order of priority scores until the annually allocated funds have been awarded.

Annually, the OOPD receives approximately 100 applications for funding and funds approximately 15–20 new awards. A sponsor can resubmit (presumably after addressing any reviewer concerns) a grant request the following year or in subsequent years without necessarily inducing any bias by the OOPD. Approximately 50% of the grants go to academia, 25% to academic/small company collaborations, and 25% to small companies.

5 REFERENCES

- 1 Public Law No. 98-551, October 1984
- 2 Public Law No. 99-91, August 1985
- 3 Public Law No. 100-290, April 1988
- 4 *Federal Register*, December 29, 1992 (57 FR 62076)
- 5 Public Law No. 105-115, November 1997
- 6 IRS Regulations on Rare Disease Research Tax Credit. Section 1.28-1, Title 26 CFR
- 7 21 CFR Part 316.20
- 8 Public Law No. 97-414, January 4, 1983