

Catalyst Pharmaceuticals, Inc. v. Becerra

SARA W. KOBLITZ*

WHY IT MADE THE LIST

The Orphan Drug Act of 1983 (the “Orphan Drug Act”) provides incentives to encourage development of treatments for rare diseases affecting less than 200,000 patients in the United States.¹ Chief among those incentives is a seven-year period of market exclusivity awarded upon approval of a drug designated for the treatment of a rare disease or condition (“orphan condition”) by the U.S. Food and Drug Administration (FDA).² By statute, this exclusivity precludes FDA from approving another application “for the same drug for the same disease or condition” for seven years after approval of the orphan-designated drug.³ For thirty years, FDA has interpreted the language “same disease or condition” in the context of orphan drug exclusivity as the indication for which the designated drug was actually approved.⁴ Consequently, the scope of orphan drug exclusivity has been narrow, protecting against competition from the “same drug” for only the same “use or indication,” rather than the more expansive “disease or condition.”⁵

In *Catalyst v. Becerra*, the Eleventh Circuit upended this nearly thirty year practice when it determined that FDA’s interpretation of the phrase “same disease or condition” as same “use or indication” contravened the plain language of the Orphan Drug Act.⁶ In September 2021, the Eleventh Circuit reversed a Southern District of Florida decision holding that the statutory phrase “same disease or condition” in the Orphan Drug Act is ambiguous and overturned its consequent deference to FDA’s interpretation of the phrase to mean “use or indication” to define the scope of orphan drug exclusivity.⁷ Accordingly, the Eleventh Circuit held that FDA’s narrow interpretation of the scope of orphan drug exclusivity must be set aside, and along with it FDA’s approval of the drug at issue in this case, as it is “the same drug” for the

* Sara W. Koblitz is a director at Hyman, Phelps & McNamara, P.C., where she advises drug and device manufacturers on applicable regulatory requirements under the Federal Food, Drug, and Cosmetic Act and Public Health Service Act, with a specific focus on the Hatch-Waxman Act, the Orphan Drug Act, and the Biologics Price Competition and Innovation Act.

¹ Orphan Drug Act of 1983, Pub. L. No. 97-414, 96 Stat 2049 (Jan. 4, 1983).

² 21 U.S.C. § 360cc(a).

³ *Id.*

⁴ *See* 21 C.F.R. § 316.3(b)(12) (Dec. 29, 1992); *see also* Orphan Drug Regulations, 56 Fed. Reg. 3,338 (explaining that the Orphan Drug Act “provides conditions under which a sponsor of an approved orphan drug enjoys exclusive approval for that drug for the orphan indication for 7 years following the date of the drug’s approval for marketing”) (Jan. 29, 1991).

⁵ *See id.*; *Catalyst Pharms., Inc. v. Becerra*, 14 F.4th 1299, 1307 (11th Cir. 2021).

⁶ *Catalyst*, 14 F.4th at 1307.

⁷ *Id.* at 1306.

“same disease or condition” as an orphan-protected drug but for a different “use or indication”⁸

Effectively, the *Catalyst v. Becerra* decision expands the scope of orphan drug exclusivity but, depending on how FDA implements it, could also limit its availability as FDA adjusts to the new interpretation of the Orphan Drug Act’s exclusivity provisions. Barring any legislative action, *Catalyst v. Becerra* will force FDA to revisit its approach to orphan drug designation and exclusivity regulations.

DISCUSSION

Legal Background

Enacted in 1983, the Orphan Drug Act amended the Federal Food, Drug, and Cosmetic Act (FDCA) to encourage the development of drugs for rare diseases and conditions.⁹ Because so few patients are affected by any given rare disease or condition, Congress recognized that a sponsor would incur financial loss in developing a drug for such a limited patient population, which would discourage innovation in this area.¹⁰ To reduce the costs of development and encourage investment in orphan drugs, Congress adopted the Orphan Drug Act.¹¹

The Orphan Drug Act provides a variety of benefits to sponsors of drugs intended to treat rare diseases or conditions. In addition to grants and tax credits for developing treatments for orphan conditions, the Orphan Drug Act awards a period of seven years of marketing exclusivity upon approval of an orphan drug during which FDA cannot approve another version of the “same drug for the same disease or condition” (“orphan drug exclusivity”).¹² Eligibility for these incentives hinges on designation as an orphan drug early in the drug development process.¹³ To receive such a designation, a manufacturer or sponsor submits a written request for designation to FDA demonstrating that a drug treats a “rare disease or condition” (i.e., an “orphan drug”), which is defined by statute as a condition that “affects less than 200,000 persons in the United States” or “affects more than 200,000 persons in the United States” but “for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.”¹⁴ Assuming that the sponsor establishes a medically plausible hypothesis of effectiveness in a demonstrably orphan condition, FDA will designate the drug as an orphan drug for that specific disease or condition.¹⁵

Once FDA approves a marketing application for an orphan-designated drug, the agency may not approve another company’s version of the “same drug” for the “same

⁸ *Id.* at 1312–13.

⁹ Orphan Drug Act of 1983, Pub. L. 97-414, 96 Stat. 2049 (codified as amended at 21 U.S.C. §§ 360aa–360ee) (Jan. 4, 1983).

¹⁰ *Id.* at § 1.

¹¹ *Id.*

¹² 21 U.S.C. § 360cc(a).

¹³ *Id.* at § 360bb.

¹⁴ *Id.* at § 360bb (a)(2).

¹⁵ 21 C.F.R. § 316.20(b)(4).

disease or condition” for seven years.¹⁶ There are, however, three narrow exceptions to this exclusivity bar: 1) FDA may only approve another sponsor’s drug if there is not enough of the initially approved orphan product to supply the market; 2) if the sponsor of the drug protected by orphan drug exclusivity consents; or 3) if the subsequent drug is “different” from the approved orphan drug.¹⁷ A drug is “different” from an approved orphan drug if it is chemically or structurally distinct from an approved orphan drug. However, even a drug that is structurally “the same” as an approved orphan drug may be approved for the same condition if it is “clinically superior” to the approved orphan drug. Sponsors must prove that the drug is clinically superior to overcome (or “break”) orphan drug exclusivity.¹⁸

Factual Background

Long used to treat Lambert-Eaton myasthenic syndrome (LEMS), a condition affecting roughly 950 to 1,300 adult patients and a “couple dozen” pediatric patients in the United States, FDA granted amifampridine orphan drug designation for use in LEMS first in 1990 upon request by Jacobus Pharmaceutical Company, Inc. (“Jacobus”), and again upon request by Catalyst Pharmaceuticals, Inc. (“Catalyst”) in 2009.¹⁹ The two companies raced for approval with each submitting its New Drug Application (NDA) in early 2018.²⁰ Catalyst won the race for approval, and FDA approved Catalyst’s orphan-designated drug product, called Firdapse (amifampridine), in November 2018 for the treatment of LEMS in adults. Firdapse was awarded seven years of orphan drug exclusivity pursuant to the Orphan Drug Act.²¹

Notwithstanding the orphan drug exclusivity barring FDA from approving another amifampridine product for the treatment of LEMS, FDA did just that when it approved Jacobus’s NDA in 2019.²² Rather than adult patients, however, Jacobus’s amifampridine product, called Ruzurgi, was approved only for use in the very small group of pediatric LEMS patients.²³

The path to approval for Ruzurgi was unusual. After FDA approved Catalyst’s Firdapse, much concern was raised about pricing.²⁴ Senators “investigated” the price of Firdapse and urged FDA to enable access to more affordable versions of amifampridine;²⁵ more affordable versions of amifampridine included Ruzurgi, which Jacobus had been giving away for free for many years under an expanded access program.²⁶ FDA’s hands were tied, though: due to the Firdapse orphan drug exclusivity, FDA could not approve the “same drug for the same disease or condition”

¹⁶ *Id.* at § 360cc(a).

¹⁷ *Id.* at § 360cc(b).

¹⁸ *Id.*

¹⁹ Catalyst Pharms., Inc. v. Becerra, 14 F.4th at 1304 (11th Cir. 2021).

²⁰ *Id.*

²¹ *Id.*

²² *Id.* at 1304–05.

²³ *Id.*

²⁴ Press Release, Sen. Bernie Sanders, Sanders Investigates a \$375,000 Price Spike on Old Drug (Feb. 4, 2019).

²⁵ *Id.*; Br. Appellant Catalyst, Catalyst Pharms., Inc. v. Alex Azar et al., Docket No. 20-13922 at 14–15 (S.D. Fla. Nov. 13, 2020).

²⁶ *Catalyst*, 14 F.4th at 1304.

as Firdapse, and thus could not approve Ruzurgi for the treatment of adult LEMS patients.²⁷

FDA, of its own volition, administratively divided the Ruzurgi NDA into two parts—one for the treatment of LEMS in pediatric patients and the other for adult patients—“to allow for independent action in these populations” even though Jacobus’s Ruzurgi NDA sought approval for all LEMS patients.²⁸ Approval for pediatric patients would not be blocked by orphan drug exclusivity, FDA determined, because treatment of the pediatric population constituted a different “use or indication” from Firdapse’s indication of LEMS in adult patients, and thus fell outside of the scope of the orphan drug exclusivity applicable to Firdapse.²⁹ With this reasoning, FDA approved Ruzurgi for the treatment of pediatric LEMS in May 2019.³⁰ Approval was based on clinical data solely in adults as Jacobus had never performed studies in pediatric patients, and pediatric safety was based on data from Jacobus’s expanded access program.³¹

Court Decision

Catalyst sued FDA in the Southern District of Florida alleging that the approval of Ruzurgi violated the Administrative Procedure Act (APA) and demanded that the court vacate FDA’s approval of Ruzurgi.³² Catalyst argued that, under the plain language of the Orphan Drug Act, FDA could not approve Ruzurgi because it is the “same drug” for the “same disease or condition” as Firdapse.³³ Catalyst also argued that the Ruzurgi labeling is false or misleading because it suggests that Ruzurgi can be used in adults—the patient population for which Firdapse has exclusivity— notwithstanding the fact that Ruzurgi obtained approval only for pediatric patients.³⁴ Jacobus intervened.³⁵

All parties agreed that Firdapse and Ruzurgi meet the definition of “same drug” under the Orphan Drug Act and even agreed that LEMS is a single disease rather than two distinct conditions—one in pediatric patients and one in adult patients.³⁶ The parties, however, disagreed as to whether FDA’s interpretation of the phrase “same disease or condition” in the Orphan Drug Act as same “use or indication” was reasonable.³⁷ A magistrate judge found that the plain language in the Orphan Drug Act is ambiguous, as the Orphan Drug Act is “unclear whether [“same disease or condition”] refers to the use for which the drug is approved after it submits its NDA.”³⁸ The magistrate judge then concluded that FDA’s interpretation was reasonable and

²⁷ *Id.* at 1304–05.

²⁸ *Id.*

²⁹ *Id.* at 1305.

³⁰ *Id.* at 1304–05.

³¹ *Id.* at 1305.

³² *Id.*

³³ *Id.*

³⁴ *Id.*

³⁵ *Id.*

³⁶ *Id.* at 1306.

³⁷ *Id.*

³⁸ *Id.*

should be afforded deference and recommended granting summary judgement to FDA.³⁹ The district court agreed, adopted the magistrate’s recommendation in full, and dismissed the case.⁴⁰

Catalyst appealed the district court’s decision, and the Eleventh Circuit reviewed Catalyst’s challenge to the agency action *de novo*.⁴¹ On appeal, Catalyst argued that the district court erred in finding the plain language of the “same disease and condition” ambiguous; even if that language is ambiguous, Catalyst argued that FDA’s interpretation limiting that phrase to “use or indications” was unreasonable.⁴² Finally, Catalyst reiterated its argument that the Ruzurgi labeling violated the FDCA’s labeling requirements.⁴³ Ultimately, the court addressed only the statutory argument, as the court determined that FDA’s interpretation clearly violated the plain language of the statutory text and reversed the district court.⁴⁴

Evaluating the term “same drug or condition” under the well-established canons of statutory interpretation, the court analyzed the plain and usual meaning of the term in the context of the Orphan Drug Act.⁴⁵ The word “same” in the Act, the court explained, is used to mean “the one under discussion or already referred to.”⁴⁶ The only “disease or condition” already referred to in the exclusivity provision of the Orphan Drug Act as codified at 21 U.S.C. § 360cc(a) is the “rare disease or condition” for which the drug was “designated” pursuant to the Act’s provisions codified in 21 U.S.C. § 360bb.⁴⁷ Thus, the court concluded, the “same drug or condition” in the exclusivity provision can be read only in one way: the “same disease or condition” for purposes of awarding exclusivity under 21 U.S.C. § 360cc refers specifically to the “rare disease or condition” designated under § 360bb.⁴⁸ Consequently, the court explained, the scope of the orphan drug exclusivity applies to the entire rare disease or condition—not just the “use or indication” for which the product is approved.⁴⁹

Applying the plain language of the term “same disease or condition” to analyze the scope of the orphan drug exclusivity protecting Firdapse, the court reasoned that if, as all parties agreed, LEMS is a single condition—rather than two separate conditions in pediatric patients and adults—then *any* amifampridine used for LEMS is blocked by the Firdapse exclusivity, regardless of patient age.⁵⁰ Under the statute, therefore, FDA should not have approved Ruzurgi for any LEMS patient population until the expiration of the Firdapse exclusivity.⁵¹ Thus, FDA’s approval of Ruzurgi contradicted the unambiguous language of the Orphan Drug Act, and as a result, “FDA’s agency

³⁹ *Id.*

⁴⁰ *Id.*

⁴¹ *Id.*

⁴² *Id.*

⁴³ *Id.*

⁴⁴ *Id.*

⁴⁵ *Id.* at 1307.

⁴⁶ *Id.* at 1308.

⁴⁷ *Id.*

⁴⁸ *Id.*

⁴⁹ *Id.*

⁵⁰ *Id.*

⁵¹ *Id.*

action was arbitrary, capricious, and not in accordance with the law” in violation of the APA.⁵²

IMPACT OF THE DECISION

The court’s ruling here upsets FDA’s decades-long interpretation of the scope of orphan drug exclusivity. FDA had, since 1992, interpreted “same drug” in the context of exclusivity as limited to the “indication or use” for which the orphan drug product was approved and codified that longstanding interpretation in 2013.⁵³ The intent of this approach was to “permit multiple orphan-drug exclusive approvals for multiple subsets of the same underlying orphan disease or condition,” which the agency believed “is consistent with the purpose of the Orphan Drug Act because it provides an important incentive for one or more sponsors to develop, or to continue to develop, a potentially promising drug for use in all persons affected by a rare disease or condition, rather than in just a subset of that orphan population, even after the drug has been approved for a different subset of the population with the disease or condition.”⁵⁴ But under this decision, that approach contravenes the plain language of the Orphan Drug Act and violates the APA.

This decision undoubtedly increases the value of orphan drug exclusivity. With the significant expansion of the scope of orphan drug exclusivity to include the entire disease or condition—rather than the indication alone—such exclusivity would block approval of the same drug even if the exclusivity-protected orphan drug does not treat a given subpopulation. Such expansive market protection would preserve the intended incentive and impede maneuvers to circumvent orphan exclusivity through subsets and carve-outs. In turn, the expansive orphan drug exclusivity interpretation would provide more assurances that an orphan drug sponsor could recoup its investment in an otherwise (likely) unprofitable drug, which would thereby increase incentives to develop products for underserved patients. It would also serve to discourage FDA from deliberately undermining existing exclusivity by artificially subsetting a patient population in response to congressional pressure, as Catalyst alleged the agency did here.

However, the expansion of orphan drug exclusivity to block approval of the entire designated disease or condition could also limit treatment options for patients where few exist. Patients that cannot be treated by a drug that is protected by orphan exclusivity—if, for example, the drug is unsafe or ineffective in that orphan subset (i.e., the patient can’t metabolize an oral drug)—but could be treated by another dosage form or salt would not have those options until the expiration of the orphan drug exclusivity. This scenario would encourage the use off-label or compounded formulations if no other treatments are available. Off-label use and compounded formulations provide no safety assurances, raising risks for already-vulnerable patients.⁵⁵

⁵² *Id.* at 1312–13.

⁵³ See 76 Fed. Reg. 64,868, 64,870–71 (Oct. 19, 2011) (“The scope of orphan exclusive approval for a designated drug is limited to the approved indication or use, even if the underlying orphan designation is broader.”); 21 C.F.R. § 316.31(b).

⁵⁴ 76 Fed. Reg. at 64,871.

⁵⁵ CONG. RSCH. SERV., R45792, OFF-LABEL USE OF PRESCRIPTION DRUGS (Feb. 23, 2021), <https://sgp.fas.org/crs/misc/R45792.pdf>; U.S. FOOD & DRUG ADMIN., MEMORANDUM, PUBLIC HEALTH

Importantly, the impact does not only affect orphan drug *exclusivity*; it also affects orphan drug *designation*. This may seem like a distinction without a difference, but it is the designation that provides tax credits, grants, user fee exemptions, and FDA development assistance.⁵⁶ Facilitating access to these benefits, orphan drug designation was intended to be granted liberally,⁵⁷ but expansion of exclusivity could cause FDA to scrutinize requests for designation more heavily, as the designated condition now determines the scope of exclusivity. FDA could do this simply by raising the burden of proof required to demonstrate a scientific rationale that the proposed product will treat the broader orphan condition rather than a subset.⁵⁸ And, in so doing, FDA effectively would limit access to important drug development resources.

Further, to limit overbroad exclusivity, FDA could subdivide a given condition into multiple conditions. This approach also raises policy concerns, as it could encourage further attempts to subtype (known as “salami slicing”) conditions to obtain exclusivity where it has already been exhausted.⁵⁹ Such salami slicing concerns have raised concerns about “gaming” the orphan drug process with critics pointing to several instances in which FDA has granted multiple periods of orphan drug exclusivity to the same drug where the drug’s sponsor obtains serial approvals for either different segments (i.e., indications) of the designated rare disease or condition, or where a drug’s indication evolves into something new, shedding and subsuming the previous indication statement (e.g., different disease stages or different lines of therapy).

Finally, the court’s decision in *Catalyst v. Becerra* could also lead to a slew of new Orphan Drug Act litigation. In some cases, particularly where drugs were designated and approved prior to this case, orphan drug exclusivity may now extend significantly farther than the approved indication for a product; another marketing application for the same drug for a different indication related to the same rare disease or condition may be subject to a legal challenge or, like here, rescission of approval. In other cases, however, there may be challenges to FDA’s award of multiple periods of orphan drug exclusivity for the same drug for different indications of the same rare disease or

INTERESTS AND FIRST AMENDMENT CONSIDERATIONS RELATED TO MANUFACTURER COMMUNICATIONS REGARDING UNAPPROVED USES OF APPROVED OR CLEARED MEDICAL PRODUCTS (Jan. 2017), <https://www.regulations.gov/document?D=FDA-2016-N-1149-0040>.

⁵⁶ Orphan Drug Regulations, 56 Fed. Reg. 3,338, 3,339 (Jan. 29, 1991); *Designating an Orphan Product: Drugs and Biological Products*, U.S. FOOD & DRUG ADMIN. (Sept. 7, 2021), <https://www.fda.gov/industry/developing-products-rare-diseases-conditions/designating-orphan-product-drugs-and-biological-products>.

⁵⁷ 56 Fed. Reg. at 3,340 (“FDA decided on a liberal designation policy, however, because the agency wants to encourage research whose aim is to produce safer and more effective drugs, even if FDA believes that the prospects are dim . . . for eventual marketing approval.”) (Sept. 7, 2021).

⁵⁸ See 21 C.F.R. § 316.10(b) (requiring an explanation to support the rationale of use of a proposed drug in the relevant orphan condition).

⁵⁹ Michael Mezher, *FDA Analyst Counters Critiques of Orphan Drug Act*, RAPS (Oct. 18, 2017), <https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/10/fda-analyst-counters-critiques-of-orphan-drug-act>.

condition because the court’s decision supports a “one and done” approach to orphan drug exclusivity.⁶⁰

As a result of the court’s decision in *Catalyst v. Becerra*, FDA likely will revisit its approach to orphan drug exclusivity and designation. However, the agency has, in the past, refused to capitulate to courts with respect to the Orphan Drug Act and continued to enforce its violative interpretation notwithstanding a court decision.⁶¹ Further, FDA previously has been successful in legislatively overriding similar decisions through an act of Congress.⁶² Both of these options remain. How exactly FDA will address or change its practices in response to this decision is unknown.

As of the time of submission, FDA has not appealed, but Jacobus has filed a Petition for Certiorari to the Supreme Court.⁶³

⁶⁰ See Kurt R. Karst, *Orphan Drugs: The Current Firestorm, a Real Evergreening Issue, and a Possible Solution*, FDA LAW BLOG (Mar. 12, 2017), <https://www.thefdalawblog.com/2017/03/orphan-drugs-the-current-firestorm-a-real-evergreening-issue-and-a-possible-solution/>.

⁶¹ See Policy on Orphan-Drug Exclusivity; Clarification, 79 Fed. Reg. 76,888 (Dec. 23, 2014) (limiting the “clinical superiority” decision in *Depomed Inc. v. HHS et al.*, Civil Action No. 12–1592 (Sept. 5, 2014) only to Gralise, the product at issue in that case).

⁶² See Food and Drug Administration Reauthorization Act, Pub. L. 115-52 § 709, 131 Stat. 1005, 1067 (enacting legislation to overturn *Depomed Inc. v. HHS et al.*) (Aug. 18, 2017).

⁶³ Petition for Writ of Certiorari, *Jacobus v. Catalyst*, No. 21- , (U.S. April 7, 2022).