NO. 21-_____

In the
Supreme Court of the United States

JACOBUS PHARMACEUTICAL COMPANY, INC.,
Petitioner,

v.

CATALYST PHARMACEUTICALS, INC.;
XAVIER BECERRA, Secretary of Health and Human Services; U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; ROBERT M. CALIFF, M.D., Commissioner of Food and Drugs, U.S. FOOD AND DRUG ADMINISTRATION,
Respondents.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Eleventh Circuit

PETITION FOR WRIT OF CERTIORARI

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QUESTION PRESENTED

Congress intended the Orphan Drug Act (ODA) to incentivize the development of drugs for the treatment of rare diseases. To be eligible for the incentives, a sponsor must obtain an orphan-drug designation from the Food and Drug Administration (FDA) for a drug that "is being or will be investigated for a rare disease or condition." 21 USC § 360bb(a)(1). The primary incentive to do so is a period of exclusivity, which prevents FDA from approving another sponsor's application for the "same drug for the same rare disease or condition" for seven years. 21 USC § 360cc(a). For the past 30 years, FDA regulations have interpreted ODA exclusivity to prohibit the agency only from approving a second "same drug" for the same "use" as the prior-approved drug.

Here, the Eleventh Circuit created a split with the Fourth and D.C. Circuits, concluding that the ODA unambiguously foreclosed FDA's regulation. FDA designated Respondent's drug, Firdapse® (amifampridine), as an orphan drug to treat Lambert-Eaton Myasthenic Syndrome (LEMS) and subsequently approved it for adults with LEMS (the only population Respondent sought approval to treat). FDA approved Petitioner's drug, Ruzurgi® (amifampridine), for a pediatric population, which Firdapse® was not approved to treat. The Eleventh Circuit held that the ODA foreclosed this result. The question presented is:

Does the ODA unambiguously foreclose FDA's decades-long, consistent interpretation that the scope of orphan-drug exclusivity is tied to a drug's approved use?

CORPORATE DISCLOSURE STATEMENT

Jacobus Pharmaceutical Company, Inc. certifies that it has no parent company and no publicly traded company owns 10% or more of its shares.

RELATED PROCEEDINGS

Catalyst Pharms., Inc. v. Becerra, 14 F.4th 1299 (11th Cir. 2021)

Catalyst Pharms., Inc. v. FDA, No. 19-cv-22425, 2020 WL 5792595 (S.D. Fla. Sept. 29, 2020)

Catalyst Pharms., Inc. v. Azar, No. 19-cv-22425, 2020 WL 551487 (S.D. Fla. July 30, 2020)

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PETITION FOR WRIT OF CERTIORARI

This Court should grant certiorari and resolve a circuit split regarding whether the ODA unambiguously forecloses FDA's interpretation of the scope of the statute's exclusivity. Enacted in the early 1980s, the ODA offers incentives to encourage the development of new drugs to treat rare diseases and conditions, including a seven-year period of marketing exclusivity. A sponsor can obtain orphan drug exclusivity when FDA approves an application for a drug that has first been designated under 21 U.S.C. § 360bb of the ODA for a "rare disease or condition." *Id.* § 360cc(a). Except in narrowly prescribed circumstances, the FDA cannot approve another application for the "same drug" for "the same disease or condition" for seven years after the first approval. *Id.* § 360cc(a).

The ODA doesn't define "same drug" or "the same disease or condition." FDA has always construed the ODA to tie the scope of exclusivity to the uses for which the orphan-designated drug is approved, not to the scope of the orphan-drug designation itself. For three decades, FDA has continuously applied that interpretation—through a codified regulation enacted through notice and comment rulemaking—to approve subsequent orphan-designated drugs to treat a population or other use that the first orphan-designated drug is not approved to treat.

This case involves two amifampridine drugs used to treat LEMS, a rare autoimmune system disorder that has no cure and that leaves its victims increasingly disabled and sometimes bedridden. FDA designated Respondent Catalyst's drug, Firdapse®, as

an orphan drug to treat LEMS but only approved it for adults suffering from LEMS. Relying on its regulations, FDA subsequently approved Petitioner Jacobus's drug, Ruzurgi®, for a pediatric population of those suffering from LEMS. The Eleventh Circuit held that the ODA foreclosed this result, leaving children who suffer from LEMS without a safe and effective treatment approved for their use.

The Eleventh Circuit eviscerated FDA's long-standing practice and created a circuit split. It held that the ODA's plain language unambiguously forbade FDA from approving a drug designated for the same rare disease or condition as a previously approved orphan drug—even though FDA limited its approval of the second drug to uses for which the first drug was not FDA-approved. In doing so, the Eleventh Circuit created a split with the Fourth and D.C. Circuits over whether the ODA unambiguously forecloses FDA's use-based approach.

The question presented over which circuits have split is also one of national importance. If allowed to stand, the results of the Eleventh Circuit's decision would be catastrophic. The FDA has vetted hundreds, if not thousands, of orphan drugs under the (correct) assumption that the agency's use-based approach was valid, but that may no longer be true depending on the circuit in which a particular challenge is brought. The result, under the Eleventh Circuit's flawed decision, is to bar approval of a drug that can treat an incurable disease for use in a population for which there is no approved treatment. That makes no sense. Moreover, the Eleventh Circuit's decision would unsettle federal law and upend the balance Congress struck in

incentivizing the development of drugs indicated for those who need them.

The Court should grant the petition and reverse.

OPINIONS BELOW

The opinion of the Eleventh Circuit is published at 14 F.4th 1299 and reproduced at App.1–27. The denial of Jacobus's petition for rehearing en banc is unpublished but reproduced at App.52– 53. The order of the U.S. District Court for the Southern District of Florida is unpublished but available at 2020 WL 5792595 and reproduced at App.28–51. That opinion adopts the recommendation of a magistrate judge, which is unpublished but available at 2020 WL 551487 and reproduced at App.54–78.

JURISDICTION

The Eleventh Circuit issued its opinion on September 30, 2021. It then denied Jacobus's petition for en banc rehearing on January 7, 2022. Pursuant to Rule 13.1, the deadline to file this petition is April 7, 2022. This Court has jurisdiction under 28 U.S.C. § 1254(1).

CONSTITUTIONAL AND STATUTORY PROVISIONS INVOLVED

This case principally concerns the meaning of the following statutory text:

> The manufacturer or the sponsor of a drug may request [FDA] to designate the drug as a drug for a rare disease or condition. A request for designation of a drug shall be made before the submission of an application under section 355(b) of this title for the drug, or the

> submission of an application for licensing of the drug under section 262 of Title 42. If [FDA] finds that a drug for which a request is submitted under this subsection is being or will be investigated for a rare disease or condition and—
>
> (A) if an application for such drug is approved under section 355 of this title, or
>
> (B) if a license for such drug is issued under section 262 of Title 42,
>
> the approval, certification, or license would be for use for such disease or condition, [FDA] shall designate the drug as a drug for such disease or condition.

21 U.S.C. § 360bb(a)(1).

> Except as provided in subsection (b), if [FDA]—
>
> (1) approves an application filed pursuant to section 355 of this title, or
>
> (2) issues a license under section 262 of Title 42
>
> for a drug designated under section 360bb of this title for a rare disease or condition, [FDA] may not approve another application under section 355 of this title or issue another license under section 262 of Title 42 for the same drug for the same disease or condition for a person who is not the holder of such approved application or of such license until the expiration of seven years from the date of

> the approval of the approved application or the issuance of the license.

21 U.S.C. § 360cc(a). These statutory provisions are reproduced in the Appendix. App.79–80.

STATEMENT OF THE CASE

1. In 1983, Congress enacted the ODA to address the problem of "orphan drugs." *See* Pub. L. No. 97-414, § 1, 96 Stat. 2049, 2049 (1983). An orphan drug is one "designed to treat a rare disease or condition that historically received little attention from pharmaceutical companies, and hence became 'orphaned' because the comparatively small demand for treatment left little motive for research and development." *Spectrum Pharms., Inc. v. Burwell*, 824 F.3d 1062, 1064 (D.C. Cir. 2016). Congress intended the ODA to "reduce the costs of developing" and "provide financial incentives to develop [orphan] drugs." ODA, § 1(b).

To obtain the benefits of the ODA, a manufacturer (or "sponsor") must first obtain orphan drug designation for a drug that "is being or will be investigated for a rare disease or condition." 21 USC § 360bb(a)(1). Under the ODA, FDA will designate a drug, typically very early in its development, as an orphan drug. 21 U.S.C. § 360bb. Based on "the facts and circumstances as of the date [of] the request for designation of the drug," FDA "shall" designate a drug which, upon subsequent approval, would be used for a disease affecting less than 200,000 persons in the United States. *Id.* § 360bb(a)(1)–(2). Only if a drug is orphan-drug designated can the manufacturer qualify for other orphan-drug incentives, including, among

other things, access to tax credits and grants to "defray[] the costs" of drug development (21 U.S.C. § 360ee; 26 U.S.C. § 45C), an exemption from paying for the application fee to obtain approval to market the orphan drug (*id.*) and, eventually, eligibility for a seven-year period of orphan drug exclusivity (*id.* § 360cc).

2. Before the sponsor of an orphan drug can sell its drug, it must obtain marketing approval from FDA. That agency must approve all "new drugs" (including new orphan drugs) before they may be introduced into interstate commerce. 21 U.S.C. §§ 321(p), 331(d), 355(a). By design, FDA designates a drug as an orphan drug *before* the manufacturer (or sponsor) of that drug submits a new drug application to FDA. *See id.* § 360bb(a)(1) ("request[s] for designation of a drug shall be made before the submission of an application . . . for the drug"). This enables the manufacturer (or sponsor) to use the tax credits and grants to develop the drugs.

FDA's decision to approve a new drug application turns on whether the applicant has demonstrated that the drug is safe and effective for the specific uses indicated on their proposed labeling. FDA considers whether the application includes clinical data demonstrating that the drug is "safe for use" and "effective in use" (21 U.S.C. § 355(b)(1)(A)) with respect to the drug's "proposed indications for use," as stated in the proposed labeling. 21 U.S.C. § 355(b); 21 C.F.R. § 314.50(a)(1). FDA may not approve the application unless it determines, among other things, that the drug is safe and effective "for use under the conditions prescribed, recommended, or suggested in

the proposed labeling thereof." 21 U.S.C. § 355(d)(1), (2), (4), (5).

New drug applicants themselves propose uses, supported by the results of research and testing during the clinical investigation process. Depending on those results, the applicant may seek approval only for a particular manifestation of the disease or a particular population afflicted with the disease. FDA in turn determines whether the application establishes that the drug is safe and effective for the proposed uses (including for particular populations or subpopulations). If the application fails to substantiate that the drug is safe and effective for its intended uses, FDA is prohibited from approving the application. 21 U.S.C. § 355(d); 21 C.F.R. § 314.125(b).

If the applicant demonstrates that the drug is safe and effective for the proposed use or uses, and there is no other ground for denial, FDA approves the application. 21 U.S.C. § 355(c)(1). Upon approval, the sponsor may market its drug solely for the approved uses. *See United States v. Caronia*, 703 F.3d 149, 154 (2d Cir. 2012). If, for example, FDA approves an application for the use of a drug to treat inflammatory bowel disease in adult patients, the applicant may not market the drug for treatment of inflammatory bowel disease in pediatric patients.

3. One of the most important incentives for orphan-drug development is orphan-drug exclusivity, eligibility for which is not determined until approval. The predicate for exclusivity occurs when FDA "approves an application filed pursuant to [§ 355] . . . for a drug designated under section 360bb of this title

for a rare disease or condition." 21 U.S.C. § 360cc(a). If that condition is met, FDA "may not approve another application under [§ 355] . . . for the same drug for the same disease or condition for a person who is not the holder of such approved application . . . until the expiration of seven years from the date of the approval of the approved application." *Id.*[1] The ODA does not define "same drug" or "same disease or condition."

In determining whether the ODA's exclusivity provision bars approval of particular new drug applications, FDA has long construed the Act to tie exclusivity to the particular uses for which it has approved the first designated and approved drug. *See* Orphan Drug Regulations, 56 Fed. Reg. 3338, 3339 (Jan. 29, 1991). For the past thirty years, FDA has interpreted orphan drug exclusivity to block approval of an application from "a subsequent sponsor of the same drug product *for the same* [*use*] for 7 years." 21 C.F.R. § 316.3(b)(12) (1992) (emphasis added).

Almost ten years ago, FDA doubled down on this position when it amended its regulations to reflect more clearly its "long-standing practice." Orphan

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[1] Section 360cc sets out two exceptions to the exclusivity that otherwise attaches under § 360cc(a). First, FDA may approve another application that would otherwise be barred during the exclusivity period if FDA finds "that during such period the holder of the exclusive approval or licensure cannot ensure the availability of sufficient quantities of the drug." 21 U.S.C. § 360cc(b)(1). Second, FDA may approve another application with written "consent of [the] holder for the approval of other applications or the issuance of other licenses." *Id.* § 360cc(b)(2).

Drug Regulations, 78 Fed. Reg. 35,117, 35,118 (June 12, 2013). While FDA "generally designates [a] drug for use by all persons with the rare disease or condition," since the designation comes before the sponsor knows the scope of approval it will seek, FDA may "approve the drug for only select . . . uses within the rare disease or condition" supported by adequate safety and efficacy data. *Id.* at 35,123. Given this backdrop, it makes perfect sense that, as FDA has always maintained, "[t]he scope of orphan-drug exclusivity is limited to the . . . use(s) for which the drug is approved for marketing, even if the orphan-drug designation for the drug is broader." *Id.*

In the preamble to the orphan-drug regulations, FDA provided a helpful example to illustrate its approach. In this hypothetical, a manufacturer obtains a "rare disease" designation to treat ovarian cancer. *Id.* at 35,123. The manufacturer then develops and tests this drug and finds that the safety and efficacy data support approval of the drug only for treatment of stage 4 ovarian cancer. *Id.* In this scenario, FDA takes the position that the ODA's exclusivity provision does not bar it from approving an application for the same drug for treatment of stage 1, stage 2, or stage 3 ovarian cancer. *Id.* As FDA reasoned, "whatever the scope of a drug's designation, its FDA-approved labeling will be determined by the data and information included in the marketing application." *Id.* at 35,124.

FDA's current regulations reflect that long-standing approach that "[o]rphan-drug exclusive approval protects only the approved . . . use of a designated drug." 21 C.F.R. § 316.31(b). FDA may

approve an orphan drug for "select . . . use(s) within the rare disease or condition for which the drug was designated," and the regulations state that "FDA will not approve another sponsor's marketing application for the same drug *for the same use* . . . before the expiration of 7 years from the date of such approval." *Id.* § 316.31(a) (emphasis added). However, FDA *can* approve another sponsor's marketing application for "the same drug for a *different* use . . . within those seven years." *Id.* § 316.31(b) (emphasis added).

4. This case concerns drugs used to treat a rare autoimmune system disorder, LEMS. LEMS attacks the immune systems of those who suffer from it and disrupts their nervous systems' ability to communicate with muscle cells. R.65-1 at 425.[2] That disruption causes muscle weakness and impedes joint function. R.65-1 at 425, 1004. As symptoms worsen, LEMS patients lose the ability to perform basic actions like rising from a chair or lifting their feet to walk. R.65-1 at 98. Some become bedridden altogether and need a feeding tube or ventilator to survive. *See* R.65-1 at 98.

There is no known cure (R.65-1 at 98), but LEMS is treatable with amifampridine, a potassium channel blocker. In 1990, Petitioner Jacobus received orphan designation for its amifampridine drug. R.65-1 at 8. Before that drug was approved, Jacobus lawfully manufactured and distributed its drug free of charge under the Federal Food, Drug, and Cosmetic Act (FDCA)'s "expanded access" provisions. R.65-1 at 8.

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[2] Unless otherwise noted, pincites for record materials refer to the page numbers listed in the district court's docket stamps.

Nineteen years later, in 2009, Catalyst obtained orphan designation for a drug with amifampridine as its active pharmaceutical ingredient. R.65-1 at 787–88.

Catalyst submitted a new drug application for its amifampridine drug in December 2015. Catalyst sought approval for its drug (Firdapse®) for the treatment of LEMS in adults, but FDA refused to file the application in February 2016, as it was "not sufficiently complete to permit a substantive review." R.65-1 at 829; 21 C.F.R. § 314.101. In March 2018, Catalyst resubmitted its new drug application for Firdapse®, again seeking approval solely for the treatment of LEMS in adults. *See Catalyst Pharm., Inc. v. FDA*, No. 19-cv-22425-BLOOM/Louis, 2020 WL 5792595, at *6 (S.D. Fla. Sept. 29, 2020) (App.42) ("Catalyst does not dispute its section 355 application was for the treatment of LEMS in adults only"). In November 2018, FDA approved Firdapse® for "the treatment of Lambert-Eaton myasthenic syndrome (LEMS) *in adults*." R.65-1 at 1027 (emphasis added); R.65-1 at 879, R.65-1 at 998.

Jacobus applied for approval of its amifampridine drug (Ruzurgi®) in 2017. R.65-1 at 53. FDA refused to file its application because it was not sufficiently complete to permit substantive review. Jacobus resubmitted its new drug application in June 2018, seeking approval for treatment of LEMS in certain pediatric and adult patients. R.65-1 at 66.

Once Firdapse® was approved for treatment of LEMS in adults in November 2018, FDA recognized that Catalyst's orphan-drug exclusivity blocked approval of Jacobus's application for Ruzurgi® for an

adult population. For administrative convenience, FDA "administratively divided" Jacobus's application into two parts, one for the treatment of LEMs in pediatric patients, and the other for the treatment of LEMS in adults, "to allow for independent actions in these populations." *Catalyst Pharms., Inc. v. Becerra*, 14 F.4th 1299, 1304–05 (11th Cir. 2021) (App.9) (quotation marks omitted).

FDA then considered whether the scope of Catalyst's orphan drug exclusivity was broad enough to block approval of Ruzurgi® for the treatment of LEMS in a pediatric population. FDA referred the issue to the agency's Center for Drug Evaluation and Research's Exclusivity Board. R.47 at 4–5. The Exclusivity Board—established to provide clear and consistent recommendations regarding exclusivity determinations—issued a thorough recommendation detailing why Jacobus's application could be approved for treatment of pediatric LEMS. R.65-1 at 424–33. In doing so, the Exclusivity Board applied FDA's longstanding regulatory rule that "[i]f a drug receives orphan designation for a given disease or condition but receives approval for only certain . . . uses within that disease or condition, a sponsor may obtain approval for additional . . . uses within that same disease or condition." *Id*. at 432. FDA accepted the Exclusivity Board's recommendation and approved Jacobus's drug for the treatment of pediatric LEMS patients in May 2019. R.65-1 at 434.

5. In June 2019, Catalyst filed this suit challenging FDA's approval of Jacobus's drug application for the treatment of LEMS in pediatric patients. R.1 at 23–26. Relevant here, Catalyst

asserted that the ODA unambiguously prohibited FDA from approving Jacobus's drug application for any use. The magistrate judge and district judge rejected this argument, reasoning that the ODA does not unambiguously require that result. The court carefully considered how the ODA's exclusivity provision, § 360cc(a), refers to the new drug approval provisions of § 355, which "contemplate[] that drug companies must provide evidence of the effectiveness of their proposed drug for a specific *use* to obtain marketing approval." *Catalyst*, 2020 WL 5792595, at *6 (App.43). The district court also reasoned that the ODA was at least ambiguous because (1) the statute does not define "same disease or condition" and (2) Congress failed to clarify whether that phrase refers to the use for which the drug is approved pursuant to its NDA or to the disease or condition for which the drug receives orphan-drug designation. *Id*. The court determined that FDA reasonably interpreted the language to tie exclusivity to the uses for which the orphan drug has been approved, such that FDA's interpretation warranted deference. *Id*. at *8–9 (App.45–48). The court granted summary judgment to FDA and Jacobus on all claims.

Catalyst appealed, and, on September 30, 2021, a panel of the Eleventh Circuit reversed the district court's summary judgment order in a published decision. According to the panel, if FDA designates a drug "for a rare disease or condition" and then approves *that* drug for a *limited* use, the ODA unambiguously bars FDA from approving the application of a subsequent "same drug" for *any* use. This is so, according to the panel, even if the first designated drug isn't approved to treat the sub-

condition or population that the subsequent applicant seeks approval of its drug to treat. *Catalyst*, 14 F.4th at 1308 (App.16). The Eleventh Circuit subsequently denied Jacobus's petition for rehearing en banc. App.52–53.

REASONS FOR GRANTING THE PETITION

This Court should grant Jacobus's petition for a writ of certiorari. In this case, the Eleventh Circuit split from two other federal appellate courts in holding that the ODA unambiguously foreclosed FDA's consistent, longstanding position on the scope of orphan-drug exclusivity, reflected in a codified rule that was enacted pursuant to notice-and-comment rulemaking. In doing so, the court of appeals read the statute the wrong way and gutted the agency's regulations. Only this Court can set the law straight.

I. The Eleventh Circuit's decision creates a circuit split on the scope of ODA drug exclusivity.

This Court should grant Jacobus's petition to resolve the split of federal appellate authority exacerbated by the Eleventh Circuit's decision. In this case, the Eleventh Circuit held that the ODA *unambiguously* ties exclusivity to the scope of a drug's designation alone. *Catalyst*, 14 F.4th at 1311–12 (App.24). In its view, the statutory phrase "same disease or condition" is not ambiguous, and thus the district court erred in reaching the contrary conclusion and "deferring to the U.S. Food and Drug Administration's interpretation of it." *Id.* at 1301 (App.2).

In the Eleventh Circuit's view, FDA could not have approved Ruzurgi® for marketing to treat *any* patient with LEMS because Firdapse®, a prior-approved "same drug," was designated "for the treatment of LEMS." *Catalyst*, 14 F.4th at 1308 (App.16). A drug's approved use, the court of appeals concluded, is simply not "relevant" to the ODA's exclusivity regime. *Id.* at 1309 (App.18). In the Eleventh Circuit's view, the scope of exclusivity is determined entirely by the scope of the designation, a non-discretionary determination that FDA must make early in development with no data regarding uses for which the drug will actually prove safe and effective. This decision creates a split with the Fourth Circuit's decision in *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002), and the D.C. Circuit's decision in *Spectrum Pharmaceuticals, Inc. v. Burwell*, 824 F.3d 1062 (D.C. Cir. 2016), both of which upheld FDA's use-based approach.

1. In *Sigma-Tau*, the Fourth Circuit reached the exact opposite conclusion than the Eleventh Circuit here. While the Eleventh Circuit held that the ODA unambiguously *forbade* FDA's use-based approach to exclusivity, the Fourth Circuit held the ODA unambiguously *required* the agency's approach. *See* 288 F.3d at 144–45.

Sigma-Tau concerned a pioneer drug called Carnitor (levocarnitine), developed to treat a rare condition called carnitine deficiency. *See id.* at 143. Carnitor was first approved for the treatment of carnitine deficiency in patients with inborn metabolic disorders only. *See id.* Sometime later, Sigma-Tau sought and obtained approval of Carnitor for the

treatment of carnitine deficiency in patients with end-stage renal disease who were undergoing dialysis. *Id.* When the first exclusivity period expired, FDA started approving generic levocarnitine for the treatment of carnitine deficiency in patients with inborn metabolic disorders. *See id.* Like Catalyst, Sigma-Tau sued on the ground that the ODA barred FDA's action.

The Fourth Circuit flatly rejected Sigma-Tau's argument that approval of generic levocarnitine violated the ODA. It held—in direct conflict with the Eleventh Circuit here—that FDA's use-based approach to exclusivity "comported with the . . . unambiguous . . . wording of the statute." *Id.* at 144–45. In the Fourth Circuit's view, Congress had "made clear its intention" that orphan exclusivity "protects uses, not drugs for any and all uses." *Id.* at 145. Specifically, the *Sigma-Tau* court explained, "[b]y using the words 'such drug for such disease or condition,' Congress made clear its intention that [orphan drug exclusivity] was to be disease-specific, not drug-specific." *Id.* Congress could have written the orphan drug exclusivity provision "more broadly by prescribing that the FDA 'may not approve another application . . . for such drug,' but it chose not to draft the statute in that way." *Id.* Thus, FDA was precluded from approving generic levocarnitine for the initially approved use, treatment of carnitine deficiency in patients with inborn metabolic disorders, only during the seven-year period following approval for that use.

2. The Eleventh Circuit's ruling likewise conflicts with the D.C. Circuit's decision in *Spectrum*. As in *Sigma-Tau*, *Spectrum* required FDA to defend its

determination that orphan-drug exclusivity protects "only . . . the uses included on a drug's [FDA-approved] label[ing]." 824 F.3d at 1067. In that case, Spectrum sued FDA after it approved a generic cancer drug, which Spectrum insisted violated its exclusive marketing rights. In 2008, Spectrum had received approval to market an orphan-designated drug to treat liver damage sustained during a type of chemotherapy involving methotrexate (the "Methotrexate Indication"). *Id.* at 1064. In 2011, FDA approved Spectrum's drug for another use: "helping patients with advanced colorectal cancer." *Id.* ("the 'Colorectal Indication'"). After Spectrum's seven-year exclusivity period for the methotrexate indication expired, FDA approved a generic version of the drug for the methotrexate indication. Even though the generic label "contain[ed] only the [m]ethotrexate [i]ndication[] and ma[de] no mention of the [c]olorectal [i]ndication," Spectrum filed suit to enjoin FDA's approval. *Id.*

Recall that the ODA provides that once FDA approves a drug "designated . . . for a rare disease or condition," it may not approve another application "for the same drug for the same disease or condition" by another company for seven years. 21 U.S.C. § 360cc(a). Spectrum argued that the phrase "for such disease or condition" required FDA "to consider the *intended* use of a drug"—i.e., the methotrexate and colorectal indications—"even if the drug is not 'designated,' or labeled, for that purpose." *Spectrum*, 824 F.3d at 1067. "In *Spectrum's* view, a drug is 'for' a disease or condition if the producer intends it to be used [off-label] for that disease or condition." *Id.* FDA disagreed, reasoning that "'for such disease or

condition' refers only to the uses included on a drug's label." *Id.*

The D.C. Circuit held that the ODA did not "unambiguously foreclose FDA's interpretation" and applied *Chevron* deference to determine whether the "agency's interpretation is 'a permissible construction' of the Orphan Drug Act." *Id.* at 1067 (quoting *Chevron, U.S.A. Inc. v. Nat. Res. Def. Council, Inc.*, 467 U.S. 837, 843 (1984)). The court concluded that the agency's use-based approach warranted deference for two reasons. *First*, "FDA's reading of the statute closely hews to the text," the court concluded, explaining that as the "Fourth Circuit reasoned in [*Sigma-Tau*], the words "for such disease or condition" suggest Congress intended to make section 360cc 'disease-specific, not drug-specific,' and the rest of the statutory language focuses on protecting approved indications, not intended off-label uses." *Id.* In the court's view, the ODA "creates limits on the approval of an 'application,' which by implication directs FDA to evaluate what is written on the application" and "[a]n application will necessarily include only stated" uses. *Id.*

Second, the court added that FDA's use-based approach "conform[ed] to the statutory purposes of the Orphan Drug Act" by "protecting a company's right to market its pioneer drugs for exclusive uses" without otherwise chilling innovation or competition. *Id.* at 1067–68.

Because the ODA did not unambiguously foreclose FDA's interpretation, the D.C. Circuit found it could "leave for another day" the question whether, as the Fourth Circuit held in *Sigma-Tau*, "the statute

unambiguously requires FDA's interpretation." *Id.* at 1067 n.3.

3. Catalyst will no doubt argue that this circuit split is illusory based on the Eleventh Circuit's erroneous conclusion that *Spectrum* and *Sigma-Tau* "addressed the application of market exclusivity in the context of the treatment of different diseases," as opposed to different populations. 14 F.4th 1311 (App.23). That is not true of *Sigma-Tau*, where the drugs were developed to treat carnitine deficiency in different populations (those with inborn metabolic disorders and those with end-stage renal disease who are undergoing dialysis). 288 F.3d at 143.

FDA confirmed the correct understanding of *Sigma-Tau* a decade ago in its preamble to its ODA regulations. One comment objected that the FDA's interpretation could create confusion because "several drugs that are the same may be approved for different . . . uses within the same rare disease or condition." 78 Fed. Reg. at 35,124. FDA rejected this comment because, "as the 4th Circuit Court of Appeals has held, orphan-drug exclusivity protects only the uses for which the drug is approved, not any and all uses of the drug." *Id.* (citing *Sigma-Tau*, 288 F.3d at 145).

In any event, the split remains regardless of any factual dissimilarities. Put simply, the circuit courts disagree over whether the text of the ODA unambiguously forecloses FDA's use-based approach. Two courts have held that the answer is "no" because the statute unambiguously supports FDA, *see Sigma-Tau*, 288 F.3d at 144–45, or because it at least leaves the matter to the agency's reasonably exercised discretion, *see Spectrum*, 824 F.3d at 1067. The

Eleventh Circuit has reached the opposite conclusion, declaring the answer to be "yes" the law unambiguously ties exclusivity to each drug's orphan designation alone. *See Catalyst*, 14 F.4th at 1309 (App.24).

The bottom line is this: FDA cannot follow both lines of precedent. Either the ODA's exclusivity provision ties exclusivity to and "protects" a drug's approved and labeled "uses," *Sigma-Tau*, 288 F.3d at 145, *or* it makes those "use[s] . . . [ir]relevant to . . . market exclusivity," *Catalyst*, 14 F.4th at 1309 (App.18). The ODA cannot do both.

II. The Eleventh Circuit's outlier decision erred in holding that the ODA unambiguously forecloses FDA's interpretation and engenders catastrophic consequences.

The Eleventh Circuit's decision is on the wrong side of the split and has broad ramifications. There is no reason to think FDA spent four decades misapplying the ODA. The Eleventh Circuit erred in reaching that conclusion by myopically focusing on one phrase in the statute without considering how the rest of the statute supports FDA's interpretation. Avoiding this conflict is why FDA brought its expertise and experience to bear in interpreting the statute 30 years ago, *see supra* pp. 8–10, offering certainty in a risky marketplace characterized by "comparatively small demand." *Eagle Pharms., Inc. v. Azar*, 952 F.3d 323, 325 (D.C. Cir. 2020) (quoting *Spectrum*, 824 F.3d at 1064). In the wake of the Eleventh Circuit's decision, that certainty is now out the window.

1. In concluding that the ODA unambiguously foreclosed FDA's interpretation, the court narrowly focused on the phrase "same disease or condition" in the text of the ODA below:

> [I]f the Secretary— (1) approves an application filed pursuant to section 355 of this title . . . for a drug designated under section 360bb of this title for a rare disease or condition, the Secretary may not approve another application under section 355 of this title . . . for the same drug for the *same disease or condition* for a person who is not the holder of such approved application . . . until the expiration of seven years from the date of the approval of the approved application[.]

21 U.S.C. § 360cc(a) (emphasis added). The court acknowledged that the statute does not define "same disease or condition," but determined that alone did not make the statute ambiguous. Because "neither . . . FDA nor Jacobus disputes that LEMS is a 'disease'" the court perceived "the issue" before it to be "the meaning of the word 'same' as used in the phrase 'same disease or condition.'" *Catalyst*, 14 F.4th at 1307 (App.15). Focusing only on the word "same," the court held that "the scope of exclusivity under § 360cc(a) is determined by what has been designated under § 360bb." *Id.* at 1308 (App.16).

For the court, this meant that FDA lacked the authority to approve Ruzurgi® for a pediatric population of LEMS patients even though no other orphan drug (including Firdapse®) had been approved for that population. In other words, orphan-drug

exclusivity barred approval of *any* use for treating LEMS, the court reasoned, because FDA had already designated Firdapse® as an orphan drug for treating the "rare disease or condition of LEMS," which "is the same disease in all people suffering from it." *Id.* The end result was to leave the pediatric population out in the cold because the drug had already been approved (only) for an adult population.

The court of appeals also rejected the notion that another section of the FDCA—21 U.S.C. § 355—rendered the ODA ambiguous. The district court noted that § 360cc(a) expressly refers to § 355 and that § 355 requires a drug manufacturer, as part of its NDA, to provide "evidence that the drug is safe and effective for its intended use." *Catalyst*, 2020 WL 5792595, at *6 (App.42). In the district court's view, because FDA's approval of Firdapse® under § 355 was for the treatment of LEMS in adults, it was not clear whether the "same disease or condition" refers to the "use" approved by FDA to treat a disease or condition pursuant to § 355 as cited in § 360cc(a)(1) *or* to the "rare disease or condition" designated by FDA pursuant to § 360bb.

The court of appeals disagreed, noting that the "the provisions of § 355, which apply generally to all NDAs and not solely those for orphan drugs, use different, more limited language, e.g., 'safe' and 'effective' for 'use,' rather than the broader, disease-specific language found in § 360cc(a)," and so "presume[d] that Congress act[ed] intentionally when it" omitted the narrower use-specific language from § 360cc(a)." *Catalyst*, 14 F.4th at 1309 (App.18). Inverting the rationale of the *Sigma-Tau* court, the

Eleventh Circuit reasoned that "[i]f Congress wanted to make the 'use' . . . inquiry relevant to a holder's market exclusivity for an orphan drug, it could have done so by including such language in § 360cc(a)." *Id.* The *Sigma-Tau* court viewed the ODA as doing just that, by using the phrase "same disease or condition" instead of "same drug." In the Eleventh Circuit's view, however, the references to § 355 "simply identify what must occur to trigger market exclusivity (approval of an application under § 355 . . .) and what FDA is prohibited from doing once both the designation and approval conditions are met (approve another application under § 355 . . ."). *Id.* (App.19). Because there was "nothing in the express language of § 360cc that incorporates by reference the substantive provisions, requirements, or limitations of" § 355, the Court concluded that the ODA unambiguously foreclosed FDA's action. *Id.* at 1311 (App.24).

2. The Eleventh Circuit erred in holding that the ODA unambiguously foreclosed the FDA's position. The threshold issue is whether Congress has unambiguously addressed the specific statutory question. *See Chevron*, 467 U.S. at 842–43. Here, that question is whether exclusivity under the ODA bars FDA from approving a subsequent application for a use for which a previously approved orphan-designated drug is not approved.

a. As discussed above, the panel's analysis centered on the question whether the phrase "same disease or condition" is ambiguous *by itself* in evaluating the meaning of the ODA. *See Catalyst*, 14 F.4th at 1301 (App.2). But "[t]he meaning—or ambiguity—of certain words or phrases may only

become evident when placed in context." *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 132 (2000). Here, FDA's position finds support from how the ODA's exclusivity provision operates as a constraint on FDA's authority under § 355, which is already limited to approving drugs for uses proposed in a drug application.

Recall that § 360cc(a) is a conditional provision that first describes the predicate for exclusivity and then describes the scope of exclusivity. Both that predicate and the resulting exclusivity are defined in terms of FDA's approval of drug applications under § 355:

> *[I]f [FDA] . . . approves an application filed pursuant to section 355* of this title . . . for a drug designated under section 360bb of this title for a rare disease or condition, [FDA] *may not approve another application under section 355 of this title* . . . for the same drug for the same disease or condition for a person who is not the holder of such approved application . . . until the expiration of seven years from the date of the approval of the approved application . . . .

21 U.S.C. § 360cc(a) (emphasis added). Thus, exclusivity does not attach *until* FDA "approves an application" under § 355 for a designated drug for a rare disease or condition *or for a specific use or population of persons with that rare disease or condition*.

Moreover, § 360cc(a) confirms that the seven-year exclusivity period begins to run on "the date of the

approval of the approved application," not at the point of designation. In other words, the statutory language calls for a comparison between an approved orphan-designated drug application and a subsequent application to ensure that FDA does not approve another application for the same drug for the same disease or condition during the seven-year exclusivity period beginning on the date of approval of the first drug.

In this case, there is no dispute that Jacobus's application sought approval for the same drug amifampridine as Catalyst's approved application. But the remaining statutory language does not unambiguously preclude FDA from approving Jacobus's drug application for a different use—the treatment of LEMS in a pediatric population when Catalyst's drug approval is limited to the treatment of LEMS in adults. Given that § 360cc(a) expressly looks to § 355 both to define the predicate for exclusivity and to define the scope of that exclusivity, the provision's operation must be informed by the concept of approved uses that is central to the approval process under § 355.

As explained in Section I, two other circuits have applied a similar interpretive approach to § 360cc(a). In short, the D.C. Circuit has observed that § 360cc(a) "focuses on protecting approved [uses]," pointing to § 360cc(a)'s express reference to "an 'application,' which by implication directs FDA to evaluate what is written on the application." *Spectrum*, 824 F.3d at 1067. Similarly, in *Sigma-Tau*, the Fourth Circuit relied on § 360cc(a)'s "textual emphasis on approved-use" to explain that, when considering whether

§ 360cc(a) stands in the way of approval, FDA must base its decisions on "*the use* for which the approvals are sought." *Sigma-Tau*, 288 F.3d at 145.

b. In addition, § 360cc's use of "another" and its express exceptions to exclusivity also suggest that the scope of exclusivity is tied to the uses for which the designated drug has been approved. Rather than stating that FDA may not approve "an" application or license for the same drug for the same disease or condition, § 360cc(a) says that FDA may not approve "another" such application or license. 21 U.S.C. § 360cc(a). One common meaning of the word "another" is "in addition to one or more *of the same kind*." Merriam-Webster.com (2022)[3] (emphasis added). Thus, Congress's limit on FDA's power to approve "another application" for the same drug for the same disease or condition directs FDA to consider whether the second application is "of the same kind" as the already-approved application—which, of course, is limited to uses. At least the ODA certainly doesn't unambiguously foreclose this interpretation.

Section 360cc's exceptions also support tethering exclusivity to the approved uses in the manufacturer's new drug application. Section 360cc(b) provides two exceptions to the exclusivity that would otherwise attach under § 360cc(a). *See supra* note 1. One of the exceptions applies when FDA determines that the holder of exclusive approval cannot supply enough drugs "*to meet the needs of persons* with the disease or condition for which the drug was designated."

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[3] https://www.merriam-webster.com/dictionary/another?utm_campaign=sd&utm_medium=serp&utm_source=jsonld.

21 U.S.C. § 360cc(b)(1) (emphasis added). The Eleventh Circuit assumes that Congress would have wanted FDA to (1) consider whether manufacturers like Catalyst are able to make the drug available to serve all individuals afflicted with the rare disease or condition (even those for whom it has *not* shown the drug is safe or effective for use) rather than (2) permit manufacturers like Jacobus to sell the drug to those who need it, i.e., a patient population for whom Jacobus has demonstrated that its drug is safe and effective to treat. It's absurd to posit that Congress would have wanted this result, especially given that the statute specifically references the "needs of persons."

c. The overall structure of the orphan drug program, in which designation predates approval (by several years or even decades in practice), lends further support to FDA's interpretation. As explained, designation typically takes place very early in the development stage so that the sponsor can take advantage of financial incentives to develop the drug. *See, e.g.*, 21 U.S.C. § 360ee(a) (grants and contracts); 26 U.S.C. § 45C (tax credit). Indeed, designation must be requested before a sponsor seeks approval for its proposed drug. 21 U.S.C. § 360bb(a); *see supra* p. 6.

Practically, this means that the scope of orphan drug designation is based solely on the sponsor's aspirations for a broad drug approval, without safety or efficacy data, and any tailoring by FDA. In light of the imperfect information available at the designation stage, limiting exclusivity to cover only approved uses makes perfect sense. A broad designation encourages sponsors to explore whether their drug can treat the

full range of how the disease may manifest including all the impacted populations. *See* 21 U.S.C. § 360ee(b)(1)(C)(ii). By the time of the request for approval, however, the sponsor's clinical studies may support only approval for certain disease manifestations or for certain subpopulations afflicted by the disease, as was the case here. Tying exclusivity to the scope of the approved application, rather than the scope of the designation, enables tailoring of the scope of exclusivity at an appropriate point in time, when FDA has determined the uses for which the drug is safe and effective. The Eleventh Circuit failed to grapple with the ODA's complexities and paid no regard to the FDA's substantial experience and expertise.

3. If allowed to stand, the results of the Eleventh Circuit's decision would be catastrophic. FDA has vetted hundreds, if not thousands, of orphan drugs under the assumption that the agency's use-based approach was valid. *See* Nat'l Org. for Rare Disorders (NORD), Orphan Drugs in the United States: An Examination of Patents and Orphan Drug Exclusivity 4, 9 (2021). Among the over 400 orphan-drug approvals from 2010 to 2018, over half were for use in adults only and a tenth were for use in children only. Lauren Kimmel et al., *Pediatric Orphan Drug Indications: 2010-2018*, 145 Pediatrics 1, 3 (2020). Under the Eleventh Circuit's reading of the law, this means that well over two thirds of approvals in that timespan would have had the effect of chilling drug development for yet-unserved patients by imposing an overly broad scope of exclusivity. It also means that the manufacturers of many orphan drugs may now claim much broader exclusivity rights than FDA has

heretofore recognized. As is the case here, it can leave some populations without any effective treatment. It could also result in a wave of follow-on lawsuits, allegations that approvals of second or subsequent drugs for novel uses are now invalid, and the abandonment of drugs currently under development that now cannot come to market without breaking a broad scope of exclusivity. Those drugs, much like Ruzurgi®, could be the only safe and effective treatment for certain patients. There is no sense in keeping those treatments off the market; Congress could not and did not legislate such a senseless result. *Cf. Perry v. Com. Loan Co.*, 383 U.S. 392, 400 (1966) ("[E]ven when the plain meaning did not produce absurd results but merely an unreasonable one plainly at variance with the policy of the legislation as a whole this Court has followed that purpose, rather than the literal words." (quoting *United States v. Am. Trucking Ass'ns*, 310 U.S. 534, 543 (1940)); *United States v. Turkette*, 452 U.S. 576, 580 (1981) ("[A]uthoritative administrative constructions should be given the deference to which they are entitled, absurd results are to be avoided . . . .").

4. In addition to those immediate consequences, the Eleventh Circuit's holding could also substantially undermine the ODA's aims going forward. As of now, there are roughly 7,000 rare diseases affecting some 30 million Americans. NORD, *supra*, at 4. A mere 5% of those diseases currently have FDA-approved drug treatments. *Id.* Developing treatments for the remainder will require maintaining the ODA's incentives on a use-by-use basis, as FDA has done for decades and as Congress implicitly affirmed in 2017 when it revised part of the ODA without suggesting

the FDA's position was wrong. Indeed, dozens of orphan drugs "were first approved to treat a prevalent [or] common condition and later earned" approval for an orphaned use. *Id.* at 3. Dozens more "were first approved to treat a rare disease and later earned [approval for] one or more additional orphan [uses]." *Id.*

Catalyst thus cannot credibly claim that this case presents a one-off circumstance affecting only a small number of pediatric LEMS patients. The entirety of orphan drug development has proceeded for decades under the FDA's clear regulations and use-based reading of the law. Prior to this case, manufacturers knew that their own exclusivity rights, and the rights of their competitors, would only run so far as the safety and efficacy data allowed. That fact encouraged them to seek the broadest possible labeling, and it incentivized further research and development of drugs for the treatment of any patient group—like children with LEMS—left unserved by a prior-approved orphan drug.

The Eleventh Circuit's designation-based reading of the law flips those incentives and harms those the ODA was trying to help. Manufacturers now stand to benefit from focusing on narrow approved uses that will nonetheless cut off competition for the treatment of an entire disease or condition—and from serial exclusivity based on subsequent narrow approvals for additional uses. (Indeed, they have every incentive to seek initially the narrowest possible designation in the interests of speed and efficiency, thus leaving even larger populations potentially underserved.) Subsequent manufacturers will also have to think

twice about exploring whether an orphan-designated drug, still under development, can be put to any use that might later be blocked by an overbroad designation.

The Eleventh Circuit's decision marks a dramatic departure from how the ODA framework always worked. The catastrophic ramifications of the Eleventh Circuit's decision support certiorari review.

* * *

This case impacts the entire field of orphan-drug development. It also offers this Court its best—maybe only—opportunity to weigh in on the meaning of the ODA. Absent further review, the Eleventh Circuit's decision is likely to steer manufacturers away from this area of drug development, potentially obviating any further percolation of the question presented.

CONCLUSION

For the foregoing reasons, this Court should grant the petition for certiorari.

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