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

REPLY IN SUPPORT OF EMERGENCY APPLICATION FOR A STAY PENDING THE FILING AND DISPOSITION OF A PETITION FOR WRIT OF CERTIORARI

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As explained in Jacobus's stay application, this Court should prevent the Eleventh Circuit from issuing its mandate because there is "(1) 'a reasonable probability' that this Court will grant certiorari, (2) 'a fair prospect' that the Court will then reverse the decision below, and (3) 'a likelihood that irreparable harm [will] result from the denial of a stay.'" *Maryland v. King*, 567 U.S. 1301, 1302 (2012) (Roberts, C. J., in chambers) (quoting *Conkright v. Frommert*, 556 U.S. 1401, 1402 (2009) (Ginsburg, J., in chambers)). Catalyst's arguments in response all fail.

REASONS FOR GRANTING THE STAY

I. The petition will present a substantial question, which the Eleventh Circuit wrongly decided.

Jacobus's petition for certiorari will present a substantial question. Despite its attempts to distinguish *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002), and *Spectrum Pharmaceuticals, Inc. v. Burwell*, 824 F.3d 1062 (D.C. Cir. 2016), the Eleventh Circuit's decision conflicts with both of those opinions and offers an unsound interpretation of the Orphan Drug Act (ODA). *See* Application 8–14. Put simply, the circuit courts do not agree on whether the ODA (1) unambiguously ties orphan-drug exclusivity to a drug's approved and labeled use, *see Sigma-Tau*, 288 F.3d at 144–45, (2) unambiguously ties orphan-drug exclusivity to the drug's orphan designation alone, without regard to the drug's approved use, *see Catalyst Pharms., Inc. v. Becerra*, 14 F.4th 1299, 1306, 1308–09 (11th Cir. 2021) (App. 13, 18–21), or (3) leaves the matter to FDA's reasonably exercised discretion, *see Spectrum*, 824 F.3d at 1067. The Eleventh Circuit's opinion in this case presents the worst take of the three, for the reasons Jacobus gave in its briefing before that

court, *see* Jacobus Appellee Br. 24–57, which the Eleventh Circuit ignored, *see* Jacobus Pet. Rehearing 10–15.

A. Catalyst doesn't dispute that the courts are split on whether the Orphan Drug Act is ambiguous and its efforts to downplay that split fail.

Catalyst essentially concedes there is a split on whether the ODA is ambiguous but attempts to diminish it. None of its arguments are persuasive.

First, while Catalyst doesn't dispute that there is a conflict on whether the ODA is ambiguous, it nevertheless asserts that the Fourth and D.C. Circuit "addressed whether [that] statute is ambiguous" as to different "issue[s]" than that "considered by the Eleventh Circuit." Response 22 n.4. That understates the extent of the holdings in these cases, which each concerned the scope of orphan-drug exclusivity and the existence or absence of ambiguity with respect to the scope of the ODA. The Eleventh Circuit held that the ODA's language unambiguously ties exclusivity to a drug's designation alone, without any regard for the scope of the drug's use-based approval. *See Catalyst*, 14 F.4th at 1309 (App. 18). In the Eleventh Circuit's view, "[i]f Congress wanted to make" a drug's approved "'use or indication' ... relevant to ... market exclusivity[,] it could have" and presumably should have "done so by including such [express] language in" the ODA. *Id.* But both *Spectrum* and *Sigma-Tau* offer interpretations of the ODA that directly oppose the Eleventh Circuit's reading. In *Sigma-Tau*, the Fourth Circuit reasoned that "the plain language of the ODA ... unambiguous[ly]" supports FDA's longstanding interpretation and regulations, emphasizing that "the statute is *clearly* directed at FDA approved-use." 288 F.3d at 144–45 (emphasis added). And in *Spectrum*, the

D.C. Circuit reasoned that the very same statutory language is ambiguous, but that FDA's interpretation and implementation of the act was reasonable. *See* 824 F.3d at 1067.

Contrary to Catalyst's assertions, *see* Response 22 n.4, all three courts considered and reached different answers on the same question: whether the ODA is ambiguous as to the scope of an orphan-drug exclusivity or whether FDA has some room to interpret it in a way that merits at least some deference. The Eleventh Circuit in this case reached the exact opposite answer than did the Fourth Circuit as to whether the ODA was ambiguous and in which party's favor, with the Eleventh Circuit concluding that the ODA unambiguously favored Catalyst's interpretation and the Fourth Circuit concluding that the ODA unambiguously favored FDA's interpretation. The Eleventh Circuit also reach the exact opposite answer than did the D.C. Circuit, when it concluded that the ODA was unambiguous, whereas the D.C. Circuit held that it was ambiguous.

Second, Catalyst attempts to downplay the split by pointing to factual differences in the case—echoing the Eleventh Circuit's refrain that both *Spectrum* and *Sigma-Tau* concerned drugs approved for marketing to treat different "diseases" or "conditions." Response 3; 19–22 (quoting *Catalyst*, 14 F.4th at 1311 (App. 23)). But even that's wrong. All the drugs at issue in *Sigma-Tau* treated the same "rare condition": "carnitine deficiency." 288 F.3d at 143. Indeed, just like the drugs in this case, the drugs in *Sigma-Tau* treated one "rare condition" in multiple patient populations: (1) "carnitine deficiency in people with inborn metabolic disorders" and

(2) "carnitine deficiency in patients with end-stage renal disease ... who are undergoing dialysis." *Id.* And just as in this case, the manufacturer of the first-approved drug in *Sigma-Tau* tried to use an active but limited exclusivity right to prevent subsequent marketing approvals on an "unprotected indication." *Id.* FDA confirmed these facts nearly a decade ago, observing that *Sigma-Tau* concerned "several drugs ... approved for different indications or uses within the same rare disease or condition." *Orphan Drug Regulations*, 78 Fed. Reg. 35,117, 35,124 (June 12, 2013). The agency then noted that the Fourth Circuit's analysis vindicated its own interpretation of the ODA as protecting "only the uses for which the drug is approved." *Id.*

B. There is a fair prospect that this Court would conclude the Eleventh Circuit's decision is wrong.

Catalyst next wrongly insists that the Eleventh Circuit's opinion "was plainly correct," and thus certain to survive Supreme Court review. Response 14; *see id.* at 14–19. As an initial matter, Catalyst ignores that both Judge Bloom and Magistrate Judge Louis sided with Jacobus in the district court, each issuing well-reasoned opinions. *See Catalyst Pharms., Inc. v. FDA*, No. 19-cv-22425-BLOOM/Louis, 2020 WL 5792595 (S.D. Fla. Sept. 29, 2020), R.107 (adopting Judge Louis's recommendation to grant summary judgment to FDA and Jacobus); *Catalyst*, 2020 WL 4573068, R.93 (Report & Recommendation). Catalyst likewise ignores, or unpersuasively tries to explain away, the conflicts between the Eleventh Circuit's opinion here and the opinions of other circuit courts discussed above. *See supra* at I.A. In short, Catalyst ignores the possibility that the Eleventh Circuit—which issued

an opinion contrary to the reasoning of several other appellate judges, and contrary to the views of several district court judges who considered these same facts—might have been wrong.

Catalyst also doesn't meaningfully grapple with Jacobus's arguments for affirmance, which the Eleventh Circuit here did not address, or even confront. *See* Jacobus Pet. Rehearing 9–15. As Jacobus has fully explained elsewhere, FDA did not act unlawfully when it approved Ruzurgi® to treat LEMS in a pediatric population only. *See* Jacobus Appellee Br. 24–57.

Contrary to Catalyst's assertions, *see* Response 3, 15–16, Jacobus has always put forward a text-based argument for why this is so. The ODA's language extends exclusivity to a drug designated "for a rare disease or condition," 21 U.S.C. § 360bb(a)(1), and then approved "pursuant to [21 U.S.C. §] 355" for that disease or condition, *id.* § 360cc(a). *See* Application 4–5; Jacobus Appellee Br. 8–10. Section 355, in turn, limits FDA's power to consider, in approving new-drug applications, whether the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 355(d); *Spectrum*, 824 F.3d at 1067 (marketing applications "will necessarily include only stated [uses]"). In other words, the best reading of the text is that the scope of orphan-drug exclusivity is determined by the scope of the approval—which is always use specific.

Catalyst is equally mistaken in its assertions that indicated use is a "relatively vague concept" compared to "disease or condition." Response 17. Catalyst points for support only to a non-binding FDA guidance regarding recommendations for the

content and format of the "indications and usage" of labeling proposed to FDA, going to extremes to blur the lines between "indications" and "usage" statements to cast doubt. What Catalyst misses, however, is that such language is used throughout the Food, Drug, and Cosmetic Act itself, in FDA's implementing regulations, and throughout FDA's guidance to reflect the scope of an FDA drug approval. *See, e.g.*, 21 U.S.C. §§ 352, 355, 355-1, 355a, 355c, 355g, 356.

In any event, Catalyst also glosses over that the ODA does not expressly contemplate the specific circumstances of this case, where a drug is designated "for a rare disease or condition" but approved for only a subpopulation of patients with that "disease or condition." Application 6; Jacobus Appellee Br. 10, 31–33. Does such a drug enjoy orphan drug exclusivity at all? Jacobus Appellee Br. 10. If so, how much? *Id*. The statute does not say. It is ambiguous. *See* Application 6; *see City of Arlington v. FCC*, 569 U.S. 290, 296 (2013) (noting that when a statute "is silent or ambiguous with respect to the specific issue, the question for the court is whether the agency's answer is based on a permissible construction of the statute") (internal quotation marks omitted).

Here, FDA carefully considered these ambiguities and for decades interpreted the Act to protect only a drug's approved, labeled uses. *See* Jacobus Appellee Br. 11–12. In 1992, after considering numerous comments, FDA promulgated a transparent rule giving all drug manufacturers—including Catalyst—ample notice of its interpretation. *See Orphan Drug Regulations*, 57 Fed. Reg. 62,076, 62,086 (Dec. 29, 1992) (defining "Orphan Drug Exclusive Approval" to follow the drug's indicated use,

or "indication"). And in 2013, FDA double downed on its interpretation when it added "clarifying language" to its regulation to make clear that the "scope of orphan-drug exclusivity is limited to the indication(s) or use(s) for which the drug is approved for marketing, even if the orphan-drug designation for the drug is broader." 78 Fed. Reg. at 35,123; *see* 21 C.F.R. § 316.31(b) ("Orphan-drug exclusive approval protects only the approved indication or use of a designated drug. If such approval is limited to only particular indication(s) or uses(s) within the rare disease or condition for which the drug was designated, FDA may later approve the drug for additional indication(s) or uses(s) within the rare disease or condition not protected by the exclusive approval."); *see also id.* § 316.31(a) ("FDA may approve a sponsor's marketing application for a designated orphan drug for use in the rare disease or condition for which the drug was designated, or for select indication(s) or use(s) within the rare disease or condition for which the drug was designated."); *id.* § 316.34(a) (noting that FDA will recognize orphan-drug exclusivity based on the scope of approval). Because FDA reasonably resolved the statute's ambiguity by recognizing exclusivity based on a drug's approved uses, its decision to approve Ruzurgi® for "unprotected" uses was neither arbitrary, nor capricious, nor unreasonable, nor unlawful. *Chevron, U.S.A., Inc. v. Nat. Res. Def. Council, Inc.*, 467 U.S. 837, 842 (1984); *see* Jacobus Appellee Br. 41–44, 53; *see infra* Section I.C.

But the Eleventh Circuit did not even address this issue. *See* Jacobus Pet. Rehearing 10–11. In so doing, it missed the ambiguity Jacobus identified, *see* Jacobus

Appellee Br. 26–41, and it missed the textual foundations and sound logic of FDA's regulations, *see id.* 41–57. In short, the Eleventh Circuit erred.

Tellingly, Catalyst also downplays the court's actual reasoning. The Eleventh Circuit held that the scope of orphan exclusivity must be based on the scope of an approved drug's designation alone, without reference to the scope of its approval. *See Catalyst*, 14 F.4th at 1306, 1308–09 (App. 13, 18–21). But according to Catalyst's Response in this Court, the ODA *does* tie exclusivity to the scope of a drug's approval. *See* Response 15. Catalyst just thinks that Firdapse® was approved "for LEMS" within the meaning of the ODA, despite it actually being approved as "indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults." *Id.* at 15, 16. No part of the ODA's text expressly states, or even implies, that a drug approved for a subpopulation of patients with a disease or condition is approved "for" that "disease or condition" in all patients within the meaning of the law. *See* 21 U.S.C. § 360cc(a). In fact, doing so would run headlong into § 355, which only permits FDA to approve drugs for certain uses or indications. That is precisely why the text does not clearly preclude FDA's action in this case.

C. FDA's interpretation of the ODA is reasonable.

Catalyst next claims that "FDA manufactured a much finer distinction than the statute permitted" when it read the text to tie exclusivity to a drug's approved use. Response 15. Not so. The ODA doesn't operate in a vacuum but instead in tandem with the limitations on FDA's power to "approv[e] ... 'application[s]'" under 21 U.S.C. § 355. *See Spectrum*, 824 F.3d at 1067. It was more than reasonable for FDA to interpret the ODA—which cross references and operates through § 355—to

permit it to approve an application for Ruzurgi® to treat a pediatric population after considering that it had not granted Catalyst's new-drug application for Firdapse® for that population. *See supra* Section I.B

Moreover, as Catalyst's own brief shows, FDA's action was not without precedent. *See Int'l Bhd. of Teamsters, Chauffeurs, Warehousemen & Helpers of Am. v. Daniel*, 439 U.S. 551, 566 n.20 (1979) ("It is commonplace in our jurisprudence that an administrative agency's consistent, longstanding interpretation of the statute under which it operates is entitled to considerable weight."). FDA can and often does approve the marketing of drugs for uses much narrower than the treatment of a "disease or condition" outright, and often distinguishes between pediatric and adult uses. *See* Response 17–18.

Catalyst makes much of the fact that FDA has not approved a drug for a pediatric indication during the pendency of that drug's orphan exclusivity for an adult indication. *See* Response 11. Catalyst fails to recognize, however, that given the relatively small total numbers of orphan-drug approvals, and the much smaller number of such approvals for which a second "same drug" product has sought approval, the absence of a precedent for a unique fact pattern is far from telling. What is informative, however, is that Congress and FDA treat pediatric and adult indications differently in myriad circumstances, as illustrated by: (1) the Pediatric Research Equity Act requirements (21 U.S.C. § 355c; 42 U.S.C. § 262(m) (FDA can require pediatric studies in certain drugs to support safe and effective pediatric use of the drug)); (2) pediatric exclusivity under the Best Pharmaceuticals for Children

Act (21 U.S.C. § 355a) (eligibility for pediatric exclusivity for drug sponsors that complete pediatric clinical studies requested by FDA)); (3) innumerable labeling carve-outs for generic and biosimilar products for which either the adult or pediatric indication is covered by orphan exclusivity while the other is not (*see, e.g., Otsuka Pharm. Co. v. Burwell*, No. GJH-15-852, 2015 WL 1962240 (D. Md. Apr. 29, 2015) (generic versions of branded drug could be approved for adult use during the period of orphan drug exclusivity with labeling related to pediatric use carved out)); (4) separate labeling for pediatric use (21 C.F.R. § 201.57(c)(9)(iv)); and (5) specific scientific standards and requirements for developing drugs for pediatric indications, to name a few (*e.g.*, FDA, Guidance for Industry, E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population (Apr. 2018); FDA, Draft Guidance, General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products (Dec. 2014)). FDA's different treatment of a pediatric indication is entirely commonplace within the drug approval paradigm.

Catalyst's suggestion that manufacturers can easily skirt used-based orphan drug exclusivity is also wrong. The FDA regulations struck down by the Eleventh Circuit in this case date to the early 1990s and codify an FDA practice that goes back even further. *See* Jacobus Appellee Br. 11–12. Yet Catalyst offers no examples of circumvention. *See* Response 18. And it stands to reason that if FDA ever had been confronted with such a situation, it would have interpreted the ODA to avoid the absurd results Catalyst posits.

Relatedly, Catalyst's silly "brown hair" hypothetical stands in sharp contrast to the serious facts of this case. *See* Response 18. Jacobus did not seek, and was not approved, to market Ruzurgi® for the treatment of LEMS in people with "brown hair," who could just as easily have treated their LEMS with Firdapse®. Jacobus sought, and obtained, approval of Ruzurgi® for the treatment of LEMS in children ages six to less than seventeen, for whom Firdapse® had not been shown safe and effective. *See* Application 6. Catalyst is quick to point out that physicians can still prescribe Ruzurgi® for off-label use to treat LEMS in adults (while simultaneously touting the off-label availability of Firdapse® to treat LEMS in children). The point of the orphan exclusivity, though, is that FDA could not and did not approve Ruzurgi® to treat LEMS in adults, and Jacobus cannot and has not marketed Ruzurgi® for treatment of LEMS in adults. Catalyst and the Eleventh Circuit painted with too broad of a brush when they concluded that the text of the ODA clearly prevented FDA from approving any amifampridine drug for LEMS in children after it approved Firdapse® for LEMS in adults only.

In sum, this case creates a circuit split that the Supreme Court will likely address, and there is a fair prospect that this Court would reverse the Eleventh Circuit's novel reading of the ODA.

II. There is good cause for a stay.

Despite Catalyst's denials, there is also good cause for a stay. When the mandate issues and takes effect, there will be no FDA-approved drug treatment for children with LEMS. *See* Application 14–15. And if the Supreme Court does reverse the Eleventh Circuit, Jacobus will have no way of recouping the losses it suffered

because of the Eleventh Circuit's errors. *See id.* at 15–16. The broader equities and the public interest likewise favor a stay. Indeed, the Eleventh Circuit's decision undeniably harms everyone but Catalyst, whose single focus is preventing the permissible, off-label use of Ruzurgi® for adults by seeking to undo FDA's approval of that drug for pediatric use.

Again, Catalyst's arguments to the contrary lack merit.

First, Catalyst suggests that FDA's decision to stop litigating this case somehow indicates that the equities do not favor a stay. Response 23. That is pure speculation. FDA has countless litigation and non-litigation priorities, not the least of which includes an ongoing public health crisis caused by the COVID-19 pandemic. In addition, the timeline to petition for rehearing in the Eleventh Circuit coincided with critical personnel changes at the Department of Justice—including the confirmation of a new Solicitor General—which could have affected FDA's representation. FDA and the Department of Justice litigated this case for two years. It is fantasy to think that they now agree with Catalyst and regret their decision to defend the Ruzurgi® approval. Regardless, the Court could also request FDA to weigh in if it was curious about this issue.

Second, Catalyst claims that "pediatric patients with LEMS will still have access to treatment with the same drug, amifampridine, after issuance of the mandate." Response 22–23. Specifically, Catalyst claims that children who currently use Ruzurgi® through normal prescriptions will be able to use Ruzurgi® or Firdapse® through special "expanded access" programs, *see id.* at 23, or simply use Firdapse®

off-label, *see id.* at 24. This again is highly speculative, and it again glosses over the details of whether Jacobus actually could restart its "compassionate use" expanded access program for Ruzurgi® as a result of this case. Indeed, Catalyst assumes that expanded access would be available for pediatric patients (1) notwithstanding the approved treatment for adult patients, and the off-label availability of that treatment, and (2) without compromising clinical development of this rare disease for pediatric patients. *See* 21 C.F.R. § 312.305. Catalyst further assumes that Jacobus has the financial wherewithal to continue producing Ruzurgi® for expanded access use regardless of the cost recovery limitations of such use. *See* 21 C.F.R. § 312.8 (setting out those limitations).

More importantly, Catalyst's argument appears to rely on an unstated conclusion that Ruzurgi® and Firdapse® are clinically interchangeable simply because FDA considers them the "same drug" for purposes of the ODA. That conclusion does not follow from the law, which deems Ruzurgi® and Firdapse® to be the "same drug" merely because they have the same "active moiety," regardless of differences like risk-benefit profiles, patient tolerance, or formulation. *See* Jacobus Appellee Br. 34 n.4 (quoting 21 C.F.R. § 316.3(b)(14)). Moreover, even if patients currently on Ruzurgi® could switch to Firdapse®, Catalyst has simply ignored the disruptions and burdens patients will face along the way. *See, e.g.*, Response Ex. A (explaining in detail the process by which Lori Dunham secured an off-label prescription of Firdapse® for her daughter with LEMS).

Third, Catalyst claims in a footnote that the Eleventh Circuit's ruling will not encourage, or even allow, manufacturers to secure exclusivity that exceeds their marketing rights. *See* Response 24 n.5. While that argument pertains more to the merits of the Eleventh Circuit's decision than the equities of the requested stay, it is still wrong. Indeed, Catalyst suggests, as did the Eleventh Circuit, that FDA could have limited Firdapse's® exclusivity by circumscribing its initial designation. *Id.*; *see also* Catalyst, 14 F.4th at 1312 (App. 26). That isn't true. Under the ODA, FDA "shall designat[e]" a drug for the "disease or condition ... request[ed]" by the drug manufacturer or sponsor. 21 U.S.C. § 360bb(a)(1). FDA does not have the authority to narrow designation requests, let alone to retrofit designation years later when research has demonstrated the drug's safety and efficacy (or lack thereof) in different clinical contexts.

Catalyst also leans heavily on the "clinical superiority" exception to exclusivity, implying that Ruzurgi® could come back to the market if only Jacobus shows that Ruzurgi® "provides a significant therapeutic advantage over" Firdapse® "in terms of greater efficacy, greater safety, or by providing a major contribution to patient care." Response 24 n.5 (citing 21 U.S.C. § 360cc(c)). This, again, is both highly speculative and disingenuous. To begin with, both Catalyst and the Eleventh Circuit have conflated and confused the distinction between the ODA's "clinical superiority" provisions, 21 U.S.C. § 360cc(c), and FDA's "clinical superiority" *regulations*, which interpret the statute's ambiguous use of the term "same drug," 21 C.F.R. § 316.3(b)(3). *See* Jacobus Appellee Br. 47–48. The latter contains an exception for a "clinically

superior" drug by deeming it not the "same" as the first-approved drug, even when they have the same active moiety. *See id.* Of course, "Congress" did not write FDA's regulation "provid[ing]" this "exception[]," as Catalyst has repeatedly and wrongly insisted throughout this litigation, including before this Court. *E.g.* Response 8, 24 n.5. In fact, the ODA, as amended in 2017, contains only two statutorily enumerated exceptions, in cases of supply shortage and waiver of exclusivity—neither addresses clinical superiority. 21 U.S.C. § 360cc(b). It is a mistake to suggest that Congress anticipated the circumstances of this case and attempted to address them through the "clinical superiority" provisions of the ODA.

Moreover, Catalyst does not provide any basis for arguing that FDA would have concluded that Ruzurgi® is "clinically superior" to Firdapse® within the meaning of the law. *See* Response 24 n.5. Even while Catalyst suggests that Ruzurgi® makes a major contribution to patient care, Catalyst undoubtedly knows that FDA does not consider the treatment of a new or different patient population to be a "major contribution to patient care." 78 Fed. Reg. at 35,125 (identifying factors for consideration and explaining that "[i]n FDA's experience, showings of major contribution to patient care remain unusual"). And Catalyst would presumably contest such a finding, given its apparent belief that Firdapse® and Ruzurgi® are interchangeable because FDA considers them the "same drug" for purposes of the ODA, *see* Response 23–24.

Fourth, Catalyst claims that the mandate will not irreparably harm Jacobus because Jacobus has no right to market Ruzurgi® anyway. Response 24–25. Indeed,

Catalyst claims that it will be harmed if the mandate does not issue, as adult patients will continue to use Ruzurgi® rather than Firdapse® "because of price." *Id.* at 26. This question-begging argument warrants no consideration. If Jacobus is right that the Eleventh Circuit erred in this case, then its revenues from Ruzurgi® could not be considered "unlawful profits," *id.* at 25, and its losses will indeed constitute irreparable harm.

Fifth, Catalyst argues that a stay of the Eleventh Circuit's mandate will somehow gut the ODA's incentive structure. According to Catalyst, "[i]n 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." *Id.* at 26. But Catalyst in no way connects this line of argument to the stay of the Eleventh Circuit's mandate. Indeed, it is the mandate that will upset the status quo by reversing the district court's summary judgment ruling, creating a circuit split, and ostensibly striking down a regulation that drug manufacturers have operated under for nearly three decades. *See supra* at 5–7. It is thus the mandate, not the requested stay, that will leave "manufacturers ... unsure" of the exclusivity rights they can expect to earn under the ODA. Response 26.

In any event, Catalyst has it backwards. The issuance of the mandate would pervert the incentive structure of the ODA by discouraging further drug development within an overbroad exclusivity. But most drugs (even orphan drugs) fail, which is why the ODA's structure of designating drugs broadly early in the development process and approving those that succeed for specific uses is important. That

structure maximizes the chances that patients with rare disease will end up with a safe and effective treatment. The structure that Catalyst proposes would collapse designation and approval, would undermine development incentives, and would result in fewer approved treatments for patients with orphan diseases and no treatment options at all for patients in orphan subpopulations.

Finally, and in any event, Catalyst has no response to Jacobus's argument that the public would continue to benefit from the availability of both Firdapse® and Ruzurgi®—one to treat adults, the other to treat children—while this case is further litigated. *See* Application at 16. For that reason, and for the other reasons given in Jacobus's application and this brief, this Court should stay the Eleventh Circuit's mandate.

CONCLUSION

Because Jacobus's petition will present a substantial question, and because Jacobus has shown good cause, the Court should stay the Eleventh Circuit's mandate.

Respectfully submitted,

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