

**Department of Health and Human Services**

**OFFICE OF  
INSPECTOR GENERAL**

**THE ORPHAN DRUG ACT  
IMPLEMENTATION AND IMPACT**



**MAY 2001  
OEI-09-00-00380**

## **OFFICE OF INSPECTOR GENERAL**

The mission of the Office of Inspector General (OIG), as mandated by Public Law 95-452, is to protect the integrity of the Department of Health and Human Services programs as well as the health and welfare of beneficiaries served by them. This statutory mission is carried out through a nationwide program of audits, investigations, inspections, sanctions, and fraud alerts. The Inspector General informs the Secretary of program and management problems and recommends legislative, regulatory, and operational approaches to correct them.

### **Office of Evaluation and Inspections**

The Office of Evaluation and Inspections (OEI) is one of several components of the Office of Inspector General. It conducts short-term management and program evaluations (called inspections) that focus on issues of concern to the Department, the Congress, and the public. The inspection reports provide findings and recommendations on the efficiency, vulnerability, and effectiveness of departmental programs.

OEI's San Francisco regional office prepared this report under the direction of Paul A. Gottlober, Regional Inspector General. Principal OEI staff included:

#### **REGION**

Cindy Lemesh, *Project Leader*  
Camille I. Harper, *Program Analyst*  
Thomas Purvis, *Program Analyst*  
Christopher Tarbell, *Program Analyst*  
Steven P. Zerebecki, *Lead Analyst*

#### **HEADQUARTERS**

Elise Stein, *Director, Public Health and Human Services*  
Genevieve Nowolinski, *Program Specialist*

To obtain copies of this report, please call the San Francisco Regional Office at 415-437-7900.

Reports are also available on the World Wide Web at our home page address:

<http://www.dhhs.gov/progorg/oei>

# EXECUTIVE SUMMARY

---

## PURPOSE

The purpose of this inspection was to assess the implementation of the Orphan Drug Act of 1983 and its impact on industry and patients.

---

## BACKGROUND

Congress passed the Orphan Drug Act of 1983 to stimulate the development of drugs for rare diseases. A rare disease is defined as a disease that affects fewer than 200,000 people in the United States. Prior to passage of this historic legislation, private industry had little incentive to invest money in the development of treatments for small patient populations, because the drugs were expected to be unprofitable. The law provides 7-year marketing exclusivity to sponsors of approved orphan products, a tax credit of 50 percent of the cost of conducting human clinical testing, and research grants for clinical testing of new therapies to treat orphan diseases. Exclusive marketing rights limit competition by preventing other companies from marketing the same version of the drug, unless they can prove clinical superiority.

The Food and Drug Administration administers the Orphan Drug Act and reviews applications for orphan designations. The Office of Orphan Products Development awards designations and administers the small grants program. The Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research review applications for marketing approval.

We reviewed FDA's database that contains information on all designations and approvals from 1983 to 2000. We interviewed regulatory affairs staff and other representatives from a purposeful sample of 36 biotechnology and pharmaceutical companies. We also interviewed representatives from 37 patient advocacy groups. We conducted a focus group with Food and Drug Administration staff and consulted with drug policy experts and representatives from trade groups. We also reviewed relevant literature.

---

## FINDINGS

**The Orphan Drug Act's incentives and the Office of Orphan Products Development's clinical superiority criteria motivate drug companies to develop orphan products.** Since Congress passed the Orphan Drug Act of 1983, the Food and Drug Administration has awarded more than 1,000 designations and approved more than 200 products.

**Advocates report that orphan products are usually accessible to patients.** Orphan products are usually accessible, although they can be costly and in limited supply. Insurance typically pays for the treatments, and companies offer patient assistance programs to help patients obtain their products.

**The Office of Orphan Products Development provides a valuable service to both companies and patients.** Companies report an excellent relationship with this office, which awards orphan product designations and disseminates public information about orphan products.

**Orphan products meet the legal prevalence limit, and most fall well below the threshold of 200,000 patients.** Average patient population has climbed since 1983 but remains well below the legal limit.

---

## CONCLUSION

Based on our survey of patient groups and sponsors and our review of the FDA database on designations and approvals, we conclude that no regulatory or legislative changes are needed at this time. Although, in some instances, companies have questioned the Office of Orphan Products Development's decisions, they generally praised the Orphan Drug Act and its implementation.

# TABLE OF CONTENTS

<b>EXECUTIVE SUMMARY</b> .....	1
<b>INTRODUCTION</b> .....	4
Purpose .....	4
Background .....	4
Methodology .....	5
<b>FINDINGS</b> .....	7
Incentives and clinical superiority .....	7
Access to orphan products .....	9
Office of Orphan Products Development .....	10
Legal prevalence limit .....	11
<b>CONCLUSION</b> .....	13

# INTRODUCTION

---

## PURPOSE

The purpose of this inspection was to assess the implementation of the Orphan Drug Act of 1983 and its impact on industry and patients.

---

## BACKGROUND

### Provisions of the Orphan Drug Act

Congress passed the Orphan Drug Act of 1983 to stimulate the development of drugs for rare diseases.<sup>1</sup> Prior to passage of this historic legislation, private industry had little incentive to invest money in the development of treatments for small patient populations, because the drugs were expected to be unprofitable. The law provides three incentives: (1) 7-year market exclusivity to sponsors<sup>2</sup> of approved orphan products, (2) a tax credit of 50 percent of the cost of conducting human clinical trials, and (3) Federal research grants for clinical testing of new therapies to treat and/or diagnose rare diseases. In 1997, Congress created an additional incentive when it granted companies developing orphan products an exemption from the usual drug application or “user” fees charged by the Food and Drug Administration (FDA). In fiscal year 2001, these fees will total almost \$500,000. Companies also may be eligible for faster review of their applications for marketing approval if their products treat a life-threatening illness. Many orphan drugs treat a serious or life-threatening disease.

Congress amended the Act in 1984, 1985, and 1988. The 1984 amendment defined a rare disease as a condition affecting fewer than 200,000 people in the United States. The threshold was an arbitrary ceiling based on the estimated prevalence of narcolepsy and multiple sclerosis. The 1985 amendment extended marketing exclusivity to patentable as well as unpatentable drugs, and the 1988 amendment required sponsors to apply for orphan designation before submitting an application for marketing approval.

The FDA administers the Orphan Drug Act and reviews applications for orphan designations. Within FDA, the Office of Orphan Products Development awards designations and administers the small grants program, which is expected to total

---

<sup>1</sup>The term “drug” refers to chemical entities and biological products used for the purpose of medical therapy or diagnosis. We use the terms “drug” and “product” interchangeably in this report.

<sup>2</sup>Since most sponsors of orphan products are pharmaceutical and biotechnology companies, we use the terms “sponsor” and “company” interchangeably in this report.

\$12.5 million in fiscal year 2001. The grants support clinical trials on the safety and effectiveness of products for rare diseases. The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) review applications for marketing approval.

To obtain an orphan designation, sponsors must submit an application to the Office of Orphan Products Development that contains details on the rare disease for which the drug will be investigated, the specific indication for the drug, a description of the drug, documentation of disease prevalence, and the regulatory and marketing status and history of the product. Although the Office's policy is that it will try to respond within 60 days of receiving an application for orphan designation, the process may take longer if the office needs more information from the sponsor. After receiving the orphan designation and conducting more research, a sponsor may seek marketing approval if the drug proves safe and effective in clinical trials. The office plays no formal role in the decision to approve a drug; CDER and CBER have this responsibility.

In 1992 FDA issued its final regulations establishing standards and procedures for granting orphan status and articulating the Agency's commitment "to protect the incentives of the Orphan Drug Act without allowing their abuse."<sup>3</sup> The final rule recognizes exclusive marketing rights as the major incentive in the Orphan Drug Act and explains the criteria a sponsor must meet to prove clinical superiority and enter the market when another product that is the same already has marketing exclusivity.<sup>4</sup>

Approximately 20 million Americans suffer from rare diseases, which number about 6,000 and include many genetic disorders as well as cancers. The prevalence of these diseases in the United States varies greatly, from as few as 300 for a rare enzyme deficiency to just under 200,000 for cancer of the thyroid gland.

---

## METHODOLOGY

We reviewed a database from FDA that contains information on all designations and approvals from 1983 to 2000. We interviewed regulatory affairs staff and other representatives from a purposeful sample of 36 biotechnology and pharmaceutical companies. We focused on companies that received multiple orphan designations. We also interviewed representatives from 37 patient advocacy groups, stratified into two groups--those for which orphan products were in development or on the market and those for which no orphan products were in development or on the market. We conducted a

---

<sup>3</sup>*Orphan Drug Regulations* (57 FR 62076), December 29, 1992 and 21 CFR Part 316 et seq.

<sup>4</sup>The FDA defined three criteria for establishing clinical superiority. The new drug must be (1) more effective than an approved orphan drug, (2) safer than an approved orphan drug, or (3) in the absence of greater effectiveness or safety, the new drug must make a major contribution to patient care.

focus group with FDA staff and consulted with drug policy experts and representatives from trade groups. We also reviewed relevant literature.

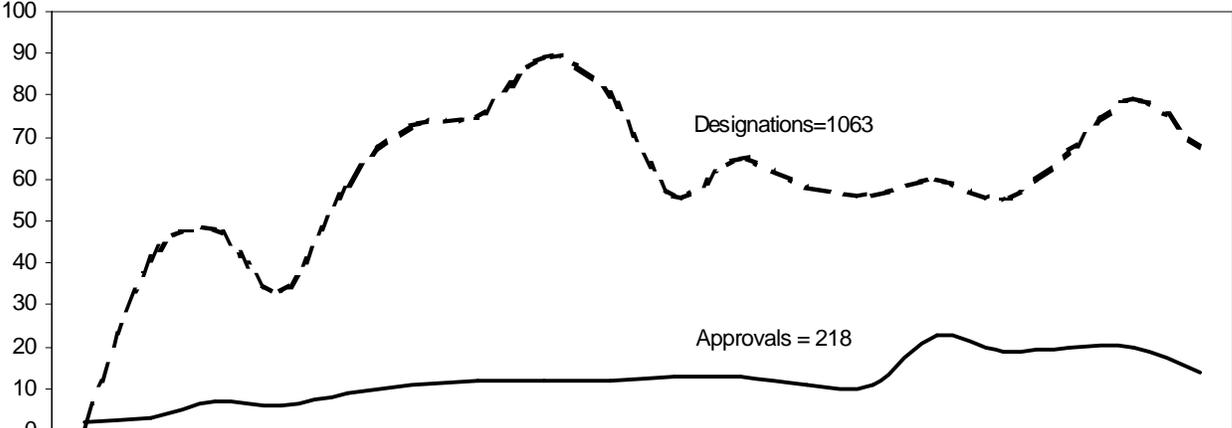
We conducted this inspection in accordance with the *Quality Standards for Inspections* issued by the President's Council on Integrity and Efficiency.

# FINDINGS

## The Orphan Drug Act’s incentives and the Office of Orphan Products Development’s clinical superiority criteria motivate companies to develop orphan products

According to FDA, the Orphan Drug Act has unquestionably stimulated the development of drugs for rare diseases. A handful of such drugs were available before 1983, but since enactment of the law the Office of Orphan Products Development has designated approximately 1,000 orphan products; over 200 of these subsequently received marketing approval (see Chart 1). Many orphan drugs, including those approved for multiple sclerosis, cystic fibrosis, and hemophilia, are considered breakthroughs.

**Chart 1**  
**Total Orphan Designations and Approvals**



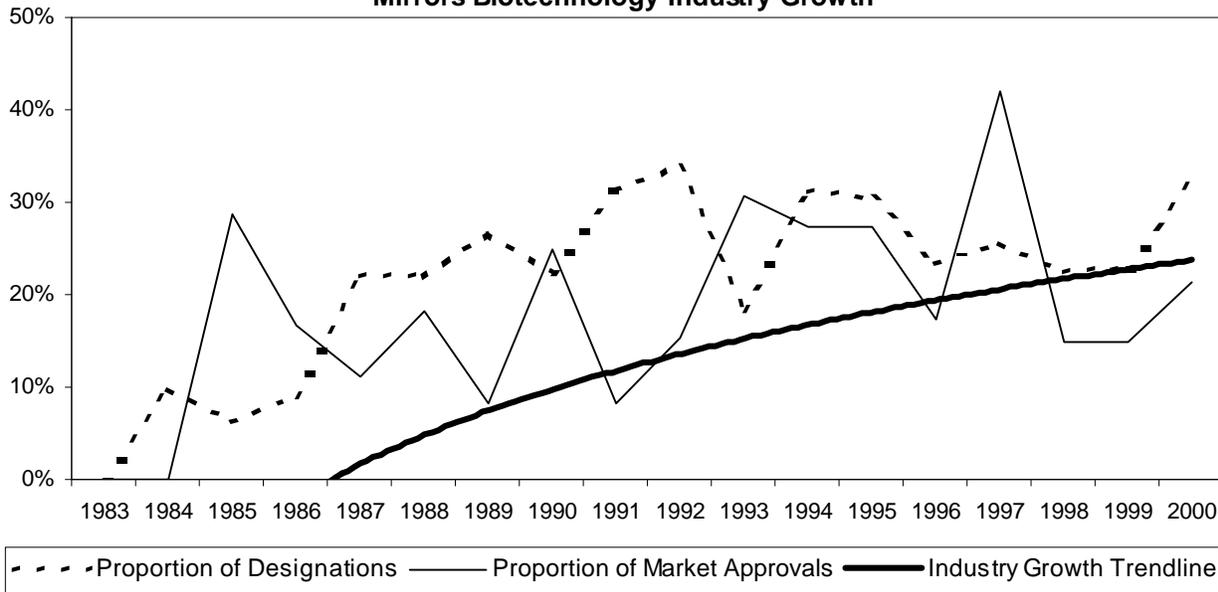
	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
Approvals	2	3	7	6	9	11	12	12	12	13	13	11	11	23	19	20	20	14
Designations	1	41	48	33	59	73	75	89	80	56	65	58	56	60	55	67	79	68

“Orphan designations” are for products that FDA has determined could be used to treat a rare disease (i.e., a condition affecting fewer than 200,000 individuals in the United States).

“Orphan approvals” are for products that FDA has determined are ready for marketing in the United States.

The Orphan Drug Act has proven particularly helpful to the biotechnology industry that emerged in the years following passage (see Chart 2).<sup>5</sup> Biotechnology involves the use of proteins, enzymes, antibodies, and other substances to treat diseases. This young, volatile industry is heavily dependent on private capital to fund research and development. The prospect of marketing exclusivity under the Orphan Drug Act helps biotechnology companies attract venture capital to support the lengthy and expensive drug development process that is

**Chart 2**  
**Growth in Biologic Orphan Products**  
**Mirrors Biotechnology Industry Growth**



estimated to take 14 years at a cost of \$300 to \$500 million.

### Marketing exclusivity remains the most important incentive

Marketing exclusivity, effective on the date of marketing approval, remains the most powerful incentive in the Orphan Drug Act, because it limits competition by prohibiting FDA from approving another version of the same orphan drug for the same indication unless the new drug is clinically superior. Other incentives, including tax credits and the waiver of user fees, are not nearly as critical as the prospect of marketing exclusivity, which is especially important to small companies trying to raise public and private capital. The lack of exclusivity, however, does not prevent companies from entering the market through conventional means. For example, we interviewed one sponsor that failed to obtain orphan designation but subsequently obtained marketing approval for its product, which is under patent. Two other sponsors failed to obtain

---

<sup>5</sup>The biotechnology industry’s annual growth was measured using the Fidelity Select Biotechnology Fund data for 1986 to 2000.

orphan designations but pursued or plan to pursue marketing approval; one sponsor's product is currently on the market, and the other sponsor has begun the clinical testing process.

## **The Office of Orphan Products Development uses clinical superiority criteria to preserve marketing exclusivity**

The Office of Orphan Products Development uses the clinical superiority criteria articulated in 1992 to preserve marketing exclusivity while allowing improved products to go to market. The market for most orphan products is not highly competitive, and, consequently, challenges to FDA's decisions regarding clinical superiority are rare. In 2000, one company challenged the Agency's decision to block its product for the treatment of multiple sclerosis from the U.S. market. The FDA allowed another company to market its treatment for the same disease because it had decided that it was clinically superior to an existing product already on the market. After congressional hearings on an amendment that would change the terms of market exclusivity, FDA submitted written testimony stating that the proposal would weaken the incentive to develop orphan products. The FDA reiterated its commitment to preserving the value of the key incentive in the orphan drug legislation.

---

## **Advocates report that orphan products are usually accessible to patients**

Most patient groups reported no problems with access to orphan products. Although the drugs can be very costly, price alone has not prevented patients from obtaining them. Supplies may be limited and, on occasion, a patient's regimen must be altered in response to the shortage.

### **Shortages rarely occur**

While the Office of Orphan Products Development has the authority to revoke marketing exclusivity if sponsors fail to produce sufficient quantities of their products, this has never happened. The office would be reluctant to revoke exclusivity, because alternative suppliers are not usually available. Orphan sponsors with exclusive marketing rights can give FDA the authority to approve competing products during the exclusivity period in the event of shortages. In fact, we interviewed one company that notified FDA of its willingness to forfeit exclusivity when its product was in short supply.

We found isolated instances of shortages. In February 2001, FDA reported that one orphan product, Depocyt, was in "limited distribution" due to "manufacturing difficulties."<sup>6</sup> Depocyt's orphan designation is for the treatment of lymphomatous

---

<sup>6</sup>Source: [www.fda.gov/cder/drug/shortages](http://www.fda.gov/cder/drug/shortages).

meningitis. Two patient groups that we interviewed reported a total of four orphan products currently in short supply. The products are used to treat emphysema in alpha-1-antitrypsin deficient patients and hemophilia. Blood-derived and recombinant products, in particular, can be especially vulnerable to supply problems. Shortages of these drugs could result in the need to adjust a patient's regimen or postpone a surgical procedure until the shortage is remedied.

## **Patients have access to even the costliest orphan products**

In passing the orphan drug legislation, Congress concluded that the benefits of access to new treatments outweighed the costs of granting a monopoly in the form of marketing exclusivity to the sponsor of an approved orphan drug. Over the years, some orphan drugs have aroused concern and sparked debate because of their prices. These drugs include some versions of human growth hormone, which can cost up to \$100,000 per year, and Alglucerase, the treatment for Gaucher's disease (an enzyme deficiency), which can cost more than \$300,000 per year. Although Congress has considered changes in the legislation because of the windfall profits of a few companies, none has passed. In many respects, the prices of orphan drugs are similar to those for comparable non-orphan drugs and, without insurance, no one could afford the costliest ones. Patients usually rely on private insurance, Medicare, and/or Medicaid to pay for their treatments.

Both companies and advocates told us that some companies offer patient assistance programs to improve access to their products. Companies may discount their products or offer them at no cost. In general, companies target the neediest populations and determine patients' eligibility for their programs based on annual income. Approximately three out of four companies that we contacted reported that they offer the programs or plan to offer them if FDA approves their orphan products. Patients may contact the companies or the National Organization for Rare Disorders (NORD), which administers some of the programs and refers patients to a variety of services. Additionally, the Pharmaceutical and Research Manufacturers of America sponsors RxHope.com, a Web-based program that helps patients obtain a variety of orphan and common drugs.

---

## **The Office of Orphan Products Development provides a valuable service to both companies and patients**

Orphan product sponsors report an excellent relationship with the Office of Orphan Products Development. Most of the sponsors we interviewed had positive comments and few reported difficulties. However, several sponsors reported that the Office took a long time to review their applications for designation. Timely designations are critical to sponsors seeking to use tax credits, since the credit takes effect from the date the product is designated. Throughout the years, the Office of Orphan Products Development has made efforts to address companies' concerns, and it has significantly decreased the time it

takes to designate orphan products. The average time the Office of Orphan Products Development takes to designate a product decreased to 160 days in 2000, down from a high of 267 days in 1996.<sup>7</sup>

Sponsors understand and accept the Office of Orphan Products Development's limited role during the review process, and some applaud its efforts to provide assistance even after their products receive designation. Sponsors complained that FDA's reviewing divisions (CDER and CBER) took too long to complete the safety and efficacy reviews. Sponsors also noted that for very rare conditions, they cannot conduct the clinical trials that FDA requires. Most acknowledged, however, that applying a different standard for the safety and efficacy of orphan products could compromise public health and safety.

The Office of Orphan Products Development compiles and disseminates important public information about orphan product development. Patients and sponsors benefit from disclosure of designation and approval information about orphan products. The Office maintains a database of product information on the Internet that patients use to identify new treatments under development and products that have been approved for their disease. The NORD uses the information to refer patients to drug companies researching treatments for rare conditions. One company told us that by publicizing the efforts of orphan sponsors, the Office of Orphan Products Development has created yet another incentive--the potential for positive relations with patients and investors.

---

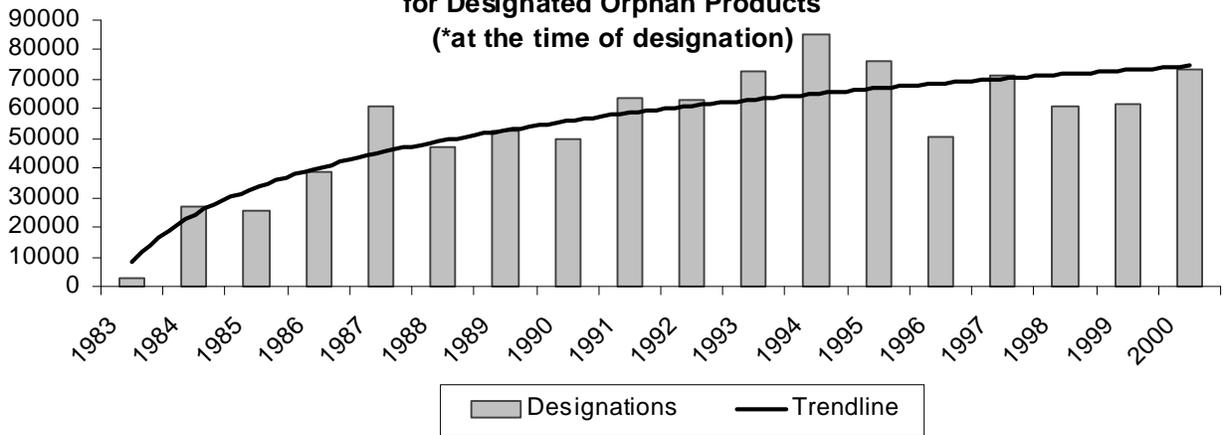
## **Orphan products meet the legal prevalence limit, and most fall well below the threshold of 200,000 patients**

Although the average patient population for designated orphan products has climbed since 1983, it remains well below the legal limit of 200,000 people in the United States. For products designated in 2000, the average prevalence was approximately 73,000 patients at the time of designation (see Chart 3, next page).

---

<sup>7</sup>Long time frames do not necessarily indicate delays on the part of the Office of Orphan Products Development; in some cases, the Office finds the application deficient and requests additional information from the sponsor.

**Chart 3**  
**Mean Patient Population\***  
**for Designated Orphan Products**  
**(\*at the time of designation)**



Sponsors applying for an orphan designation must document that the condition for which their product is intended affects fewer than 200,000 patients in the United States. Documenting patient prevalence for some very rare conditions may be a challenge. The Office of Orphan Products faces similar challenges when it attempts to verify the prevalence data that sponsors provide. Sponsors are sometimes unable to satisfy the Office of Orphan Products Development that the prevalence does not exceed the legal limit, and the Office denies the request for orphan designation. Companies can challenge the Office’s decision, but no company that we contacted had exercised this option.

# CONCLUSION

Based on our surveys of patient groups and sponsors and our review of the FDA database on designations and approvals, we conclude that no regulatory or legislative changes are needed at this time. Although, in some instances, companies have questioned the Office of Orphan Products Development's decisions, they generally praised the Orphan Drug Act and its implementation.