

An hourglass-shaped graphic with a globe inside. The top bulb is dark blue, and the bottom bulb is light blue. The globe is centered in the narrow neck of the hourglass. The top bulb is filled with a dark blue color, and the bottom bulb is filled with a light blue color. The globe is centered in the narrow neck of the hourglass.

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February 2, 2009

Congressional Research Service

Report RS20971

*Orphan Drug Act: Background and Proposed Legislation in  
the 107th Congress*

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Updated July 25, 2001

**Abstract.** The Orphan Drug Act (P.L. 97-414) provides incentives for pharmaceutical manufacturers to develop drugs, biotechnology products, and medical devices for the treatment of rare diseases and conditions. These products are commonly referred to as orphan drugs. Legislation has been introduced in the 107th Congress to modify marketing exclusivity provisions, and to accelerate and expand tax benefits for orphan drug manufacturers.

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# CRS Report for Congress

Received through the CRS Web

## Orphan Drug Act: Background and Proposed Legislation in the 107<sup>th</sup> Congress

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### Summary

The Orphan Drug Act (P.L. 97-414) was signed into law on January 4, 1983. The Act provides incentives for pharmaceutical manufacturers to develop drugs, biotechnology products, and medical devices for the treatment of rare diseases and conditions. These products are commonly referred to as orphan products. Incentives for orphan product development include marketing exclusivity for orphan drug sponsors, tax incentives, and research grants. Since the Act was passed in 1983, the Food and Drug Administration (FDA) has approved 183 new orphan products. Critics of the Act argue that, because the Act relies on market-oriented strategies to promote orphan drug development, overpricing of drugs can limit patient access to orphan drug treatment, especially among those who lack health insurance. Others argue that the Act has been very successful in finding new treatments for rare diseases and conditions, and that any changes to the incentives provided in the law would suppress research and development. Legislation has been introduced in the 107<sup>th</sup> Congress to modify marketing exclusivity provisions, and to accelerate and expand tax benefits for orphan drug manufacturers.

### Background

The Orphan Drug Act (P.L. 97-414) was signed into law on January 4, 1983.<sup>1</sup> The purpose of the law was to address congressional concerns about the lack of pharmaceuticals to treat rare diseases and conditions. According to the National Organization for Rare Disorders (NORD)<sup>2</sup>, about 25 million people in the United States suffer from an estimated 6,000 conditions known as orphan diseases. The Orphan Drug Act provides incentive for drug manufacturers to develop orphan drugs for the treatment of rare diseases and conditions. Incentives for orphan product development include

<sup>1</sup> For more information see FDA Office of Orphan Products Development Program Overview [<http://www.fda.gov/orphan/progovw.htm>].

<sup>2</sup> For more information see the NORD website [<http://www.rarediseases.org>].

marketing exclusivity for orphan drug sponsors, tax incentives, and research grants. These drugs are commonly referred to as orphan drugs<sup>3</sup> because, prior to the Act, few drug companies were willing to “adopt” products to treat these diseases. Before the early 1980's, very few orphan products had been developed because pharmaceutical companies had few financial incentives to develop products for treating small target patient populations. In addition, firms faced further difficulties in recruiting a sufficient number of subjects for clinical trials. Amendments to the Orphan Drug Act were passed by Congress in 1984, 1985 and 1988.

The original purpose of the 1983 Orphan Drug Act was to provide incentives in the development of drugs for the treatment of rare diseases that would normally be unprofitable or unpatentable. Initially, to qualify for orphan drug status, manufacturers had to demonstrate that the development of a particular orphan drug would be unprofitable. An amendment to the Act in 1984 established a numeric prevalence threshold to the definition of a rare disease or condition. To qualify for orphan drug status, a rare disease or condition was defined as any disease or condition (1) affecting less than 200,000 persons in the United States, or (2) affecting more than 200,000 persons in the United States, but for which there is no reasonable expectation that the sales of the drug treatment will recover the costs.<sup>4</sup> Prior to this amendment, a drug sponsor was required to provide financial information regardless of the size of the proposed target patient population. With the amendment, a sponsor could still seek orphan drug designation by demonstrating that the financial criteria of the law were applicable, but was not required to do so if the target patient population was less than 200,000.

In 1985, the Act was amended again, this time to extend marketing exclusivity for both patentable and unpatentable products. The purpose was to protect those products that were patentable, but whose patents would expire before or shortly after marketing approval. Many of these drugs were biotech drugs that had difficulties in obtaining patents. The earlier assumption about most orphan drugs being unpatentable was found to not always be true. Patents had been issued for many potential orphan products, but because of prolonged research, the patent protection had sometimes expired before marketing approval was obtained.<sup>5</sup>

In 1988, an amendment to the Act changed the requirement for submitting applications for orphan drug status. Under the revised Act, the application for Orphan Drug Designation now has to be made prior to the submission of an application for marketing approval, New Drug Application (NDA) or Product License Application (PLA).<sup>6</sup> Prior to the 1988 amendment, the designation request could be filed at any time

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<sup>3</sup> Congress did not use the term “orphan drug” in the actual text of the law. Instead, the statute focuses upon definitions of and treatments for “rare diseases and conditions”.

<sup>4</sup> P.L. 98-551.

<sup>5</sup> Shulman, Sheila; Bienz-Tadmor, Brigitta; Seo, Pheak Son; DiMasi, Joseph A.; and Lasagna, Louis. “Implementation of the Orphan Drug Act: 1983-1991.” *Food and Drug Law Journal*, v. 47, No. 4, 1992.

<sup>6</sup> For more information on the drug approval process, see CRS Report No. RL30989, *The U.S.* (continued...)

before the U.S. Food and Drug Administration's (FDA) approval to market the product.<sup>7</sup>

## Incentives for Orphan Product Development

A sponsor seeking to obtain orphan designation for a drug or biological product must first submit an application to the FDA Office of Orphan Products Development (OOPD), which was created as part of the Act. The OOPD administers the Act's incentives of the Act, reviews sponsors' applications for orphan designation, and administers the orphan products grant program. Approval of an orphan designation request does not alter the regulatory requirements for obtaining marketing approval.

The Act provides various incentives for manufacturers in the development of orphan drugs including marketing exclusivity for sponsors of designated orphan drugs, tax incentives, and research grants.<sup>8</sup> After obtaining marketing approval by the FDA for a designated orphan drug, a sponsor has seven years of marketing exclusivity for that product.<sup>9</sup> Marketing exclusivity may be the most motivating incentive provided by the Act. Without marketing exclusivity, unpatentable products could face competition from lower-priced generic versions of the drug. The period of exclusivity begins on the date that the marketing application is approved by the FDA and applies only to the indication for which the drug has been designated. The FDA could approve a second application for the same drug for a different use. The FDA cannot, however, approve the same drug made by another manufacturer for the same indication during the marketing exclusivity period unless it has the consent of the sponsor or the sponsor is unable to provide sufficient quantities.

Manufacturers may claim a tax credit of up to 50% for clinical research performed for designated orphan drugs. Congress extended the tax credit permanently in August 1997 (P.L. 105-34). The Internal Revenue Service administers the tax credit provisions of the Act. Another financial incentive for orphan product development is a research grants program administered by the OOPD in which researchers may compete for grants to conduct clinical trials to support the approval of orphan drugs. The objective of the grants program is to fund clinical research that will accelerate or assist in the approval of unapproved products, or unapproved new uses for marketed products that demonstrate promising uses for rare diseases or disorders. The grants program may also fund studies leading to publications on the safety and efficacy of designated orphan drugs.<sup>10</sup>

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<sup>6</sup> (...continued)

*Drug Approval Process: A Primer*, by Blanchard Randall, IV, June 1, 1961.

<sup>7</sup> OOPD Program Overview, p. 1.

<sup>8</sup> *Ibid*, pp. 2-3.

<sup>9</sup> Market exclusivity differs from patent protection and the two rights may actually conflict. See CRS Report RL30756, "Patent Law and Its Application to the Pharmaceutical Industry: An Examination of the Drug Price Competition and Patent Term Restoration Act of 1984 ("The Hatch-Waxman Act")," December 18, 2000.

<sup>10</sup> For more information see the orphan drug grants program website [<http://www.fda.gov/orphan/grants/index.htm>].

Manufacturers may request protocol assistance for research and study design assistance to ensure a successful and expeditious review process by the FDA. The Center for Drug Evaluation and Research (CDER) or the Center for Biologic Evaluation and Research (CBER) conduct the formal review of a request for protocol assistance. The OOPD ensures that the request qualifies for consideration and monitors the review process.

## Orphan Product Production

The Orphan Drug Act has led to the development of new products for the treatment of rare diseases and conditions such as cystic fibrosis, complications affecting HIV-infected people, Gaucher's disease, hemophilia, and rare forms of cancer. Since the passage of the Act, the number of orphan product designations and marketing approvals has risen considerably. To date, the FDA has granted marketing approval to 217 orphan products and designated orphan product status to 1,090 products, including drugs, biologics, and medical devices.<sup>11</sup> By contrast, in the ten years prior to the enactment of the Act, the number of orphan products that were marketed by manufacturers was 34, with only ten of these products developed by the pharmaceutical industry. The remainder came from research and development funded by the federal government.<sup>12</sup>

The low number of marketed orphan drugs that existed prior to the Act is usually attributed to the lack of financial incentives for manufacturers to develop drugs that would treat a small target patient population. The small size of the market for rare diseases, combined with the difficulty in predicting the cost of development, created few market incentives for pharmaceutical manufacturers to develop orphan drugs. The unfavorable expected return on investment did not encourage much interest in investing in the development of these products. In addition, the issue of product liability may have also limited potential interest in developing orphan drugs. The risk of adverse effects in orphan drugs may be somewhat higher than for other prescription drugs because of the smaller number of participants in clinical trials. According to one report, in 1991, liability claims had been filed against nearly one-fifth of industry-sponsored orphan products. However, because of the lack of comparable data, there is no conclusive evidence that orphan drugs have higher liability risk than other prescription drugs.<sup>13</sup>

In addition to seven years of market exclusivity, manufacturing firms that develop orphan products face no regulatory restrictions in setting prices for the product. Like other pharmaceutical products, prices are determined by market conditions. Because of the limited size of the market and the high research and development costs associated with some orphan drugs, the manufacturing process can lead to very high per unit costs. Also, the limited market size often prevents companies from acquiring economies of scale in the production process.

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<sup>11</sup> For complete list of orphan product designations and approvals see OOPD Orphan Product Designation website [<http://www.fda.gov/orphan/designat/index.htm>].

<sup>12</sup> Asbury, Carolyn H. "The Orphan Drug Act, The First 7 Years." *Journal of the American Medical Association*, v. 265, no. 7, February 20, 1991. p. 893.

<sup>13</sup> *Ibid*, p. 894.

Accurate data on the prices, sales, and profit margins for orphan products are very limited and vary by source. Because of the lack of available data, it is not possible to provide an accurate analysis on total sales, price ranges, or profit margins of orphan products. Some reports claim that orphan drugs are among the pharmaceutical industry's biggest money producers.<sup>14</sup> These reports point out that certain "blockbuster" drugs, such as a replacement enzyme treatment for Pompe disease which has a treatment cost of \$170,000 to \$340,000 per year, can be very costly. Such cases have received media attention over the years. However, other reports claim that most orphan drugs have relatively low revenues, while only a very few produce extremely high revenues. Some of the smaller biotechnology companies that have been successful in producing orphan products for the treatment of diseases, such as narcolepsy, cystic fibrosis, and Fanconi anemia, have yet to make a profit.<sup>15</sup> A 1991 report stated that 75 percent of orphan drugs earned less than \$10 million in their first year of marketing, while 20 percent had sales of more than \$26 million. Two products had sales in excess of \$100 million. The report found that orphan drug sales had a highly skewed distribution that was similar to the distribution of sales revenues for other pharmaceutical sales.<sup>16</sup>

The financial incentives provided by the Act appear to have engendered only limited interest from the large pharmaceutical firms. According to John McCormick, M.D., Deputy Director of the OOPD, only 15 percent of applications for orphan drug designation have come from the larger pharmaceutical companies. He believes that the provisions of the Act have encouraged the creation of small companies involved in orphan drug production, especially in the American biotechnology industry.<sup>17</sup>

## Policy Issues and Concerns

Over the years, Congress has debated several amendments to the Act that would prevent companies from using orphan drug status as a means to charge excessive prices or make excessive profits. Some critics of the Orphan Drug Act argue that because the law relies exclusively on market-oriented strategies to promote orphan drug development, it has led to overpricing of drugs. They argue that many orphan drugs are often overpriced, which can limit patient access to affordable treatment, especially for those patients who do not have health insurance coverage. Critics also argue that the definition of an orphan drug, one that will treat a disease affecting 200,000 people or less, does not necessarily mean that the drug will not be profitable. In response, other analysts have said that dramatic changes to the Act's incentives would suppress research on orphan drugs, which, in the long run, would lead to fewer drugs being developed to treat rare diseases.<sup>18</sup> They also argue that any retroactive termination of orphan exclusivity by Congress would

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<sup>14</sup> Denise Gray. "In Quest to Cure Rare Diseases, Some Get Left Out." *The New York Times* On the Web, November 16, 1999. pp. 1-5.

<sup>15</sup> Licking, Ellen. Jekyll and Hyde Drug. *Business Week* Online, October 23, 2000. pp. 1-3.

<sup>16</sup> *Implementation of the Orphan Drug Act: 1983-1991*, pp. 379-380.

<sup>17</sup> Henkel, John. "Orphan Drug Law Matures into Medical Mainstay." *FDA Consumer*, May/June 1999. p. 3.

<sup>18</sup> Thamer, Mae; Brennan, Niall; Semansky, Rafael. "A Cross-National Comparison of Orphan Drug Policies: Implications for the U.S. Orphan Drug Act." *Journal of Health Politics, Policy, and Law*, Vol. 23, No. 2, April 1998. p. 267.

constitute an uncompensated “taking of a property right in violation of the Fifth Amendment.”<sup>19</sup>

Since its enactment in 1983, Congress has considered amending the Orphan Drug Act on several occasions. In the late 1980s and early 1990s, proposed amendments to the Act addressed concerns that orphan products developed with federal assistance were producing excessive profits for drug companies. Proposed changes to the Act included sales cap provisions, but these were not passed. Some analysts cautioned that such changes could damage the incentives and success of the Act.<sup>20</sup> One proposal, which limited market exclusivity, was passed by Congress in October 1990. It was subsequently vetoed by President Bush, who believed that it would weaken the exclusivity provision and discourage the development of orphan drugs. The amendment would have allowed more than one manufacturer of the same drug to share market exclusivity of the drug and terminated market exclusivity if the prevalence of the disease increased to more than 200,000 people.<sup>21</sup> The President believed that changing the provisions on population limit would send a “troublesome signal of unilateral rule change to developers.”<sup>22</sup>

**Legislation in the 107<sup>th</sup> Congress.** In the 107<sup>th</sup> Congress, measures have been introduced to modify some provisions of the Orphan Drug Act. The Orphan Drug Program Improvement Act of 2001 (H.R. 386) was introduced to amend the Federal Food, Drug, and Cosmetic Act to require that an orphan drug’s designation and approved labeling conform with each other, and to modify the scope of marketing exclusivity for clinically superior orphan products. The bill would require that the description of the disease or condition on the labeling for an orphan product be the same as the description on the OOPD list of orphan drug designations. In addition, the bill would limit marketing exclusivity awarded to a clinically superior product so that the exclusivity would apply only to the characteristic or feature that rendered the drug clinically superior to a previously approved drug. The bill was referred to the House Subcommittee on Health.

The Orphan Drug Tax Credit Act of 2001 (H.R. 1298) was introduced to amend the Internal Revenue Code to move up the date for which the developer may claim the credit for clinical testing of orphan drugs from the date of designation to the date the application for designation was filed. Another measure, the American Breakthrough Research Act of 2001 (H.R. 2153 and S. 1049), would provide manufacturers the option to exchange research-related tax benefits for a refundable tax credit. H.R. 1298 and H.R. 2153 were referred to the House Ways and Means Committee. S. 1049 was referred to the Senate Finance Committee.

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<sup>19</sup> *Implementation of the Orphan Drug Act: 1983-1991*, p. 368.

<sup>20</sup> Levitt, Joseph A.; Kelsey, John V. “The Orphan Drug Regulations and Related Issues.” *Food and Drug Law Journal*, Vol. 48, No. 4, 1993. pp. 530-531.

<sup>21</sup> *Implementation of the Orphan Drug Act: 1983-1991*, p. 367.

<sup>22</sup> *The Orphan Drug Act, The First 7 Years*, p. 896.