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The Orphan Drug Act: Legal Overview and Policy Considerations

Just under half of all Food and Drug Administration (FDA) drug approvals between 2017 and 2021 were for orphan drugs, which are drugs used to treat rare diseases or conditions. Historically, orphan drugs received little attention from drug manufacturers, as their development was often financially infeasible due to high cost and an inability to recoup those costs as a result of small patient populations.

Congress enacted the Orphan Drug Act (ODA) (P.L. 97-414) in 1983 as a way to "facilitate the development of drugs for rare diseases or conditions." The ODA attempts to balance the competing interests of pharmaceutical companies and patients with rare diseases by creating financial incentives for companies to develop and market orphan drugs in the United States. The ODA amends the Food, Drug, and Cosmetic Act (FDCA) to create two primary mechanisms to encourage orphan drug development: orphan-drug designation (described in 42 U.S.C. § 360bb), and market exclusivity (described in 42 U.S.C. § 360cc). Since the ODA's enactment, the FDA has approved more than 500 orphan drugs. The mechanisms of designation and market exclusivity, explained further below, are designed to spur continued innovation in the orphan drug field.

Orphan-Drug Designation

Drug manufacturers or sponsors may apply to obtain an orphan-drug designation for drugs in development at any time before the drug receives FDA approval. If granted, designation enables a manufacturer to access various forms of financial assistance for drug research and development, including tax credits for clinical testing costs, grant funding to cover research expenses, and a waiver of the FDA's prescription drug user fee if the manufacturer submits an application for FDA approval of the drug.

Orphan-drug designations are granted by the FDA if the drug is currently being or will be investigated for a rare disease or condition and the approval or licensure of the drug would be for the treatment of that disease or condition. The FDCA defines "rare disease or condition" as one either that affects fewer than 200,000 people in the United States or for which a manufacturer has no reasonable expectation of recovering drug treatment research and development costs.

The ODA's orphan-drug designation was designed to encourage innovation and research in the orphan drug field. A manufacturer may seek an orphan-drug designation for either a previously unapproved drug or a new use of a drug that is already FDA approved. More than one manufacturer may be granted an orphan-drug designation for the same drug. Additionally, if the FDA has already designated and approved an orphan drug for a particular rare disease or condition, a manufacturer may receive a subsequent orphan designation for a drug with the same active ingredient or active moiety that is used to treat the same disease or condition if it can present a "plausible hypothesis" that the second drug is clinically superior to the first.

Orphan-Drug Exclusivity

The FDA may grant regulatory exclusivity to certain products upon approval or licensure. During the exclusivity period, the FDA may not approve another application for a competing product. For example, if a drug manufacturer receives FDA approval to market a drug designated as an orphan drug, the manufacturer is generally entitled to a seven-year market exclusivity period. During the exclusivity period, the FDA cannot approve an application from a different drug manufacturer to market the same drug for the same disease or condition.

Similar to the ODA's orphan-drug designation provisions, its market exclusivity provision was designed to spur innovation in the orphan drug arena. For example, the statute provides an exception to the seven-year exclusivity period so that the FDA may approve a competing orphan drug if it finds that the manufacturer of the original orphan drug cannot provide sufficient quantities of the drug to meet its demand. Following some litigation concerning the scope of the ODA's exclusivity provisions, Congress also codified the FDA's policy of clinical superiority. After the seven-year exclusivity period expires, the FDA will not grant another market exclusivity to a subsequent manufacturer of the same orphan drug for the same disease or condition unless the second drug is clinically superior to the first. This requirement ensures that the seven-year exclusivity is not perpetual, and it encourages manufacturers to continue researching new and improved treatments, which in turn is intended to benefit patients.

The FDA's implementing regulations have narrowly interpreted the ODA's exclusivity provision in Section 360cc. For example, the regulations state that exclusivity protects only the approved indication or use of a designated drug, and thus the FDA allows two different manufacturers to have orphan-drug exclusivity for the same drug for the same disease, if the drug is indicated for use in different patient populations. In other words, the FDA treats orphan-drug exclusivity as specific to the designated use or indication of the drug, rather than extending exclusivity to cover multiple indications for use. At least one federal circuit court has expressed disagreement with this interpretation of the ODA, which the FDA still uses (*see, e.g., Catalyst Pharmaceuticals Inc. v. Becerra*, 14 F.4th

1299 (11th Cir. 2021)). For more information on the *Catalyst* case, *see* CRS Report R47653, *The Orphan Drug Act and Catalyst Pharmaceuticals, Inc., v. Becerra*, by Hannah-Alise Rogers.

Policy Considerations and Proposals for Congress

Various stakeholders have identified concerns regarding the FDA's administration of the Orphan Drug Designation Program. These concerns include inconsistencies in the FDA's review and approval processes, the high cost of orphan medications potentially leading to limited patient utility, potential misalignment of incentives under the Orphan Drug Program, and a disproportionately high number of authorized orphan drug products that are aimed at treating particular therapeutic areas. This section reviews some of these concerns and highlights possible considerations for congressional action.

Issues

Inconsistencies in the FDA Review and Approval Process

A 2018 report from the Government Accountability Office (GAO) found several inconsistencies with the FDA's review process for orphan drug products. For example, in its review, GAO found that the FDA had granted orphan-drug designation to multiple applications that were missing required information. GAO recommended that the FDA take action to improve the consistency of its reviews, including by clarifying some of the guidance its reviewers use to evaluate orphan drug applications, which the FDA implemented the following year.

High Cost of Approved Medications

High prices may lead to decreased utilization of orphan drug products, which may impact patient health outcomes. For example, a 2023 study assessing treatment costs of newly approved drugs at market entry from 2017 to 2021 indicated that drug treatment costs were higher for patients who used orphan drugs than for those who did not. This study analyzed the treatment costs of 242 drugs approved between 2017 and 2021, including 118 orphan drugs, and calculated the median treatment cost for an orphan drug at more than $218,000, while the treatment cost for non-orphan drugs was just under $13,000.

Potential Misalignment of Incentives Under the Orphan Drug Program

Various stakeholders have noted instances of manufacturers obtaining multiple orphan designations and associated incentives for the same drug product, as well as obtaining orphan designations for drugs that are also used to treat more common conditions. While the ODA's incentives may motivate some drug manufacturers to develop products with multiple indications for use, some stakeholders have expressed concerns regarding this practice. For example, a study published in 2024 found that between 1990 and 2022, of the 491 novel orphan drugs that were approved, 100 were indicated for use in both rare and common diseases. The study also reported that of the 73 orphan drugs that were among the top globally selling branded drugs in 2021, 34 were approved to treat both rare and common diseases, suggesting that these products may represent a lucrative opportunity for manufacturers.

Overrepresentation of Orphan Drug Products in Certain Disease Areas

A 2018 GAO report indicated that between 2008 and 2017, the FDA received a total of 3,690 orphan-drug designation applications. Of those, 3,491 had a therapeutic area captured in FDA's internal database. These applications had a significant focus on smaller patient populations and specific therapeutic areas. Approximately 71% of the applications targeted diseases affecting no more than 100,000 individuals, and half were aimed at populations of 50,000 or fewer. Over half of these applications were concentrated in the following therapeutic areas: oncology (30%), neurology (13%), hematology (7%), and gastroenterology and liver (6%) products. The remaining 44% were dispersed across 37 other therapeutic areas, each area representing 5% or fewer of the total applications. A more recent study estimated that there are approximately 7,000-10,000 rare diseases that cumulatively affect more than 30 million Americans. That study further found that 4% to 6% of rare diseases have an FDA-approved drug and that up to 15% of rare diseases may have at least one drug that has shown promise in development.

Legislative and Policy Proposals

Researchers and other stakeholders have suggested various policy options for optimizing the ODA. Some of the reforms suggested include revising the definitions used for rare diseases and orphan drugs, directing the development of patient assistance programs to ensure eligible patients have an affordable supply of medication, directing the creation of mechanisms to better collect real-world evidence stemming from the use of these medications via patient registries, and ensuring payor coverage of orphan drugs. Other stakeholders have suggested reviewing the incentivization model for orphan drugs and have proposed that a realignment of these incentives may allow the federal government to both ensure that these products are being developed for more rare diseases and that prices remain affordable to patients. Some of these stakeholders have also suggested reviewing and limiting the market exclusivity granted by the ODA, including granting market exclusivity only for drugs whose combined population across all orphan indications is fewer than 200,000 individuals and granting market exclusivity only for those drugs that exclusively treat orphan populations.

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