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# FDA Doubles Down on Its Pre-Catalyst Stance on Orphan Drug Exclusivity

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On January 24, 2023, the Food and Drug Administration published a notice in the Federal Register to "address the uncertainty" created by the US Court of Appeals for the Eleventh Circuit's September 30, 2021, decision in *Catalyst Pharms., Inc. v. Becerra*. In the notice, the FDA noted that it had complied with the court's order to set aside its approval of Jacobus Pharmaceutical Co.'s drug, but explained that "in matters beyond the scope of that court order," the agency intends to apply its existing regulations and long-standing approach to grant orphan drug exclusivity based on the indications for which the drug is approved rather than granting the exclusivity for the entire rare disease or condition that was the subject of the orphan drug designation (as the *Catalyst* court instructed the FDA to do).

While the FDA's recent announcement may calm the waters for industry, it also leaves the agency open to legal challenge, particularly in the Eleventh Circuit, where *Catalyst* is binding precedent. That said, the FDA's public Federal Register notice also could serve a protective role in any future Administrative Procedure Act litigation based on the agency's failure to more broadly apply the *Catalyst* court's interpretation of the statute, in that the FDA could assert that industry is on notice about the agency's planned approach, which is consistent with its past, pre-*Catalyst* precedent.

## FDA historically tied orphan drug exclusivity to the scope of the drug's approval

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug or biologic intended to treat a rare disease or condition, defined as a patient population of fewer than 200,000 individuals in the United States, or a patient population of 200,000 or more in the US where there is no reasonable expectation that the cost of developing and making available the drug or biologic will be recovered from sales in the US.

In the US, orphan drug designation entitles a party to financial incentives, such as tax advantages and user fee waivers. In addition, if a drug or biologic with an orphan drug designation subsequently receives the first marketing approval for a particular active ingredient or principal molecular structural features for the indication for which it has such a designation, the product is entitled to a seven-year period of marketing exclusivity, which precludes the FDA from approving another marketing application for the same drug for the same indication during that time period, except in limited circumstances, such as a showing of clinical superiority to the product with existing orphan drug exclusivity, or if the FDA finds that the holder of the orphan drug exclusivity has not shown that it can ensure the availability of sufficient quantities of the product to meet the needs of patients with the disease or condition for which the drug was designated.

Traditionally, the FDA has taken a narrow approach to the meaning of the phrase "same drug," interpreting it in the context of exclusivity as limited to the "indication or use" for which the orphan drug product was approved. The intent of this approach was to "permit multiple orphan-drug exclusive approvals for multiple subsets of the same underlying orphan disease or condition," which the agency believed "is consistent with the purpose of the Orphan Drug Act because it provides an important incentive for one or more sponsors to develop, or to continue to develop, a potentially promising drug for use in all persons affected by a rare disease or condition, rather than in just a subset of that orphan population, even after the drug has been approved for a different subset of the population with the disease or condition."[1] Therefore, historically, orphan drug exclusivity did not offer products total protection from competition from the same or a different drug approved for the same disease or condition, because orphan drug exclusivity did not prevent the FDA from approving the same or a different drug in a different indication (including different patient populations) for the same disease or condition. This means that even after an orphan drug is approved and granted orphan drug exclusivity, the FDA could approve a later application for the "same drug" for the "same condition" before the expiration of the seven-year exclusivity period because the FDA has interpreted "same disease or condition" to meant same "use or indication."

# A brief detour: The *Catalyst* decision

*Catalyst* involved a dispute between two entities that had been granted orphan drug exclusivity by the FDA for the same drug for the same rare disease. Catalyst Pharmaceuticals was the orphan drug exclusivity holder for its drug FIRDAPSE to treat adults with Lambert-Eaton myasthenic syndrome (LEMS), a rare autoimmune disease that causes the immune system to attack the body's own tissues. Jacobus was approved subsequently, during the window of FIRDAPSE's exclusivity, for its drug, RUZURGI, which also received orphan drug exclusivity, but not because it showed clinical superiority to FIRDAPSE or because FIRDAPSE was unavailable in sufficient quantities to meet patient need. Rather, the FDA approved RUZURGI during FIRDAPSE's orphan exclusivity period because RUZURGI was approved to treat **pediatric patients** with LEMS, and not adults. To the FDA, this distinct patient population meant that RUZURGI was not approved for the "same disease or condition" because the FDA's view was that the scope of the orphan drug exclusivity was tied to the scope of approval – where two drugs were approved for the same rare disease, but had different indications (i.e., one drug indicated to treat adults and the other to treat pediatric populations), both could be approved as orphan drugs. As noted by the *Catalyst* court, however, Jacobus never submitted a New Drug Application (NDA) seeking pediatric-only approval, and never conducted any clinical trials in children.[2] All of the patients involved in Jacobus' clinical trials were adults.[3] Jacobus *did* submit limited data on pediatric safety, but not efficacy – even though both safety and efficacy data are required for approval of an NDA.[4] Against the backdrop of these compelling facts, the Eleventh Circuit rejected the lower court's application of *Chevron* to defer to the FDA's statutory interpretation, and concluded that the FDA's argument that orphan drug exclusivity is tied to the scope of a drug's approval had no basis in the plain language of the Federal Food, Drug, and Cosmetic Act (FDCA). Rather, the Eleventh Circuit held that the phrase "same disease or condition" in the statute referred to the rare disease or condition that was the subject of the orphan drug designation and, therefore, the corresponding orphan drug exclusivity properly referred to the **entire** rare disease or condition, and not just a narrowed indication. Accordingly, the Eleventh Circuit ordered the FDA to set aside the RUZURGI approval due to FIRDAPSE's orphan drug exclusivity.

Since the Eleventh Circuit held that the FDA's interpretation violated the plain language of the FDCA, rare disease sponsors remained in limbo wondering how the FDA would define the scope of orphan drug exclusivity in a post-*Catalyst* world.

# FDA's response to *Catalyst*

The FDA may have been waiting for a legislative fix to the problem, such as the proposed Retaining Access and Restoring Exclusivity (RARE) Act, consistent with how the agency dealt with similar setbacks in previous orphan drug cases.[5] While the agency was waiting for Congress to come to its rescue, it was reported that the FDA's Office of Orphan Products Development had deferred pending orphan drug exclusivity determinations, listing them as "TBD" in the Orange Book. With the recent passage of the Food and Drug Omnibus Reform Act, which did not include any provisions of the RARE Act that could support the agency's long-standing approach to grant exclusivity based on the scope of approval rather than the scope of the orphan drug designation, the FDA turned to other means and landed on a public announcement of the dire impact of the *Catalyst* case on its website, and the Federal Register notice drumming the same beat in support of the agency's public rebuff of the Eleventh Circuit's rationale.

What remains to be seen is how legal challenges in the Eleventh Circuit will be handled in light of the direct affront the FDA has raised to *Catalyst*. After all, while the Eleventh Circuit's decision is only persuasive authority in the rest of the country, it is binding in that circuit. Whether a litigant can succeed in relying on *Catalyst* likely will depend on the key factual issues that made *Catalyst* an ideal vehicle to challenge the FDA's statutory interpretation, such as the agency's decision to "administratively split" an NDA to allow a pediatric-only indication to move forward based on efficacy data from trials only conducted with adults,[6] and an underlying rare disease where "the disease mechanism, the pathophysiology, the clinical symptoms, the treatment regimens, and even adverse events" are the same for both adults and children.[7]

# Takeaways

The FDA's long-held view about the goals of the Orphan Drug Act, which jibe with the agency's overarching public health mission, resulted in a Federal Register notice that openly challenges a federal appellate court's interpretation of the FDCA. While rare disease sponsors can take some comfort in having clarity on the agency's

position (and hopefully the logjam of orphan drug exclusivity decisions will now subside), sponsors seeking to challenge the agency's interpretation can attempt to use the *Catalyst* playbook – at least until a(nother) legislative fix comes along to support the FDA's long-held interpretation.

*Law clerk Madelon Bird also contributed to this alert.*

**Notes**

1. 76 Fed. Reg. 202, 64871 (October 19, 2011).
2. *Catalyst Pharms., Inc. v. Becerra*, No. 20-13922, DC Docket No. 1:19-cv-22425-BB, 9 (11th Cir. 2021); *see also* 21 USC § 355(b).
3. *Id*.
4. *Id*; *see also* 21 USC § 355(b).
5. *See e.g., Eagle Pharm. v. Azar,* 952 F.3d 323 (DC Cir. 2020). While the *Eagle* case was pending, Congress amended the Orphan Drug Act to allow the FDA to impose a clinical superiority requirement when determining whether a drug will obtain orphan drug exclusivity, thus resolving the issue in the case as of the date of the revised legislation. *See* the FDA Reauthorization Act of 2017, Pub. L. No. 115-52, § 607(a), 131 Stat. 1005, 1049-50 (amending 21 USC § 360cc). The *Eagle* case proceeded, however, as the appellant in that case was subject to the earlier version of the law, and thus a case or controversy remained for the court to decide.
6. *Catalyst Pharms., Inc. v. Becerra*, No. 20-13922, DC Docket No. 1:19-cv-22425-BB, 9 (11th Cir. 2021).
7. *Id*. at 7.



# Key Contacts



| | |
|---|---|
| Sonia Nath<br>Washington, DC | snath@cooley.com<br>+1 202 776 2120 |
| Natasha Leskovsek<br>Washington, DC | nleskovsek@cooley.com<br>+1 202 728 7131 |