No. 21A328

IN THE

Supreme Court of the United States

JACOBUS PHARMACEUTICAL COMPANY, INC.,

Applicant,

v.

CATALYST PHARMACEUTICALS, INC.; XAVIER BECERRA, SECRETARY OF HEALTH AND HUMAN SERVICES; U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; JANET WOODCOCK, ACTING COMMISSIONER OF FOOD AND DRUGS, U.S. FOOD AND DRUG ADMINISTRATION,

Respondents.

ON APPLICATION TO STAY THE MANDATE OF THE UNITED STATES COURT OF APPEALS FOR THE ELEVENTH CIRCUIT

OPPOSITION OF CATALYST PHARMACEUTICALS, INC. TO EMERGENCY APPLICATION FOR A STAY PENDING THE FILING AND DISPOSITION OF A PETITION FOR A WRIT OF CERTIORARI

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January 14, 2022

RULE 29.6 STATEMENT

Pursuant to Rule 29.6 of the Rules of this Court, Respondent Catalyst Pharmaceuticals, Inc. hereby states that it has no parent corporation, and no publicly held corporation owns 10% or more of its stock.

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To the Honorable Clarence Thomas, Associate Justice of the Supreme Court of the United States and Circuit Justice for the Eleventh Circuit:

Catalyst Pharmaceuticals, Inc. ("Catalyst") respectfully submits the following response in opposition to Jacobus Pharmaceutical Company, Inc.'s ("Jacobus") emergency application for a stay of the mandate of the United States Court of Appeals for the Eleventh Circuit pending the filing and disposition of its forthcoming petition for a writ of certiorari.

INTRODUCTION

Jacobus's forthcoming petition for certiorari rests entirely on two false premises—a nonexistent Circuit split and a threat of grave consequences that is unmoored from reality. Jacobus raised those arguments in its briefing to the Eleventh Circuit, and a unanimous panel rejected them. It then again raised those same arguments in a petition for panel rehearing and rehearing en banc, and no active Judge on the Eleventh Circuit called for an en banc vote based on them. Its stay application is meritless. The Orphan Drug Act's exclusivity period lasts seven years, and the United States Food and Drug Administration's ("FDA") mistaken decision has allowed Jacobus to infringe Catalyst's exclusivity for almost 40% of its duration. Jacobus's application (which has not been joined by FDA, the party better suited to assess the decision's impact on patients) is a transparent attempt to delay issuance of the Eleventh Circuit's mandate for a few extra months to reap additional, unlawful profits during that period. This Court should reject that attempt and deny the application.

First, there is no reasonable probability that this Court will grant certiorari and no fair prospect that this Court will reverse the Eleventh Circuit's decision. This case concerns the scope of orphan drug exclusivity under the Orphan Drug Act (the "Act"). The Act unambiguously provides that if FDA "designate[s]" a drug as an orphan drug for a "rare disease or condition" during the drug development stage, and then later "approves" that drug, FDA "may not approve another application" for "the *same drug* for the *same disease or condition*" until "the expiration of seven years." 21 U.S.C. § 360cc(a) (emphasis added).

Here, FDA designated Catalyst's Firdapse® for treatment of the rare disease Lambert-Eaton Myasthenic Syndrome ("LEMS"), approved Firdapse®, and accordingly recognized that Firdapse® was entitled to seven years of market exclusivity. But then FDA did something unprecedented. Notwithstanding that the plain language of the Act prohibits subsequent approvals of the "same drug" for the "same disease or condition" during Firdapse®'s ongoing exclusivity period, FDA approved Jacobus's Ruzurgi®, a drug which all parties agree (1) is the "same drug" (amifampridine) as Firdapse® and (2) treats the "same disease or condition" (LEMS) as Firdapse®. According to FDA, because the agency had approved Catalyst's Firdapse® only for *adult* LEMS patients (98-99% of the U.S. patient population with LEMS), Catalyst's exclusivity did not block approval of Jacobus's drug for *pediatric* LEMS patients (estimated at two dozen patients nationwide). FDA's decision had predictable results: Because physicians are free to prescribe an approved drug "off-

label" to any patient for any purpose, the vast majority of Jacobus's sales for its purportedly pediatric drug are now "off-label" prescriptions for adult patients.

The Eleventh Circuit's opinion, which faithfully applies the statutory text as written by Congress, correctly rejected FDA's atextual approach. The court applied longstanding principles of statutory construction and held that the Act means what it says: exclusivity blocks a subsequent approval for the same drug for the disease or condition for which an orphan drug was already designated and subsequently approved. It rightly concluded that FDA could not rewrite the statutory text of "disease or condition" into "indication and use," as it sought to do, and was instead bound by the plain text of the Act. In this case, that meant that FDA could not slice-and-dice a single disease—LEMS—into subdivisions based on patient population.

In its application, Jacobus offers no textual argument for why its preferred approach is correct. Indeed, it offers this Court only one short paragraph on the reasoning of the Eleventh Circuit's decision (referring only to another court's decision) and fails to address the relevant statutory text at all.

Moreover, Jacobus primarily relies on a purported Circuit split between the Eleventh Circuit and the Fourth and D.C. Circuits. But no such split exists. As the Eleventh Circuit's decision explicitly and cogently explains, neither of the supposed conflicting decisions bore on the question at issue in this case. The Fourth Circuit and D.C. Circuit cases relied on by Jacobus both involved instances where FDA approved a drug to treat a *different* disease or condition than that for which an orphan drug already held exclusivity. By contrast, here, FDA approved a drug to treat the

same disease that was already covered by exclusivity. Indeed, under the Eleventh Circuit's holding, both of those allegedly conflicting cases would come out the same way. As the Eleventh Circuit explained, construing either of those cases as contrary to the holding it reached would require ignoring the facts of each case, which "address[] the application of market exclusivity in the context of the treatment of different diseases," and those courts' holdings that exclusivity is "disease-specific." Appendix to Stay Application ("App.") 23. And it would also require reading isolated language in those opinions "out of context." *Id.*

Second, even if Jacobus had a meritorious issue for certiorari, there is no irreparable harm here. Jacobus centrally relies on supposed irreparable harm to third parties (pediatric patients) not before this Court. But that assertion is, at best, misleading: As explained below, no pediatric patient with LEMS will be left without treatment as a result of the Eleventh Circuit's mandate issuing. Tellingly, FDA—the primary defendant below and a party better suited than Jacobus to assess impacts on patients—chose not to file a petition for rehearing and has not sought to stay issuance of the mandate. As FDA has acknowledged throughout this litigation, the drug that should not have been approved, Jacobus's Ruzurgi®, is the "same drug" as Catalyst's Firdapse®. And the approximately two dozen pediatric patients with LEMS will still have multiple avenues to access treatment, including access to Firdapse®. Indeed, contrary to Jacobus's representations (at 15), the very patient referenced in its application *has already received access to Firdapse®.*

Moreover, Catalyst will suffer irreparable harm if the Court stays the mandate. Under the statute, Catalyst is entitled to seven years of exclusivity. Jacobus's drug has now infringed that period for almost 40% of its duration. Each day that Jacobus's drug remains on the market, in contravention of the Orphan Drug Act, Catalyst's statutory exclusivity is infringed, and Jacobus unlawfully profits. The loss of a statutory exclusivity right is unquestionably irreparable harm. The loss of future illegal gains, which Jacobus asserts here, is not. And Jacobus's contention that its loss is not Catalyst's gain is simply false, because, in reality, Jacobus's drug is sold primarily to the adult LEMS patients for which only Catalyst's drug is indicated and approved.

Finally, Jacobus's efforts at delay here threaten the public interest. Congress created orphan drug exclusivity to incentivize the development of treatments for diseases that affect small numbers of the population. In order for that exclusivity to provide an incentive, manufacturers must have confidence that they will be able to reap the benefits of their investments. If manufacturers are left unsure of whether a competitor will be permitted to infringe on the promised exclusivity, the incentive provided by the Act will be nullified. Accordingly, Jacobus's request, which would involve eating into Catalyst's exclusivity period for another four to five months, threatens to undermine the very purpose of the Act. The stay application should be denied.

STATEMENT OF THE CASE

A. Statutory Background

The Federal Food, Drug, and Cosmetic Act ("FDCA") generally prohibits the introduction of any "new drug" into interstate commerce absent premarket approval by FDA. 21 U.S.C. § 355(a). The primary pathway for premarket approval for a new drug product is through a New Drug Application ("NDA"). *Id.* § 355(b)(1); *see also* 21 C.F.R. § 314.50. A drug product's principal feature is its "[a]ctive moiety," the component that is "responsible for the physiological or pharmacological action of the drug substance." 21 C.F.R. § 314.3(b).

"The process of submitting an NDA is both onerous and lengthy," *Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 476-77 (2013), and involves significant "risk and expense," *Ethypharm S.A. France v. Abbott Laboratories*, 707 F.3d 223, 226 (3d Cir. 2013). To encourage drug manufacturers to undertake that onerous process, Congress has enacted several statutory market exclusivities. FDA has not always seen eye-to-eye with Congress about the wisdom of these exclusivities and has made various attempts to limit them through administrative action. Courts, respecting *Congress's* policy-making role in our constitutional system, have repeatedly rebuked these efforts. *See, e.g.*, *Eagle Pharms., Inc. v. Azar*, 952 F.3d 323, 340 (D.C. Cir. 2020) (rejecting FDA's efforts to limit orphan drug exclusivity); *Ranbaxy Laboratories, Ltd. v. Leavitt*, 469 F.3d 120, 121 (D.C. Cir. 2006) (rejecting FDA's efforts to attach extra-statutory condition to retain exclusivity); *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1069 (D.C. Cir. 1998) (same).

This case involves orphan drug exclusivity, which Congress added to the FDCA through the Orphan Drug Act in 1983, to incentivize development of drugs for "rare disease[s] and condition[s]" (*i.e.*, those affecting 200,000 or fewer persons in the United States). Pub. L. No. 97-414, § 1(b), 96 Stat. 2049, 2049 (1983) (codified at 21 U.S.C. §§ 360aa-360ee). Under the Act, drugs designated for treatment of a rare disease or condition—so-called "orphan drugs"—generally receive a seven-year period of market exclusivity upon approval. Recognizing that pharmaceutical manufacturers could "reasonably expect . . . to incur a financial loss" for drugs that treat only a small number of patients, Congress concluded that "it [wa]s in the public interest to provide . . . incentives," for development of these drugs, including a period of market exclusivity. *See id.*

Under this regime, a drug manufacturer, early in the drug development process, may request that FDA designate a potential drug for a rare disease or condition as an "orphan drug." 21 U.S.C. § 360bb. A "rare disease or condition" is statutorily defined as "any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and 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." *Id.* U.S.C. § 360bb(a)(2).

To receive a designation as an orphan drug, the manufacturer must show that its potential new drug is being developed for a "rare disease or condition" and, if

approved, would be used for that disease or condition. *Id.* § 360bb(a). Designation is the first step toward receiving orphan drug exclusivity.

If the manufacturer completes all the required clinical and non-clinical studies and FDA ultimately approves the designated drug as safe and effective, then FDA cannot approve applications by other companies to market the (1) "same drug" for the (2) "same disease or condition" for seven years. *Id.* § 360cc(a); *Eagle*, 952 F.3d at 325 ("After a sponsor's drug has been designated as an orphan drug and approved for marketing, the FDA provides the sponsor with a seven-year period of exclusive approval rights . . . .").

Congress provided three narrow exceptions to orphan drug exclusivity, none of which apply here—as FDA and Jacobus have conceded. App. 26. FDA "may" approve another manufacturer's drug if (1) the orphan drug's manufacturer "cannot ensure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated," or (2) the orphan drug's manufacturer consents to approval of "other applications . . . before expiration of [the] seven-year period." 21 U.S.C. § 360cc(b). Of particular note, FDA may also break exclusivity if (3) a subsequent manufacturer can demonstrate that its drug is "clinically superior" to the previously approved drug with existing exclusivity. *Id.* § 360cc(c); 21 C.F.R. § 316.25.

Finally, although manufacturers are prohibited from "promoting or marketing their drugs for off-label uses," *see Ironworkers Local Union 68 v. AstraZeneca Pharms., LP*, 634 F.3d 1352, 1356 n.5 (11th Cir. 2011); 21 U.S.C. § 331 (prohibiting

"misbranded" drugs), physicians do not face the same restriction. They "may prescribe FDA-approved drugs . . . for any therapeutic use that is appropriate in their medical judgment," including unapproved uses. *United States v. Caronia*, 703 F.3d 149, 153 (2d Cir. 2012) (alteration in original) (citation omitted).

B. Factual Background

This case arises from Catalyst's lengthy and intensive efforts to develop a drug for the treatment of LEMS, a "rare, autoimmune" disease where the immune system attacks the body's own tissues. Doc. 65-1, Pg. JA993. LEMS affects the body's "neuromuscular junction" and in essence impedes nerve cells from sending signals to muscle cells. *Id.* According to FDA, there are only approximately 950 to 1,300 individuals diagnosed with LEMS in the United States. *Id.*, Pg. JA885. Of those individuals, there are only a couple of dozen pediatric patients. *See id.*, Pg. JA269. While diseases sometimes manifest themselves differently in children and adults, such that they are medically considered separate diseases, FDA has explicitly recognized that LEMS is the same disease in adults and children. Doc. 65-1, Pg. JA268. Jacobus has also conceded the same fact throughout this litigation. Doc. 98, Pg. 9.

Catalyst spent approximately $100 million to develop Firdapse® (amifampridine phosphate) to meet the need for a treatment for LEMS. Doc. 65-1, Pg. JA784. Amifampridine, the "active moiety" in Firdapse®, counteracts LEMS by enhancing neuromuscular transmission and improving muscle function. *Id.*, Pg. JA884. In 2009, FDA designated Firdapse® as an "orphan drug" for the treatment of LEMS. *Id.*, Pg. JA781. After years of drawn-out and complicated regulatory

proceedings, FDA approved Firdapse® on November 28, 2018, for treatment of adults with LEMS. *Id.*, Pgs. JA1021, 1027. FDA then recognized that Firdapse® was entitled to orphan drug exclusivity through at least November 28, 2025. *Id.*, Pgs. JA1040-41.

Jacobus's drug Ruzurgi® (amifampridine) is the "same drug" under the Orphan Drug Act as Catalyst's Firdapse® because both drugs use the same active moiety (active ingredient). *See, e.g.*, Doc. 107, Pg. 4. Beginning many years ago (before it was approved), Jacobus began supplying its drug, including to pediatric patients, as part of a program that provides unapproved drugs to treat patients "under an expanded access I[nvestigational] N[ew] D[rug] [IND] application." Doc. 65-1, Pg. JA126; *see also* 74 Fed. Reg. 40,900 (Aug. 13, 2009) (explaining FDA's "expanded access" program). This program is authorized under 21 U.S.C. § 360cc, and is unaffected by Catalyst's exclusivity.[1] However, even after Firdapse® was approved (and granted orphan drug exclusivity), Jacobus pursued approval for Ruzurgi® for the treatment of LEMS. Doc. 65-1, Pg. JA428.

Jacobus filed the NDA at issue here on June 15, 2018, seeking approval for pediatric and adult patients. *See* Doc. 47, Pgs. 3-4; Doc. 65-1, Pgs. JA64-67. But after Catalyst's Firdapse® was approved, both FDA and Jacobus recognized that Jacobus's product would likely be blocked by Catalyst's orphan drug exclusivity. Doc. 47, Pgs.

[1] Catalyst also operated for many years an "expanded access" program that until Ruzurgi®'s approval supplied medication for pediatric patients with LEMS and has since restarted that program. Doc. 65-1, Pg. JA1011; *see also* Catalyst Pharmaceuticals, https://catalystpharma.com/ (last visited Jan. 13, 2022) (explaining options for pediatric patients in light of the Eleventh Circuit's decision).

4-5. At some point around this time (FDA's record does not reveal exactly when), FDA opted unilaterally to "administratively divide[]" the patient groups for which Jacobus sought approval. *See* Doc. 47, Pg. 4; Doc. 65-1, Pg. JA395; Doc. 66, Pg. JA395. Specifically, 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 action in these populations.'" Doc. 47, Pg. 4; Doc. 65-1, Pg. JA401; Doc. 66, Pg. JA401.[2]

On May 6, 2019, FDA approved Jacobus's Ruzurgi® for treatment of LEMS "in patients 6 to less than 17 years of age" (pediatric patients). Doc. 65-1, Pgs. JA428, JA436. By FDA's own admission this was the first time the agency ever "approved an application for a drug with an indication to treat pediatric patients for a certain disease while another sponsor has obtained orphan drug exclusivity for a drug application for the same drug with only an indication to treat adult patients for that disease." Doc. 22, Pg. 12 (Answer ¶ 54). FDA concluded that it was allowed to do this, notwithstanding Catalyst's orphan drug exclusivity and the clear text of the statute which extends exclusivity across the entire "disease or condition," 21 U.S.C. § 360cc(a), because Jacobus's Ruzurgi® approval for pediatric patients constituted a

[2] No explanation appears in the record for why the agency would do this, especially without a specific request from Jacobus. But context demonstrates what likely happened. The administrative division occurred at around the exact time that Senator Bernie Sanders began publicly campaigning against Catalyst and complaining about Firdapse®'s price. Then, even though FDA is explicitly forbidden from considering pricing as part of drug approvals, *see* 57 Fed. Reg. 62,076, 62,079 (Dec. 29, 1992) ("FDA has no authority over drug pricing or any authority to consider it in drug approval."), FDA held an internal meeting where it did exactly that. Doc. 70-1, Pgs. FDACDER001150-55.

different "indication[] or use[]" than Catalyst's Firdapse® adult approval, even though the indication was "*within* th[e] same disease or condition" (LEMS). Doc. 65-1, Pg. JA426 (emphasis added).

That approval had significant consequences for Catalyst. As previously mentioned, physicians "may prescribe FDA-approved drugs . . . for any therapeutic use that is appropriate in their medical judgment." *Caronia*, 703 F.3d at 153 (alteration in original) (citation omitted). Physicians may therefore prescribe Ruzurgi® for adult patients with LEMS as an off-label use, effectively eliminating Catalyst's exclusivity.

C. Procedural Background

In June 2019, Catalyst filed suit against FDA, asking the court to set aside the approval of Ruzurgi® as arbitrary, capricious, an abuse of discretion, and/or contrary to law in violation of the Administrative Procedure Act. Jacobus intervened. On September 29, 2020, the district court granted summary judgment to FDA and Jacobus and denied Catalyst's motion for summary judgment. Catalyst appealed. Recognizing the continuing harm to Catalyst—infringement of its time-limited statutory right—the Eleventh Circuit granted expedited review. Order Granting Expedited Review (11th Cir. Nov. 3, 2020).

On September 30, 2021, a unanimous panel held that "FDA's interpretation of [the] Orphan Drug Act is contrary to the clear statutory language enacted by Congress." App. 25. As the court observed, "[t]he framework established by the Orphan Drug Act is fairly straightforward: designation as an orphan drug followed by FDA approval results in market exclusivity." *Id.* at 3. The court undertook a

careful analysis of the statutory text and concluded that the scope of orphan drug exclusivity "is determined" by the disease or condition for which a drug was designated by FDA. *Id.* at 16.

Based on the undisputed record evidence, which established that Firdapse® was designated and approved for the treatment of LEMS, that LEMS was the same disease in both adult and pediatric patients, and that Firdapse® and Ruzurgi® were the same drug, the Eleventh Circuit concluded that FDA's approval of Ruzurgi® "was contrary to the unambiguous language of the Orphan Drug Act." *Id.* at 25-26. The court reversed the grant of summary judgment in favor of FDA and Jacobus and ordered the district court on remand to enter summary judgment in favor of Catalyst. *Id.* at 27.

On November 15, 2021, Jacobus (but not FDA) filed a petition for panel rehearing and rehearing en banc. In that petition, Jacobus asserted that the Eleventh Circuit's holding regarding the scope of exclusivity conflicted with precedent from another Circuit and that the holding would have "serious ramifications" for patients. Reh'g Pet. 1, 15-18. The court denied Jacobus's petition on January 7, 2022. "No Judge in regular active service . . . requested that the Court be polled." Order Denying Reh'g Pet. (11th Cir. Jan. 7, 2022).

On January 10, 2022, Jacobus filed a motion to stay the mandate in the Eleventh Circuit, and Catalyst filed its response on January 12. Jacobus also filed the instant emergency application for a stay with this Court on January 12, without

awaiting the Eleventh Circuit's determination on the motion Jacobus filed with that court.

ARGUMENT

To obtain a stay of the mandate pending disposition of a petition for certiorari, a movant "must demonstrate (1) a 'reasonable probability' that this Court will grant certiorari, (2) a 'fair prospect' that the Court will reverse the decision below, and (3) a 'likelihood that irreparable harm [will] result from the denial of a stay." *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 572 U.S. 1301, 1301 (2014) (Roberts, C.J., in chambers) (alteration in original) (citation omitted). "In close cases, the Circuit Justice or the Court will balance the equities and weigh the relative harms to the applicant and to the respondent." *Hollingsworth v. Perry*, 558 U.S. 183, 190 (2010). Jacobus cannot satisfy any of the requirements for a stay: Its forthcoming certiorari petition is meritless, there is no fair prospect the Court will reverse, and Jacobus and pediatric LEMS patients will suffer no irreparable harm from the denial of a stay. Indeed, Catalyst and the public interest would suffer from a stay.

I. THERE IS NO PROSPECT THAT THIS COURT WILL GRANT CERTIORARI OR REVERSE

The Eleventh Circuit's decision was plainly correct and did not create a Circuit split. There is no reasonable probability that this Court will grant certiorari and no fair prospect it will reverse the Eleventh Circuit's judgment.

A. The Eleventh Circuit's Decision Was Correct

The Eleventh Circuit correctly held that FDA's approval of Ruzurgi® violated the Orphan Drug Act. The text of the Act is clear: Once an orphan drug is designated

and approved, FDA cannot approve a second drug that is (1) the "same drug" as the orphan drug (2) for the "same disease or condition." 21 U.S.C. § 360cc(a). Jacobus offers only a single paragraph to this Court rebutting the Eleventh Circuit's carefully reasoned decision and does not grapple with the statutory text at all. That alone warrants denial of its application. In any event, the Eleventh Circuit's decision is correct.

The dispute in this case centers around whether FDA could designate a drug for the treatment of a single rare disease—LEMS—and approve it for the treatment of LEMS but nonetheless also approve a second drug for the treatment of the undisputed same disease, LEMS. The broader provision states:

> Except as provided in subsection (b), if the [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) (emphasis added). Although the statute uses the terms "disease or condition," FDA manufactured a much finer distinction than the statute permitted, arguing that it could subdivide a disease or condition into "indications" for the

purpose of exclusivity.[3] The court correctly rejected that atextual approach, holding "that the disease referred to in the phrase 'same disease or condition' is the 'rare disease or condition' for which the drug received designation under [Section] 360bb" and that FDA could not create finer distinctions than those permitted by the statute. App. 23-24.

Applying that unambiguous text to the undisputed facts of this case, the court concluded that FDA violated the statute when it approved Jacobus's Ruzurgi® because Catalyst's Firdapse® and Ruzurgi® are the same drug, LEMS is a single disease, Firdapse® had been designated and approved for the treatment of LEMS, and Ruzurgi® had also been (impermissibly) approved for the treatment of LEMS. *Id.* at 16-17.

As part of its analysis, the Eleventh Circuit considered the same argument passingly asserted by Jacobus here. Jacobus contends that orphan drug exclusivity is tied to the "indications" for which any given drug is approved under Section 355. But noticeably absent from Jacobus's application is any argument linking its preferred approach to the actual text of Section 360cc. Indeed, Jacobus fails to identify any textual hook for its reading. Appl. 13.

In any event, the Eleventh Circuit aptly explained (based on the text) why Jacobus's argument is incorrect. *First*, as the court noted, Section 360cc(a) refers to Section 355 (the drug approval provision). But the court explained that

[3] Congress did use the terms "indication" and "use" in other statutory provisions to draw distinctions between approved uses of a drug, but it chose not to do so here. *See* 21 U.S.C. § 355f(c)(2); *id.* § 355(c)(5)(D)(i), (b)(1); *id.* § 355h(a)(3)(ii).

Section 360cc(a) refers to Section 355 and Section 262 (a licensing provision) "simply to identify what must occur to trigger market exclusivity (approval of an application under [Section] 355 or issuance of a license under [Section] 262) and what the FDA is prohibited from doing once both the designation and approval conditions are met (approve another application under [Section] 355 or issue another license under [Section] 262)." App. 19.

Second, while Section 355 referred to a drug's "use," Section 360cc(a) referred explicitly (and only) to the broader concepts of "disease or condition." *Id.* at 18. As the court observed, "[i]f Congress wanted to make the 'use or indication' inquiry relevant to a holder's market exclusivity for an orphan drug, it could have done so by including such language in [Section] 360cc(a)." *Id.*

Third, Congress defined "rare disease or condition," which was referred to in Section 360cc(a). *Id.* at 20. And the definition of "rare disease or condition" did not provide any finer breakdown within those terms for "indications or uses." *See id.* at 20-21. Based on the plain statutory text, the Eleventh Circuit rightly rejected the argument that exclusivity under Section 360cc(a) is limited by terms ("indication" or "use") nowhere referenced in Section 360cc(a).

This makes sense. "Indication" is a relatively vague concept that can be highly detailed and include "other information in addition to the identification of the disease or condition at issue." *See* FDA, *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products—Content and Format: Guidance for Industry – Draft Guidance* 6 (July 2018), https://www.fda.gov/media/

114443/download. For example, an indication may also state whether the drug product should be taken with "concomitant therapy" such as "exercise or *another* drug" or identify whether "specific tests are necessary for selection or monitoring of patients who need the drug." *Id.* at 7-9 (emphasis added). Thus, sometimes, FDA may approve a drug with an indication to treat only a very limited and highly technical subcategory of a given disease or condition or with other limitations. *See, e.g.*, *BTG Int'l Ltd. v. Amneal Pharms. LLC*, 352 F. Supp. 3d 352, 371 (D.N.J. 2018) (describing drug product "indicated for use [1] in combination with prednisone for [2] the treatment of patients with metastatic castration-resistant prostate cancer who [3] have received prior chemotherapy [4] containing docetaxel" (citation omitted)).

Because manufacturers propose their own labeling "indication" to FDA, and FDA will approve that indication so long as the manufacturer's data shows that the drug would be safe and effective for that indication, if orphan drug exclusivity were tied to an indication, drug manufacturers could easily circumvent orphan exclusivity by copying the drug and using a slightly different indication—for example, treatment of cluster headaches in those with brown hair. Because that drug could then be prescribed off-label to everyone else with cluster headaches, *United States v. Caronia*, 703 F.3d 149, 153 (2d Cir. 2012), the statutory promise of exclusivity would be made a nullity. The facts of this case demonstrate the point: Ruzurgi® is purportedly approved to treat a few dozen pediatric LEMS patients, but in reality nearly all sales of Ruzurgi® are to adult LEMS patients. There are infinite permutations of this "indications" gamesmanship that would have been possible under FDA's

interpretation. *See* Doc. 65-1, Pg. JA269; Pandolfo Decl. ¶ 10, attached hereto as Exhibit A (and submitted as an exhibit to Catalyst's opposition to Jacobus's Eleventh Circuit motion). Congress, quite sensibly, adopted a different approach, as the Eleventh Circuit recognized.

In short, Jacobus offers no credible argument that the Eleventh Circuit erred in holding that Ruzurgi®'s approval was barred by the Act. And it certainly makes no showing of a "fair prospect" that five Justices would agree with its textually unmoored and unsupported reading of Section 360cc(a). *Hollingsworth v. Perry*, 558 U.S. 183, 190 (2010).

B. There Is No Circuit Split

Despite the fundamental flaw in Jacobus's merits argument, it nonetheless asserts that this Court is likely to grant certiorari because the Eleventh Circuit's ruling created a Circuit split with the Fourth Circuit and the D.C. Circuit. Appl. 12. Jacobus is mistaken.

As the Eleventh Circuit ruling itself explained, it did not disagree or conflict with the Fourth Circuit's or D.C. Circuit's holdings. App. 21-24. Indeed, it agreed with those decisions that Section "360cc(a) is 'disease-specific, not drug-specific" regime. *Id.* at 23. And, to the extent the Eleventh Circuit's holding would have any relevance to the issue presented in those cases, the outcomes would be *exactly the same* under the Eleventh Circuit's holding.

As the Eleventh Circuit explained, the cases on which Jacobus relies "addressed the application of market exclusivity in the context of the treatment of *different* diseases; neither court was asked to address [the question in this case]."

App. 23. In this case, the Eleventh Circuit was asked to address the application of market exclusivity where Ruzurgi® (the "same drug" as Catalyst's Firdapse®) was subsequently approved for the *same disease*—LEMS—for which Firdapse® was already designated and approved. That fact is key because the Orphan Drug Act provides exclusivity as to the "same disease or condition" for which an orphan drug is already designated.

A review of the decisions from the D.C. and Fourth Circuits confirms the point. In *Spectrum Pharmaceuticals, Inc. v. Burwell*, the plaintiff Spectrum Pharmaceuticals held orphan drug exclusivity for a specific condition (treatment of liver damage that occurred during chemotherapy). 824 F.3d 1062, 1064 (D.C. Cir. 2016). Spectrum later received orphan drug exclusivity for treatment of *another*, additional condition: pain in patients with advanced colorectal cancer. *Id.* After the expiration of exclusivity for the first condition (liver damage), but before expiration of the second (colorectal cancer), FDA approved an application from a generic manufacturer for the same drug for the treatment of liver damage. *Id.* Spectrum argued that its remaining orphan drug exclusivity over *colorectal cancer* blocked that approval because, although the generic manufacturer was only *approved* for liver damage (which no longer was subject to exclusivity), the generic manufacturer intended to distribute its drug "off-label" to treat colorectal cancer. *Id.* There was no dispute regarding whether the generic manufacturer sought *approval* for the "same disease or condition." The parties all accepted that the generic manufacturer sought approval for a condition for which Spectrum no longer had exclusivity.

Rather, the case centered around whether FDA was required to evaluate only the disease or condition for which the generic manufacturer sought approval or whether it also had to consider potential off-label uses. *Id.* at 1066-67. The D.C. Circuit concluded only that FDA does not have to consider potential off-label uses in approving the drug for a disease or condition for which there was no exclusivity when that second drug was approved. Unlike in *Spectrum*, FDA did not approve Jacobus's Ruzurgi® for the treatment of a distinct "disease or condition" for which exclusivity no longer exists. Instead, it approved Ruzurgi® for the treatment of the same disease—LEMS—for which Catalyst's Firdapse® was already designated and approved, and for which almost the full seven years of exclusivity remained when Ruzurgi® was approved. The Eleventh Circuit's opinion here laid out just this point in its decision, noting that "the question before the court [in *Spectrum*] was whether intended off-label use mattered for purposes [Orphan Drug Act] exclusivity." App. 21.

The same is true of *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002)—as the court below explained. *Sigma-Tau* involved the approval of a subsequent drug for a *different condition*. *Id.* at 143 (noting first period of exclusivity for a "rare condition" and second period for "a second rare condition"). As in *Spectrum*, the challenge in *Sigma-Tau* was premised on potential off-label uses—not on FDA's approval of the same drug for treatment of the "same disease or condition." As the court stated, to read the Fourth Circuit's off-hand use of "uses" or "indications" as "supportive of the FDA's interpretation [here], or as supportive of ambiguity in

general, is to take the court's language out of context, as it [was] clear that the Fourth Circuit [wa]s comparing use of the same drug to treat *different* diseases and [wa]s using those terms to refer to that situation." App. 23.

Put another way, the Eleventh Circuit's decision cannot conflict with decisions of other Circuits that answered different questions altogether.[4] And Jacobus's argument to the contrary relies on pulling single words or phrases out of context. As a result, Jacobus's arguments do not merit a stay. *See United States v. Silver*, 954 F.3d 455, 458 (2d Cir. 2020) (denying to stay mandate when the movant "opt[ed] to rely upon cribbed quotations from those and other cases that are taken out of context in order to contrive a nonexistent conflict").

II. DENIAL OF A STAY WILL NOT WORK IRREPARABLE HARM

Jacobus claims a stay is warranted because issuance of the mandate will irreparably harm pediatric LEMS patients and Jacobus. Appl. 14-16. But pediatric patients with LEMS will still have access to treatment with the same drug,

[4] Jacobus may argue that there is a Circuit conflict as to whether the statute is ambiguous, as it did in its recently filed Eleventh Circuit reply in support of its stay motion. But courts consider whether a statute directly speaks to the "precise question at issue," *City of Arlington v. FCC*, 569 U.S. 290, 296 (2013) (citation omitted), they do not engage in a free-floating inquiry of whether the statute is unambiguous or ambiguous in *all* respects. That makes good sense—a statute may be unambiguous in some respects, *i.e.* on specific issues, and ambiguous in other respects. *See, e.g.*, *In re McGough*, 737 F.3d 1268, 1275 n.6 (10th Cir. 2013) (statute was unambiguous as to issue before court, notwithstanding that a different court had found the same statute to be ambiguous as to a *different* issue); *Scheerer v. U.S. Att'y Gen.*, 513 F.3d 1244, 1250-51 (11th Cir. 2008) (considering whether statute was ambiguous as to issue before court despite previously concluding that the statute was ambiguous as to a different issue). Here, neither *Spectrum* nor *Sigma-Tau* addressed whether the statute is ambiguous as to the same issue considered by the Eleventh Circuit.

amifampridine, after issuance of the mandate. And it is Catalyst that will be irreparably harmed should this Court stay the mandate's issuance.

First, Jacobus's suggestion (at 14-15) that pediatric patients with LEMS will be left without treatment is incorrect. FDA, which administers the Orphan Drug Act, chose not to file a petition for rehearing. Nor has it joined Jacobus's motion to stay issuance of the mandate. That choice is telling—it is FDA, not Jacobus, who is in a better position to determine the consequences of the Eleventh Circuit's decision for patients.

In any event, no pediatric patient with LEMS will be left without access to amifampridine. Beginning many years ago (before Jacobus's drug Ruzurgi® was approved), Jacobus began supplying its drug, including to pediatric patients, as part of a program that provides unapproved drugs to treat patients "under an expanded access I[nvestigational] N[ew] D[rug] [IND] application." Doc. 65-1, Pg. JA126; *see also* 74 Fed. Reg. 40,900 (Aug. 13, 2009) (explaining FDA's "expanded access" program). That program is authorized under the statute here and is unaffected by Catalyst's exclusivity. Additionally, prior to approval of Jacobus's drug, Catalyst operated for many years an "expanded access" program that did supply medication for pediatric patients with LEMS, and Catalyst has since restarted that program. Doc. 65-1, Pg. JA1011; *see also* Catalyst Pharmaceuticals, https://catalystpharma.com/ (last visited Jan. 13, 2022) (explaining options for pediatric patients in light of the Eleventh Circuit's decision). And, of course,

physicians are free to exercise their own medical judgment to prescribe Catalyst's drug Firdapse® to pediatric patients. *See supra* at 9.

Nonetheless, Jacobus asserts (at 15) that this Court "need look no further than the testimonial of Lori Dunham" regarding her daughter G.D., contained in a declaration attached to Jacobus's Eleventh Circuit motion, to confirm its argument. That is false. Jacobus contends that if its drug "leaves the marketplace—even for a short time—it will impede G.D.'s ability to manage her LEMS symptoms." Appl. 15. But Ms. Dunham has already secured treatment for her daughter with Catalyst's drug Firdapse®. *See* Pandolfo Decl. ¶ 8. To the extent Jacobus's example proves anything, it is evidence that pediatric LEMS patients will still have access to treatment. In short, Jacobus has submitted no evidence that pediatric patients with LEMS would be harmed by issuance of the mandate. [5]

Second, claims of financial injury come poorly from Jacobus. Jacobus is asking this Court to preserve its ability to reap unlawful profits, which does not constitute

[5] Jacobus contends that broader harm could occur because "[t]ying exclusivity to orphan drug designations alone . . . will entice drug developers to seek broad designations and narrower marketing rights." Appl. 14. That argument ignores both FDA's authority and the statute's explicit exceptions to exclusivity. FDA has ultimate authority over designation decisions. App. 25-26. And, in the event Jacobus's posited circumstance occurred, the Act contains an exception to exclusivity based on clinical superiority. A clinically superior drug can be approved notwithstanding exclusivity, where it has greater efficacy or makes a major contribution to patient care. *See* 21 U.S.C. § 360cc(c) (a drug can be clinically superior by having a "significant therapeutic advantage" through "greater efficacy"); 21 C.F.R. § 316.3(b)(3). Where a drug cannot be used for a certain patient population because it is not effective for that population or where a drug "provid[es] a major contribution to patient care," 21 U.S.C. § 360cc(c), FDA could deem the second drug clinically superior if the manufacturer could show the statutory criteria are met.

an irreparable harm. *See, e.g.*, *Sprint Sols., Inc. v. Fils-Amie*, No. 14-60224-CIV, 2014 WL 11776939, at *4 (S.D. Fla. Dec. 10, 2014) (reiterating that loss of profits from a product violating a statutory right warrants little consideration); *Fox Television Stations, Inc. v. FilmOn X LLC*, 966 F. Supp. 2d 30, 51 (D.D.C. 2013) (similar); *cf. United States v. Diapulse Corp. of Am.,* 457 F.2d 25, 29 (2d Cir. 1972) (holding that there is no legally protected interest in distributing products that are unapproved).

Indeed, Catalyst would be injured by staying the mandate. *See Books v. City of Elkhart*, 239 F.3d 826, 828 (7th Cir. 2001) (balancing the equities); *see also California v. Am. Stores Co.*, 492 U.S. 1301, 1307 (1989) (O'Connor, J., in chambers). Catalyst invested over $100 million to develop and obtain approval of Firdapse®. Yet, as the Eleventh Circuit concluded, Jacobus's sale of Ruzurgi® actively infringes on Catalyst's statutorily guaranteed period of exclusivity. App. 26-27. So far, it has infringed on almost three years (40%) of Catalyst's seven-year right. *See* Doc. 65-1, Pgs. JA428, 436 (Jacobus's drug approved on May 6, 2019). That constitutes irreparable harm. *See, e.g.*, *Sandoz, Inc. v. FDA*, 439 F. Supp. 2d 26, 32-33 (D.D.C.) (denying a pharmaceutical manufacturer market exclusivity constitutes harm), *aff'd*, No. 06-5204, 2006 WL 2591087 (D.C. Cir. 2006); *see also Apotex, Inc. v. FDA*, No. Civ.A 06-0627 JDB, 2006 WL 1030151, at *17 (D.D.C. Apr. 19, 2006) (same). Staying the mandate pending disposition of Jacobus's petition would likely consume almost *another* five months of Catalyst's rightful period of exclusivity. Meanwhile, Jacobus would continue to reap unlawful profits—enriching itself at Catalyst's expense.

And it is patently false to claim—as Jacobus does—that "Jacobus's loss will not be Catalyst's gain." Appl. 16. Catalyst will directly benefit from enforcement of its exclusivity through issuance of the mandate. As described, *supra* at 9, physicians are able to prescribe Jacobus's drug off-label for adult patients so long as it is approved. Approximately 75 to 100 (and likely more) adult LEMS patients are currently being treated with Ruzurgi®, likely due to payer preference for Ruzurgi® because of price. *See* Pandolfo Decl. ¶ 10. If Ruzurgi® were not infringing Catalyst's exclusivity, those patients would otherwise be purchasing Catalyst's drug Firdapse®.

Finally, broader equities counsel against staying the mandate. Congress concluded that "it [wa]s in the public interest to provide . . . incentives" for development of orphan drugs, including a period of market exclusivity. Pub. L. No. 97-414, § 1(b), 96 Stat. 2049, 2049 (1983). Absent those incentives, including exclusivity, "there . . . would be no financial incentive to research and develop treatments" that would serve such a small segment of the population. App. 2-3. In order for exclusivity to function properly as an incentive, manufacturers must be sure when they are making investments to develop a drug that their period of exclusivity will be honored. If manufacturers are left unsure of whether a competitor will be permitted to infringe on the promised period of exclusivity, the value of the incentive decreases dramatically. In this case, Jacobus, after already infringing almost 40% of Catalyst's exclusivity period, now asks for an additional infringement period of four to five months. That type of delay directly undermines the explicit purpose of the Act and should be rejected.

Accordingly, Jacobus has not shown good cause to stay issuance of the mandate.

CONCLUSION

For the foregoing reasons, this Court should deny Jacobus's application for a stay of the Eleventh Circuit's mandate pending disposition of its forthcoming petition for certiorari.

January 14, 2022

Respectfully submitted,

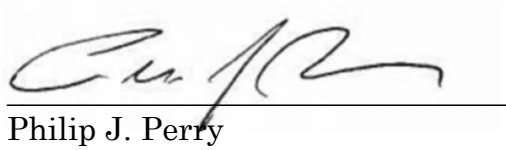

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Exhibit A

No. 20-13922

IN THE UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

CATALYST PHARMACEUTICALS, INC.,

Plaintiff-Appellant,

v.

XAVIER BECERRA, Secretary of Health and Human Services, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, JANET WOODCOCK, Acting Commissioner of Food and Drugs, U.S. FOOD AND DRUG ADMINISTRATION,

Defendants-Appellees,

JACOBUS PHARMACEUTICAL COMPANY, INC.,

Intervenor-Defendant-Appellee.

On Appeal from the United States District Court for the Southern District of Florida, No. 1:19-cv-22425-BB (Hon. Beth Bloom)

DECLARATION OF MARIA PANDOLFO IN SUPPORT OF CATALYST PHARMACEUTICALS, INC.'S RESPONSE IN OPPOSITION TO THE MOTION TO STAY THE MANDATE

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January 12, 2022

Counsel for Appellant Catalyst Pharmaceuticals, Inc.

DECLARATION OF MARIA PANDOLFO

I, Maria Pandolfo, declare as follows:

1. I am the Vice President for Patient Services for Catalyst Pharmaceuticals, Inc., and I oversee Catalyst's Patient Services program, known as Catalyst Pathways®, which supports and educates Lambert-Eaton Myasthenic Syndrome (LEMS) patients through the payer-approval process and during their titration and ongoing therapy with Firdapse® (amifampridine) Tablets 10 mg.

2. I have been employed by Catalyst in this role for three and a half years. Prior to that, I was employed in similar roles with other pharmaceutical companies for the last 20 years.

3. My first awareness of Ms. Lori Dunham was on September 30, 2021, when she contacted Catalyst Pathways soon after the Eleventh Circuit's decision in favor of Catalyst was announced.

4. She introduced herself as the mother of a pediatric LEMS patient who wanted to understand how her daughter might be able to access Firdapse after the decision. Since the decision was that day, she was asked to contact us back in a couple of days when we were better prepared to specifically address her questions.

5. On October 12, 2021, Ms. Dunham called the Catalyst main office and asked to speak with someone from the company. Her message was forwarded to me, and I called her back.

6. On that call, I outlined the options available to her physician in determining how her daughter might best access Firdapse, since as a pediatric patient she was outside of Firdapse's approved indication. I also explained that I would ask one of our Medical Science Liaisons (MSLs) to contact her daughter's physician and explain these same options. The process I described to her was that her daughter's physician could decide to: 1) refer her daughter to one of the existing Expanded Access Program sites Catalyst operates, which have provided Firdapse under compassionate use to patients with specific conditions – including pediatric LEMS; 2) the physician could choose to open a compassionate use Investigational New Drug Application (IND) with the U.S. Food and Drug Administration (FDA), and Catalyst could support the physician in that process and also supply Firdapse to the physician for the patient at no charge once the IND was approved by the FDA; or 3) the physician could choose to exercise his/her own medical judgment and prescribe Firdapse off-label.

7. After that call, I asked one of our MSLs to contact Ms. Dunham's daughter's physician and review these options. I was told that the physician elected to write an off-label prescription for Ms. Dunham's daughter for Firdapse, and it was forwarded to a pharmacy who worked with the physician to obtain payer approval.

8. On or about November 10, 2021, I had my last contact with Ms. Dunham. In that call, she informed me that her daughter's prescription was approved for Firdapse and that the pharmacy had dispensed it and she had received it.

9. As Catalyst's VP of Patient Services, I also have a reasonable basis to estimate how many adult LEMS patients are being treated with Jacobus's drug Ruzurgi rather than Firdapse, despite Ruzurgi being indicated only for pediatric LEMS.

10. Based on the number of patients who we saw leave Catalyst Pathways after Ruzurgi's approval, the number of patients who discontinued enrollment with Catalyst Pathways due to a payer preference for Ruzurgi because of price (notwithstanding that it is not approved for adults) and the number of forecasted patients who never materialized, I would estimate that there are between 75 and 100 adult LEMS patients currently being treated with Ruzurgi, and potentially more.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on January 12, 2022

Maria Pandolfo

Maria Pandolfo, Vice President of Patient Services