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Catalyst Pharms., Inc. v. Becerra: When the Food and Drug Administration Repeatedly Ignores the Plain Language of the Orphan Drug Act (ODA)

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CATALYST PHARMS., INC. V. BECERRA: WHEN THE FOOD AND DRUG ADMINISTRATION REPEATEDLY IGNORES THE PLAIN LANGUAGE OF THE ORPHAN DRUG ACT (ODA)

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INTRODUCTION

In *Catalyst Pharms., Inc. v. Becerra*, the Court of Appeals for the Eleventh Circuit found that the marketing exclusivity provided for in the Orphan Drug Act (ODA) covers all uses or indications of the drug for the diseases or conditions for which the drug was originally designated as an orphan drug.[1] The decision is in contrast to the practice of the Food and Drug Administration (FDA) to narrowly construe the exclusivity to apply only to the uses or indications for which the drug is approved.[2] The FDA has repeatedly ignored the plain language of the ODA, and its previous extra-statutory interpretation negatively impacts orphan drug development.[3] The court's decision, like in the previous litigation,[4] is consistent with the language of the ODA.[5] However, the court's decision may have negative public health impacts, such as delaying drug development for children.[6] While Congress is drafting bills to amend the ODA, the FDA should consider changing its orphan drug designation regulations accordingly.[7]

The court in *Catalyst Pharms., Inc. v. Becerra* addressed whether the statutory phrase "same disease or condition" of the ODA under the 21 U.S.C. § 360cc(a) is ambiguous and, if so, whether the FDA's interpretation is reasonable.[8] More specifically, the issue was whether the scope of orphan drug exclusivity applies to the diseases or conditions for which the drug is designated (broader) or the uses or indications for which the drug is approved (narrower).[9] The court ruled in favor of Catalyst Pharmaceuticals, Inc., holding that the orphan drug exclusivity applies to all uses or indications related to the disease or condition for which the drug is designated.[10] This note will argue in line with the court's holding and that the FDA should fix its regulations of orphan drug designation.

Part I summarizes the factual and procedural background leading to the court's opinion.[11] Part II explores the means and ends of the Orphan Drug Act,[12] the qualifications of orphan drug exclusivity under the ODA,[13] and previous litigation relevant to orphan drug exclusivity.[14] Part III explains the reasoning underlying the court's decision.[15] Finally, Part IV (1) asserts that the court correctly reached its holding using statutory interpretation tools;[16] (2) contends that the FDA's interpretation of the ODA is an overreach beyond its statutory authority;[17] (3) maintains that the FDA is acting beyond its institutional competence to solve orphan drug affordability issues;[18] and (4) proposes a potential solution for the FDA to fix the regulation of the orphan drug exclusivity.[19]

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[1] Catalyst Pharms., Inc. v. Becerra, 14 F.4th 1299, 1301 (11th Cir. 2021).
[2] *See supra* Part II.B.
[3] *See supra* Part IV.B.
[4] *See supra* Part II.C.
[5] *See supra* Part IV.A.
[6] *See supra* Part IV.C.
[7] *Id.*
[8] Catalyst Pharms., Inc. v. Becerra, 14 F.4th 1299, 1306 (11th Cir. 2021).
[9] *Id.* at 1308.
[10] *Id.* at 1313.
[11] *See infra* Part I.
[12] *See infra* Part II.A.
[13] *See infra* Part II.B.
[14] *See infra* Part II.C.
[15] *See infra* Part III.
[16] *See infra* Part IV.A.
[17] *See infra* Part IV.B.
[18] *See infra* Part IV.C.
[19] *See infra* Part IV.D.

I. THE CASE

Lambert-Eaton myasthenic syndrome (LEMS) is a rare condition affecting roughly 905 to 1,300 adult patients and a couple dozen pediatric patients.[20] The FDA granted amifampridine orphan drug designation for use in LEMS in 1990 upon request by Jacobus Pharmaceutical Company.[21] In 2009, the Agency granted the designation again, this time upon request by Catalyst Pharmaceuticals.[22] Both companies submitted their New Drug Applications in 2018, seeking approval and marketing exclusivity under the ODA.[23] Catalyst Pharmaceutical's Firdapse (amifampridine) won the race for FDA approval in November 2018 to treat LEMS in adult patients.[24] Under the ODA, FDA granted Firdapse seven years of orphan drug exclusivity.[25] In May 2019, the FDA approved Jacobus Pharmaceutical Company's Ruzurgi (amifampridine) for treating LEMS in pediatric patients, likewise granting 7-year exclusivity.[26]

Catalyst Pharmaceutical sued the FDA in the Southern District of Florida, alleging that the approval of Ruzurgi violated the Administrative Procedure Act (APA), because the FDA acted in an arbitrary and capricious manner in limiting Catalyst's exclusivity to adult patients and granting Jacobus approval for pediatric use.[27] Jacobus Pharmaceutical Company intervened.[28] Each party moved for summary judgment.[29] The parties disagreed as to whether the "same disease or condition" in the ODA refers to the use for which the drug is designated or approved.[30] A magistrate judge, relying on the *Chevron* doctrine's deference to agencies, recommended granting summary judgment to the FDA.[31] The district court agreed with the magistrate judge's recommendation and dismissed the case.[32] Catalyst Pharmaceutical appealed to the Eleventh Circuit, which reviewed the FDA's action *de novo*.

II. LEGAL BACKGROUND

A. The Orphan Drug Act (ODA)

About one in ten people in the United States are affected by rare diseases.[33] By definition, rare diseases are those that 1) affect fewer than 200,000 people in the United

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[20] Catalyst Pharms., Inc. v. Becerra, 14 F.4th 1299, 1304 (11th Cir. 2021).
[21] *Id.*
[22] *Id.*
[23] *Id.*
[24] *Id.*
[25] *Id.*
[26] *Id.*
[27] *Id.* at 1305.
[28] *Id.*
[29] *Id.*
[30] All parties agreed that Firdapse and Ruzurgi meet the definition of "same drug" under the Orphan Drug Act and agreed that LEMS is a single disease regardless of the patient population. *Id.*
[31] Catalyst Pharmaceuticals, Inc. v. Azar, 2020 WL 5514187 (S.D. Fla. July 30, 2020).
[32] *Id.* at 1306. The district court also denied Catalyst's Motion for Summary Judgment and granted the Federal Defendant's Motions. Catalyst Pharmaceuticals, Inc. v. FDA, 2020 WL 5792595 (S.D. Fla. Sept. 29, 2020).
[33] *About GARD*, NIH, https://rarediseases.info.nih.gov/about (last visited Mar. 30, 2023).

States[34] or 2) affect more than 200,000 people in the United States but can be treated only by drugs that are not likely to yield significant profit.[35] Pharmaceutical companies often have insufficient incentives to research and develop treatments for rare diseases due to the lack of a sufficiently profitable market.[36] The ODA, enacted in 1983, stimulates the development of drugs for rare diseases by empowering the FDA to incentivize the production and address the general accessibility of drugs used to treat rare diseases (orphan drugs).[37]

The means and the ends of the ODA have been clear since its enaction. The "ends" of the ODA are to improve social welfare by providing treatments for orphan diseases.[38] The statutory text explicitly states that "it is in the public interest to provide such changes and incentives for the development of orphan drugs."[39] As a House Report explained, providing incentives under the ODA allows sponsors to "recoup the cost of development by capturing all revenues from the sale of the drug for the rare disease," free from competition.[40] In 2017, the FDA released the Orphan Drug Modernization Plan to ensure continued progress toward more treatments for rare diseases.[41] The Plan clearly articulates the FDA's understanding of the ODA's purpose: to incentivize research and development of orphan drugs.[42] Courts have considered the FDA's interpretation of the ODA's purpose consistent with the statutory language and legislative history.[43] Therefore, the "ends" of the ODA is to allow more resources to be allocated to unmet medical needs.[44]

On the other hand, the means specified in the ODA are limited to providing a variety of financial incentives to support the research and development of new treatments for rare diseases. The most attractive incentive is seven years of market exclusivity.[45] The FDA will grant orphan drug exclusivity if the drug receives orphan drug designation and premarket approval.[46] The exclusivity precludes the FDA from approving another drug product application "for the same drug for the same disease or condition" for seven years after approval of the orphan-designated drug.[47] Orphan drug exclusivity is a bargain that strikes a delicate balance.[48] The scheme grants innovators enough monopoly to encourage orphan drug development but not too much monopoly to extract from the patients and insurers more than Congress thought necessary to spur the innovation. Other financial

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[34] The threshold was an arbitrary ceiling based on the estimated prevalence of two rare diseases: narcolepsy and multiple sclerosis. *The Orphan Drug Act: Implementation and Impact*, OFFICE INSPECTOR GEN., OEI-09-00-00380 (May 2001), https://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf.

[35] 21 U.S.C. § 360bb(a)(2).

[36] John W. Sheridan, *Billion Dollar Orphans: Tension Between the Legal Intent and Social Purpose of the Orphan Drug Act*, 6 TEX. A&M L. REV. 731, 732 (2019).

[37] Orphan Drug Act of 1983, Pub. L. No. 97-414, 96 Stat. 2049.

[38] Sheridan, *supra* note 36, at 742.

[39] Orphan Drug Act of 1983, Pub. L. No. 97-414, 96 Stat. 2049.

[40] H.R. REP. NO. 99–153, *reprinted in* 1985 U.S.C.C.A.N. 301, 303.

[41] *FDA's Orphan Drug Modernization Plan*, U.S. FOOD & DRUG ADMIN. (June 29, 2017), https://www.fda.gov/media/106012/download.

[42] Sheridan, *supra* note 36, at 743.

[43] Genetech v. Bowen, 676 F. Supp. 301, 312 (D.D.C. 1987); Mut. Pharm. Co. v. Ivax Pharm., Inc., 459 F. Supp. 2d 925, 929-30 n.1 (C.D. Cal 2006) (noting that "the legislative history is replete with reference to the fundamental need to provide treatment for presently untreated patients.").

[44] Eagle Pharms., Inc. v. Azar, 952 F.3d 323, 325 (D.C. Cir. 2020).

[45] 21 U.S.C. § 360cc(a).

[46] *See infra* Part II.B.

[47] *Id.*

[48] *Eagle Pharms., Inc*, 952 F.3d at 342 (Williams, J., dissenting).

incentives under the ODA include federal funding of grants and contracts for clinical trials of orphan products, a tax credit of a certain percentage of clinical testing costs, and a waiver of FDA User Fees.[49] In addition, ODA allows patients access to the drug even before FDA marketing approval through an Orphan Drug Open Protocol.[50]

The ODA successfully reduces financial barriers and promotes the availability of drugs to treat rare diseases. The success of the ODA is most apparent from the increasing number of orphan drug designations and approvals each year. Since ODA's enaction, the FDA has granted 6,242 orphan drug designations and approved 1,085 orphan drugs.[51] In 2021 alone, there were 93 orphan drug approvals. The uptick in designations and approvals reflects substantial medical progress and scientific understanding of rare diseases.[52] Another implicit measure of ODA's success is its embedded flexibility to address scientific advances. For example, the degree of chemical and structural similarity that allows the FDA to determine whether two drugs are the "same drug" depends on whether the drugs have small or large molecules.[53] The definition of the "same drug" under the ODA has withstood the test of time to accommodate scientific advances.[54]

Although the ODA has successfully stimulated the development of orphan drugs, it has been criticized for not sufficiently addressing orphan drug affordability. Critics allege that the ODA helps to create blockbuster orphan drugs with billions in sales.[55] Some are concerned that pharmaceutical companies abuse the tax credit and market exclusivity for profit.[56] Two common examples of pharmaceutical companies gaming the ODA are "recycling" and "salami slicing." In "recycling," a manufacturer finds a cheap drug with expired patents that is approved for one indication but is widely used off-label for an orphan disease. Then the manufacturer runs clinical trials of the drug for that orphan disease and seeks FDA's approval for the new indication.[57] On the other hand, "salami slicing" occurs because many diseases have subtypes; the disease may affect more than 200,000, but each subtype may not. The manufacturer may seek approval for one subtype after another and earn seven years of marketing exclusivity for each subtype, even though the drug can be

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[49] Roberta Szydlo, *Office of Orphan Products Development: Financial Incentives for CDER Medical Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/media/135236/download (last visited Mar. 29, 2023).

[50] 21 U.S.C. § 360dd (permitting investigations of persons with orphan diseases or conditions who need the orphan drug and who cannot be satisfactorily treated by available alternative drugs).

[51] *FDA Database for Orphan Drug Designations and Approvals*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm (last visited Mar. 29, 2023).

[52] *FDA's Orphan Drug Modernization Plan*, U.S. FOOD & DRUG ADMIN. (June 29, 2017), https://www.fda.gov/media/106012/download.

[53] 21 C.F.R. § 316.3(b)(14).

[54] Kurt R. Karst, *Fitting New Scientific Advances Into an Old Regulatory Paradigm: Fusion Proteins and Orphan Drug "Sameness*," FDA L. BLOG, (July 25, 2017), https://www.thefdalawblog.com/2017/07/fitting-new-scientific-advances-into-an-old-regulatory-paradigm-fusion-proteins-and-orphan-drug-same/.

[55] Lydia Raw, *Are We Adopting the Orphans, or Creating Them: Medical Ethics and Legal Jurisprudential Guidance for Proposed Changes to the Orphan Drug Act*, 9 WASH. U. JURISPRUDENCE REV. 295, 295 (2017).

[56] Grace Lee, *Orphan Drug Act: Fostering Innovation or Abuse?* THE SOURCE BLOG (Dec. 12, 2017), https://sourceonhealthcare.org/orphan-drug-act-fostering-innovation-or-abuse/.

[57] Nicholas Bagley, *Thinking Straight about Orphan Drugs, Part 4*, THE INCIDENTAL ECONOMIST, (Sept. 14, 2016), https://theincidentaleconomist.com/wordpress/thinking-straight-about-orphan-drugs-part-4/.

targeted at a population much larger than 200,000 people.[58] Critics are concerned that the ODA abuses drive up drug prices and contribute to patients' inaccessibility to medication.[59]

B. Qualification of Orphan Drug Exclusivity

The seven-year orphan drug exclusivity qualification is a two-step process: orphan drug designation [60] and drug approval. [61] The orphan drug designation process is administered by the FDA's Office of Orphan Products Development (OODP).[62] To receive such designation, a sponsor submits a written request for designation to OODP demonstrating that a drug treats a "rare disease or condition."[63] The written request should include certification that the product is for a rare disease or condition, scientific rationale for using the drug for that disease or condition, and supporting epidemiologic data.[64] If the sponsor establishes a medically plausible hypothesis of effectiveness, OODP will designate the drug as an orphan drug for that specific disease or condition.[65]

The second step of orphan drug exclusivity is receiving FDA drug approval through FDA's Center for Drug Evaluation and Research. The standard of premarket approval is rigid because the FDA comprehensively reviews the quality, safety, and efficacy of the drug for its intended use.[66] To support the drug approval process, a sponsor must submit extensive scientific and medical data, including chemical, toxicological, pharmacological, and clinical studies.[67]

The scope of the orphan drug designation may differ from the scope of the new drug approval. When OODP designates an orphan drug, it generally designates the drug for use by all patient populations with the rare disease or condition because it expects that the sponsor will seek marketing approval of the drug for all persons with the rare disease or condition.[68] However, suppose the sponsor provides data only to support drug approval for select indications or uses within rare diseases or conditions. In that case, the FDA can only approve the drug for select indications or uses.[69] As a result, the scope of the orphan drug designation can be broader than the scope of the new drug approval.

Upon designation and approval of the orphan drug, the FDA will grant the orphan drug sponsor a seven-year market exclusivity.[70] Specifically, the ODA provides:

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[58] Lee, *supra* note 56.
[59] Sheridan, *supra* note 36, at 734.
[60] 21 U.S.C. § 360bb(a)(1).
[61] 21 U.S.C. 355(a)-(b).
[62] *Office of Orphan products Development*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/office-clinical-policy-and-programs/office-orphan-products-development (last modified Dec. 13, 2022).
[63] 21 U.S.C. § 360bb(a)(2) defines a "rare disease or condition" as one that "(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 of such drug."
[64] 21 C.F.R. § 316.20 (providing content and format requirements of a written request for orphan drug designation).
[65] 21 C.F.R. § 316.20(b)(4).
[66] 21 C.F.R. §§ 601.2(a), 314.2; 42 U.S.C. § 262.
[67] 21 C.F.R. § 314 (providing requirement of new drug applications); 21 C.F.R. § 601 (providing requirement of application for biologics licenses).
[68] Orphan Drug Regulations, 78 Fed. Reg. 35,117, 35,123 (June 12, 2013) (to be codified 21 C.F.R. pt. 316).
[69] *Id.*
[70] 21 U.S.C. § 360cc(a).

> Except as provided in subsection (b), if the Secretary
>
> (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, the Secretary 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 such license until the expiration of seven years from the date of the approval of the approved application or the issuance of the license.[71]

The statutory phrase "same disease or condition" is not defined in the ODA.[72] For the past thirty years,[73] the FDA has interpreted the phrase "same disease or condition" as the use or indication for which the drug was approved (narrower), rather than the disease or condition for which the drug was designated (broader) as an orphan drug.[74] As a result of that interpretation, the FDA has granted market exclusivity more narrowly, leaving opportunity for other sponsors to gain approval and exclusivity for a different indication. Consequently, the scope of orphan drug exclusivity can be narrower than the scope of the orphan drug designation. For example, if a drug is designated for use in lung cancer but approved only for use in stage four lung cancer based on the data provided in the marketing application, the orphan drug exclusivity only applies to the drug for stage four lung cancer. When new data is available to support FDA approval of additional indications or uses (e.g., for stages one, two, or three of lung cancer), additional orphan drug exclusivity may attach upon approval of these new indications or uses.[75]

The ODA provides three exceptions to the seven-year exclusivity of orphan drugs. The first exception applies when the exclusivity holder cannot provide sufficient quantities of the drug to patients.[76] The second exception applies when the exclusivity holder consents to waive its exclusivity.[77] The third exception is often called the "clinically superior" exception.[78] It applies if a different manufacturer of the same drug demonstrates that its drug "provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, or by providing a major contribution to patient care."[79] The "clinically superior" concept was originally FDA's extra-statutory requirement imposed on the industry. After a series of lawsuits,[80] Congress codified this concept as part of the 2017 reauthorization and amendment to the ODA.[81]

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[71] *Id.*
[72] Catalyst Pharms., Inc. v. Becerra, 14 F.4th 1299, 1303 (11th Cir. 2021).
[73] Sara W. Koblitz, *Catalyst Pharmaceuticals, Inc. v, Becerra*, FOOD & DRUG L. INST., https://www.fdli.org/2022/06/catalyst-pharmaceuticals-inc-v-becerra/#_ftn5 (last visited Mar. 29, 2023).
[74] *Catalyst Pharms., Inc.* 14 F.4th at 1307.
[75] Orphan Drug Regulations, 78 Fed. Reg. 35,117, 35,124 (June 12, 2013) (to be codified 21 C.F.R. pt. 316).
[76] 21 U.S.C. § 360cc(b)(1).
[77] 21 U.S.C. § 360cc(b)(2).
[78] 21 U.S.C. § 360cc(c).
[79] 21 U.S.C. § 360cc(c).
[80] *Id. See infra* Section II.C.
[81] FDA Reauthorization Act of 2017, Pub. L. No. 115-52, Stat. 1005, 1049–50.

C. Previous Orphan Drug Exclusivity Litigation

FDA implements regulations that further specify the requirements for orphan drug exclusivity. Litigation arose when the FDA's interpretation of the ODA imposed an extra-statutory requirement on the industry. For example, FDA's orphan drug regulations add a "clinically superior" requirement for a drug to qualify for the seven-year exclusivity if the drug has the same active moiety as an already approved orphan drug.[82] The regulations further require a "clinically superior" drug to provide a significant therapeutic advantage compared to an approved orphan drug by showing greater effectiveness, greater safety, or a major contribution to patient care.[83]

Courts have repeatedly struck down the FDA's extra-statutory "clinically superior" requirement. In *Depomed v. FDA*, orphan drug sponsor Depomed alleged the FDA's clinical superiority requirement violated the ODA's plain language.[84] Depomed had developed the drug Gralise for a rare condition.[85] It sought and obtained orphan drug designation for Gralise, which the FDA subsequently approved.[86] However, the FDA denied Depomed a seven-year exclusivity because Depomed failed to prove that Gralise was clinically superior to a previously approved drug with the same active moiety.[87]

The court in *Depomed* applied *Chevron* analysis and held that the plain language under the ODA is unambiguous.[88] The ODA requires the FDA to grant marketing exclusivity when it has designated an orphan drug and approved it for marketing. Therefore, the FDA placed additional hurdles by attempting to impose the "clinically superior" requirement found nowhere in the statute.[89] After the *Depomed* decision, the FDA published a notice of clarification on policy, addressing the effects of the *Depomed* decision.[90] In that notice, the FDA explained the Agency's perspective that the *Depomed* decision was limited to a specific case and reiterated its intent to continue applying the "clinically superior" requirement in evaluating orphan drug exclusivity. Later, the FDA asserted that *Depomed* was wrongly decided because the court ignored the purpose and structure of the ODA.[91]

The FDA's post-*Depomed* policy left the door open for future litigation. *Eagle Pharmaceutical v. Azar* raised in court for a second time the issue of whether the FDA can

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[82] 21 C.F.R. § 316.20(a) ("a sponsor of a drug that is otherwise the same drug as an already approved drug may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug.").
[83] 21 C.F.R. § 316.3(b)(3).
[84] Depomed, Inc. v. U.S. Dep't of Health & Hum. Servs., 66 F. Supp. 3d 217, 220 (D.D.C. 2014).
[85] Gralise is indicated for the management of postherpetic neuralgia. GRALISE, https://www.gralise.com (last visited Mar. 29, 2023).
[86] FDA designated it as an orphan drug in November 2010 and approved the drug in January 2011 for the designated indication. *Drug Approval Package*, U.S. FOOD & DRUG ADMIN. (Oct. 18, 2011), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022544_gralise_toc.cfm.
[87] *Id.* FDA required a plausible hypothesis of clinical superiority because FDA previously approved drug Neurontin, which has the same active moiety gabapentin as Depomed's Gralise. Kurt R. Karst, *Another Orphan Drug Battle; Depomed Sues FDA Over GRALIST Orphan Drug Exclusivity*, FDA L. BLOG, (Sept. 27, 2012), https://www.thefdalawblog.com/2012/09/another-orphan-drug-battle-depomed-sues-fda-over-gralise-orphan-drug-exclusivity-/.
[88] *Depomed, Inc.*, 66 F. Supp.3d at 230.
[89] *Id.* at 231.
[90] Policy on Orphan-Drug Exclusivity; Clarification, 79 Fed. Reg. 76,888 (Dec. 23, 2014) (to be codified 21 C.F.R. pt. 316).
[91] Eagle Pharms., Inc. v. Azar, 952 F.3d 323, 329 (D.C. Cir. 2020).

require a sponsor to demonstrate "clinical superiority" before obtaining orphan drug exclusivity.[92] Orphan drug sponsor Eagle Pharmaceuticals developed Bendeka for a rare disease.[93] The FDA accepted Bendeka's clinical superiority hypothesis,[94] designated it as an orphan drug, and approved Bendeka for marketing. However, the FDA denied granting the seven-year market exclusivity because Eagle had failed to prove Bendeka's clinical superiority over a previously approved drug.[95] As in *Depomed*, the court in *Eagle Pharmaceutical* applied *Chevron* analysis and concluded that the ODA is unambiguous and does not allow the FDA to impose the clinical superiority requirement, ruling in favor of Eagle Pharmaceutical.[96] The court further noted that the plain language of the statutory text is clear and "leaves no room" for the FDA to review the legislative history.[97]

After courts struck down the FDA's "clinically superior" requirement, Congress amended the ODA to codify the clinical superiority requirement as part of the FDA Reauthorization Act of 2017.[98] Although the "clinically superior" requirement itself is not in dispute in the *Catalyst* case, the *Depomed* and *Eagle* cases forecast three patterns of the FDA's standpoint in the *Catalyst* case. First, the FDA justifies its extra-statutory requirement to implement the ODA based on its interpretation of the legislative history and purpose. Second, the FDA rejects the courts' plain language approach to interpreting the ODA. Third, the FDA has the lobbying capability in Congress to codify its extra-statutory requirement primarily because FDA's user fee programs require reauthorization by Congress every five years. Because user fee reauthorization is a must-pass bill, it is an excellent opportunity for the policy riders to attach.[99]

III. THE COURT'S REASONING

The court in *Catalyst* addressed whether the statutory phrase "same disease or condition" under the ODA is ambiguous, and if so, whether FDA's interpretation is reasonable.[100] The court analyzed the scope of the orphan drug exclusivity provision and held that the statutory phrase is unambiguous, and therefore, the FDA's approval of Ruzurgi for the treatment of pediatric patients violated the ODA's market-exclusivity provision.[101] The court concluded that the FDA's action was arbitrary, capricious, and not in accordance with the law.

The court's reasoning relied on a plain meaning approach to statutory interpretation. The court acknowledged that the ODA does not define "same disease or

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[92] *Id.* at 325.
[93] *Id.* at 328 (FDA designated Bendeka for two types of cancer: chronic lymphocytic leukemia and non-Hodgkin's lymphoma).
[94] Bendeka had the same active moiety as a previously approved drug, Teva Pharmaceutical Industries's Treanda. However, because Bendeka's formulation, it is ready-dilute concentrate solution for injection administered within a shorter time. *Id.*
[95] *Id.* at 329.
[96] Eagle Pharms., Inc. v. Azar, 2018 WL 3838265, *230 (D.D. Cir. June 8, 2018).
[97] Eagle Pharm., Inc. v. Azar, 952 F.3d 323, 331 (D.C. Cir. 2020).
[98] FDA Reauthorization Act of 2017, PUB. L. NO. 115-52, 131 Stat. 1005, 1049-50 (amending 21 U.S.C. § 360cc).
[99] *Congress Enacts Clean Reauthorization of FDA User Fees, Leaving Uncertain Future for Important Policy Reforms,* ROPES & GRAY (Sept. 31, 2022), https://www.ropesgray.com/en/newsroom/alerts/2022/September/Congress-Enacts-Clean-Reauthorization-of-FDA-User-Fees-Leaving-Uncertain-Future.
[100] Catalyst Pharms., Inc. v. Becerra, 14 F.4th 1299, 1301 (11th Cir. 2021).
[101] *Id.*

condition."[102] In looking for the plain meaning of the statutory phrase "same disease or condition," the court first looked at the dictionary definition of the word "same" and then interpreted the meaning in its statutory context. The word "same" means "the one under discussion or already referred to." In the context of ODA, the only "disease or condition" already referred to in the exclusivity provision is the "rare disease or condition" for which the drug was designated.[103] Therefore, the scope of orphan drug exclusivity applies to the entire rare disease or condition for which the drug is designated, rather than the use or indication for which the product is approved.[104]

The court also rejected the district court's determination that the phrase "same disease or condition" is ambiguous because the statutory text does not support it.[105] First, the court rejected that the phrase "same disease or condition" is related to the "use or indication" inquiry for which the product is approved.[106] If Congress wanted to make the "use or indication" inquiry relevant, it could have done so by expressly using such language. Second, the court considered that the way the drug approval provision[107] is referenced in § 366cc(a) simply identifies the condition to trigger market exclusivity. The reference to the drug approval provision does not substantively limit the scope of the market exclusivity. Third, the court justified the plain language approach by looking at the definitions under the ODA. Congress did not define "same disease or condition" but defined what a "rare" disease or condition is.[108] By leaving "disease or condition" without a statutory definition, Congress left the courts to interpret those words as they are commonly understood. Fourth, the court distinguished two previous cases that the district court relied upon because, unlike the case at issue, the earlier cases addressed the application of orphan drug market exclusivity for treating different diseases.[109] Therefore, the court reversed the district court's judgment.[110]

IV. THE ANALYSIS

In *Catalyst Pharms., Inc. v. Becerra*, the court ruled in favor of Catalyst Pharmaceuticals, Inc., holding that the orphan drug exclusivity applies to the disease or conditions for which the drug is designated, not the more narrow uses or indications for which the drug is approved.[111] The court correctly reached its holding using statutory interpretation tools.[112] In addition, the FDA's interpretation of the ODA is an overreach beyond its statutory authority[113] and institutional competence.[114] Instead of repeatedly ignoring the courts' rulings under the ODA, the FDA should have fixed its regulation and limited the scope of the orphan drug designation based on preliminary clinical evidence.[115]

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[102] *Id.* at 1307 ("a statute is not ambiguous merely because it contains a term without a statutory definition.").
[103] *Id.* at 1308.
[104] *Id.*
[105] *Id.* at 1308-09.
[106] *Id.* at 1309.
[107] 21 U.S.C. § 355.
[108] Catalyst Pharms., Inc. v. Becerra, 14 F.4th 1299, 1310 (11th Cir. 2021).
[109] *Id.* at 1011.
[110] *Id.* at 1310-11.
[111] *Id.* at 1312-13.
[112] *See infra* Part IV.A.
[113] *See infra* Part IV.B.
[114] *See infra* Part IV.C.
[115] *See infra* Part IV.D.

A. The Court Correctly Reached Its Holding Using Statutory Interpretation Tools.

The court correctly started its statutory interpretation with a plain language analysis of the text. Under the plain language approach, the starting point is to read the statute carefully, looking at the prototypical meaning of the statutory words.[116] If the statutory words are defined within the statute, courts interpret them as defined. If the statutory words are not defined anywhere within the statute, courts give the words ordinary meaning when the statute was enacted.[117] The Supreme Court frequently uses the plain meaning approach for statutory interpretation and consults dictionaries when construing key statutory words and phrases.[118] Among 532 majority/plurality opinions of the Court between 2005 and 2017, almost half (49.8%) of the majority/plurality opinions used the plain meaning approach.[119] The court correctly relied on the dictionary meaning of the word "same." Therefore, the court's interpretation is well-grounded that the phrase "disease or condition" in the exclusivity provision refers to the "rare disease or condition" for which the drug was designated.

The court's interpretation of the statutory phrase "same disease or condition" is also supported by the whole act rule.[120] When interpreting a statute, courts not only look to a particular clause in which the words or phrases are used, but also consider its connection to the whole statute.[121] The whole act rule assumes that the legislature drafted the statute as a document that is internally consistent in its use of language.[122] Relatedly, the whole act rule further assumes that a change of wording denotes a change in meaning.[123] In the context of the ODA, the phrase "same disease or condition" has consistent usage with the "rare disease or condition" for which the drug was designated. The consistent use of the phrase "rare disease or condition" suggests that the scope of exclusivity should be the same as the scope of the orphan designation. In addition, the phrase "disease or condition" is different from the word "use" or "indication" from the referenced drug approval provision.[124] The meaningful variation supports the court's interpretation that the drug approval provision does not limit the scope of orphan drug exclusivity.

The court correctly rejected the FDA's argument based on legislative history and purpose. Courts generally examine legislative documents and debates because the formal history of a statute's evolution is relevant to statutory interpretation.[125] However, the use of legislative history from committee reports has limitations because they can be "as

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[116] WILLIAM N. ESKRIDGE JR. ET AL., CASES AND MATERIALS ON LEGISLATION AND REGULATION: STATUTES AND THE CREATION OF PUBLIC POLICY 583 (6th ed. 2019).
[117] Taniguchi v. Kan Pac. Saipan, Ltd., 566 U.S. 560, 566 (2012) ("[w]hen a term goes undefined in a statute, the court gives the term its ordinary meaning.").
[118] ESKRIDGE, *supra* note 116, at 585.
[119] Anita S. Krishnakumar, *Cracking the Whole Code Rule*, 96 N.Y.U. L. REV. 76, 77 (2021).
[120] The court, however, stopped at the plain language approach and did not analyze under the whole act rule.
[121] Kokoszka v. Belford, 417 U.S. 642, 650 (1974); Doe v. Chao, 540 U.S. 514 (2004).
[122] ESKRIDGE, *supra* note 116, at 617. Among 532 majority/plurality opinions of the Court between 2005 and 2017, 199 (37.4%) of the opinions used the whole act rule. Krishnakumar, *supra* note 119, at 77.
[123] ESKRIDGE, *supra* note 116, at 623.
[124] 21 U.S.C. § 355.
[125] ESKRIDGE, *supra* note 116, at 727.

ambiguous as the statute[,]…[and] may even be misleading."[126] Similarly, the Supreme Court in recent years used legislative intent and purpose less frequently for statutory interpretation.[127] Courts generally effectuate legislative intent from plain language unless the plain language leads to absurd results.[128] Here, the FDA pointed out that committee reports accompanying the original public law and 1985 amendments both mention extending exclusivity to "uses" or "indications."[129] The FDA further argued that its interpretation is consistent with the ODA's purpose because it rewards the sponsor for the invested uses or indications during the new drug development.[130] However, the plain meaning of the statutory text is clear and leaves no room for FDA's argument based on evidence from committee reports and legislative purposes. Therefore, the court correctly rejected FDA's argument because the statutory text is clear.

B. FDA's Interpretation of the Orphan Drug Act Is an Overreach Beyond Its Statutory Authority and Has Negative Impacts on Orphan Drug Development.

It is a fundamental principle in administrative law that an administrative agency "literally has no power to act…unless and until Congress confers power upon it."[131] In addition to statutory interpretation analysis of an agency's organic statute,[132] courts also review agency action under the "major questions" doctrine.[133] In 2022, the Court in *West Virginia v. EPA* followed the "major questions" doctrine when reviewing an agency's claim of extraordinary power to regulate issues of national importance.[134] Specifically, the Court asked whether the agency action implicates a major question and, if it does, whether such power is conferred in the agency's organic statute.[135] The recent decision suggests that the Court will start with skepticism toward any significant agency action that is not explicitly included in the statutory grant of power.[136] The case also signifies the Court's understanding that decisions of magnitude and consequence rest with Congress and, absent clear delegation, an agency cannot overreach beyond the statutory scheme.

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[126] ESKRIDGE, *supra* note 116, at 750; *See also* Conroy v. Aniskioff, 507 U.S. 511, 519 (1993) (Scalia J., concurring) (describing "the use of legislative history as the equivalent of entering a crowded cocktail party and looking over the heads of the guests for one's friends").

[127] Among the 532 majority/plurality opinions from the Supreme Court between 2005 and 2017, only 152 (28.6%) opinions used purpose approach and 58 (10.9%) opinions used intent approach. Krishnakumar, *supra* note 119, at 77.

[128] Tennessee Valley Auth. v. Hill, 437 U.S. 153, 166-67 (1978); Griffin v. Oceanic Contractors, Inc., 458 U.S. 564, 575 (1982).

[129] Federal Defendants' Cross-Motion for Summary Judgement, Catalyst Pharmaceuticals, Inc. v. Alex Azar, Sec'y of Health and Hum. Servs., et al., 2020 WL 1616646 (S.D. Fla. July 30, 2020) (No. 1:19-cv-22425).

[130] *Id.*

[131] La. Pub. Serv. Comm'n v. FCC, 476 U.S. 355, 374 (1986); FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 159-60. (2000).

[132] *See supra* Section I.

[133] Joshua S. Sellers, *"Major Questions" Moderation*, 87 GEO. WASH. L. REV. 930, 931 (2019).

[134] In that case, the Court invalidated the Clean Power Plan, an EPA regulation aimed at reducing carbon emissions by requiring coal-fired power plants to limit their electricity production or subsidize increased energy generation by natural gas, wind, or solar sources. W. Va. v. EPA, 142 S. Ct. 2587, 2616 (2022).

[135] *Id.* at 2595.

[136] *Id.* at 2609.

The *Catalyst* decision fits under the framework outlined in *West Virginia v. EPA*.[137] First, the orphan drug industry is of vast economic and political significance. The orphan drug market in the U.S. was estimated at $ 59.1 billion in 2020,[138] and the orphan drug market is growing more than twice as fast as the non-orphan market.[139] In addition, although rare diseases are individually rare, they collectively affect nearly thirty million Americans of all ages.[140] Regulations that impact patient access to orphan drugs are thus of significant impact. Second, § 360cc(a) only gives the FDA authority to grant orphan drug exclusivity based on two expressly stated conditions: designation and approval. No language in the statute gives the FDA broad discretion in considering additional market factors, such as drug pricing, to determine exclusivity eligibility. Therefore, the *Catalyst* decision is consistent with the Supreme Court's approach to reviewing agency actions. The Supreme Court would likely affirm the circuit court's decision if the FDA case were heard on certiorari.

The FDA's previous overreach of its statutory authority under ODA already negatively impacts the orphan drug community. For example, courts have repeatedly struck down FDA's extra-statutory "clinically superior" requirement.[141] When the FDA imposes the "clinically superior" regulation to allow approval of a subsequent product,[142] one of the three ways to demonstrate clinical superiority is a "demonstration that the drug makes major contribution to patient care," or MC-to-PC determination.[143] Although the MC-to-PC determination is case-specific, it is not uncommon.[144] Many MC-to-PC determinations are based on the reformulation of a previously approved product.[145] Reformulating of an existing product has a lower failure risk than discovering novel compounds and targets for specific diseases.[146] Additionally, the reformulation of an approved product does not address the critical challenges in orphan disease therapeutic discovery. Considering that a majority of the estimated 7,000 known rare diseases still do not have approved therapies, regulations should provide incentives to compound and target discovery for the areas of

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[137] The court in *Catalyst* did not go beyond the statutory interpretation analysis and analyze under the "major questions" doctrine.

[138] *Global Orphan Drugs Market to Reach $545.4 Billion By 2027*, YAHOO (Oct. 18, 2022), https://www.yahoo.com/now/global-orphan-drugs-market-reach-131000866.html.

[139] *The Rise of Orphan Drugs,* AHIP (Sept. 2019), https://www.ahip.org/documents/AHIP_OrphanDrugs.pdf; Melanie Senior, *Orphan Drugs: From Niche to Mainstream*, 42 PHARMACEUTICAL EXEC. (June 15, 2022), https://www.pharmexec.com/view/orphan-drugs-from-niche-to-mainstream.

[140] *About GARD,* NAT'L CTR. FOR ADVANCING TRANSLATIONAL SCI., https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases (last visited Mar. 29, 2023).

[141] *See supra* Part II.C.

[142] 21 C.F.R. pt. 316 (allowing approval of subsequent drug notwithstanding an unexpired period of seven-year orphan drug exclusivity for another product).

[143] *Id.*

[144] Kurt R. Karst, *Orphan Drug Clinical Superiority: An Overview of Precedents Shows that MC-to-PC Clinical Superiority is Not So Unusual,* FDA L. BLOG (Mar. 27, 2016), https://www.thefdalawblog.com/2016/03/orphan-drug-clinical-superiority-an-overview-of-precedents-shows-that-mc-to-pc-clinical-superiority/.

[145] *Clinical Superiority Findings,* U.S. FOOD & DRUG ADMIN., https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings (last modified June 24, 2021).

[146] Claude-Henry Volmar, et al., *Orphan Diseases: State of the Drug Discovery Art*, 167 WIEN MED WOCHENSCHR 197, 197 (2017).

greatest unmet medical need.[147] On the contrary, the FDA's MC-to-PC determination is more likely to encourage the industry to pick the lower-hanging cherries to get around the exclusivity barrier. Sponsors may be more willing to optimize existing approved drugs than to invest in rare diseases that have no approved drugs. Consequently, patients with orphan diseases that do not have approved drugs may have to wait longer for new therapies.

The FDA's interpretation of the phrase "same disease or conditions" under the ODA is another overreaching act. Specifically, the approval of Ruzurgi for pediatric patients is the FDA's own invention to get around Firdapse's exclusivity. Although Firdapse's exclusivity barred the FDA from approving another amifampridine drug for LEMS for use in adults, the FDA determined that treatment of the pediatric population consisted of a different use or indication from Firdapse's indication for adult patients. Therefore, the FDA administratively carved out the pediatric indication from Ruzurgi's marketing application to allow for independent action of approval.[148]

Under the FDA's overreaching interpretation, orphan exclusivity is limited to the specific indication for which an orphan-designated drug obtains approval.[149] This interpretation, coupled with the current FDA practice of granting orphan designation to all patient populations by default, encourages an unhealthy orphan drug gaming system. Specifically, sponsors can first play "salami slicing" by splitting certain common diseases into several artificial subgroups.[150] Then, sponsors conduct clinical trials on a specific subgroup to receive the orphan drug exclusivity for which the drug is approved. This practice of seeking approval for disease subtypes will result in fewer clinical trials on whether a drug works for the disease as a whole.[151] As a result, many patients outside of the specific subgroup who could benefit from the drug will not receive the treatment.

The FDA would rather ask Congress to affirm its overreaching interpretations than work within its statutory authority. The Agency previously succeeded in working with Congress to seek an amendment of the ODA as part of the reauthorization of user fee bills when courts struck down its overreaching actions under the ODA.[152] After the *Catalyst* decision, the FDA's Center Directors testified in Congress that the decision would "send a chill" and create "a potential problem for the development of drugs for rare disease."[153] However, unlike the 2017 Reauthorization that codified the FDA's "clinically superior" requirement, adding a policy rider in a fractured Congress this time appears to be more challenging. The House and the Senate drafted their versions of the FDA reauthorization

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[147] Kathleen L. Miller, et al., *Using Four Decades of FDA Orphan Drug Designations to Describe Trends in Rare Disease Drug Development: Substantial Growth Seen in Development of Drugs for Rare Oncologic, Neurologic, and Pediatric-onset Diseases*, ORPHANET J. RARE DISEASES (June 9, 2021), https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-01901-6.

[148] *Catalyst Pharms., Inc.* 14 F.4th at 1305.

[149] *Id.* at 1308.

[150] Sven Bostyn, *Tackling Salami Slicing and Indication Stacking in Orphan Drug Innovation Incentives*, BILL OF HEALTH (Sept. 15, 2021), https://blog.petrieflom.law.harvard.edu/2021/09/15/orphan-drug-innovation-incentives/; *See supra* Section II.A.

[151] Aaron Carroll, *Healthcare Triage: Gaming the System – Orphan Drugs Part 3*, THE INCIDENTAL ECONOMIST (Apr. 24, 2017), https://theincidentaleconomist.com/wordpress/healthcare-triage-gaming-the-system-orphan-drugs-part-3/.

[152] *See supra* Part II.C.

[153] Jill Wechsler, *Congress Presses FDA on Key Policies and Operations*, APPLIED CLINICAL TRIALS (May 4, 2022), https://www.appliedclinicaltrialsonline.com/view/congress-presses-fda-on-key-policies-and-operations.

bill, including provisions to overturn the *Catalyst* decision.[154] Substantial differences between both bills complicated negotiations. After the House and Senate could not negotiate a suitable resolution, Congress ultimately passed a clean reauthorization as a short-term continuing resolution without any policy riders included in either House or Senate bills.[155] While members of Congress are still trying to negotiate additional legislation, FDA is now depending on a fractured Congress to codify its overreaching interpretations. What the Agency could do in the interim is to reconsider its regulations within the statutory authority to mitigate the problems.[156]

C. FDA Acts Beyond Its Institutional Competence to Solve Orphan Drug Affordability Issues.

FDA should not consider market factors such as drug pricing to grant orphan drug exclusivity selectively. During the review of Jacobus's marketing application, the FDA received a letter from Senator Bernie Sanders of Vermont complaining about Ruzurgi's high drug price.[157] The *Catalyst* litigation also revealed that FDA top officials exchanged emails about the cost of Ruzurgi and how approval of Firdapse may improve patient access through off-label use.[158] The FDA claimed that these email records did not support the speculations that the Agency was improperly motivated by the cost of the drug.[159] However, the email communications at least suggest the Agency's awareness of the backdrop of the drug competition and price issues related to amifampridine, which inevitably made the exclusivity decision more difficult.

The FDA should base its decision-making about new approvals on science, not market factors. First, the FDA repeatedly stated that it does not consider drug prices in its approval decision, and the Agency has no legal authority to investigate or control drug prices.[160] There were rare instances when the FDA was aware of market factors.[161]

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[154] On June 8, the House of Representatives passed their version of user fee legislation—H.R. 7667, the Food and Drug Amendments of 2022—with bipartisan support. On June 14, the Senate Health, Education, Labor and Pensions ("HELP") Committee advanced the Senate's counterpart legislation—S. 4348, the Food and Drug Administration Safety and Landmark Advancements Act of 2022—out of committee. H.R. 7667, 117th Cong. (2022); S. 4348, 117th Cong. (2022).

[155] H.R. 6833. 117th Cong. (2022) (enacted).

[156] The legislative window is narrow considering the midterm election in November 2022, followed by a "lame duck" session. *See infra* Part IV.D.

[157] Exhibit A, Catalyst Pharmaceuticals, Inc. v. Alex Azar, Sec'y of Health and Hum. Servs., et al., 2020 WL 1616646 (S.D. Fla. July 30, 2020) (No. 1:19-cv-22425).

[158] Brenda Sandburg, *FDA Broke Catalyst's Orphan Exclusivity Due to Pricing, Not Clinical, Concerns, Firm Claims*, PINK SHEET (Feb. 13, 2020), https://pink.pharmaintelligence.informa.com/PS141683/FDA-Broke-Catalysts-Orphan-Exclusivity-Due-To-Pricing-Not-Clinical-Concerns-Firm-Claims.

[159] *Id.*

[160] *Frequently Asked Questions about CDER,* U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/frequently-asked-questions-about-cder (last visited Mar. 29, 2023).

[161] The limited instances are approval of Sarepta Therapeutics's Exondys 51 when FDA reportedly considered the financial situation of the company, and approval of KV Pharmaceutical's Makena when FDA appeared to consider drug pricing. *FDA Grants Accelerated Approval to First Drug for Duchenne Muscular Dystrophy,* U.S. FOOD & DRUG ADMIN., https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-drug-duchenne-muscular-dystrophy (last visited Mar. 29, 20223); *Makena (hydroxyprogesterone caproate injection) Information,* U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/postmarket-drug-safety-

Nonetheless, the approval process of these drugs was still based on scientific evaluation of evidence with "flexibility to address the challenge we often see with rare, life-threatening diseases."[162] Second, no express language in the ODA contemplates the price at which orphan drugs should be made available. Although orphan drug costs are a general concern,[163] the ODA does not instruct the FDA to address drug pricing under §360cc(a). Third, the FDA does not have the institutional competence to consider market factors. The FDA is fully equipped with trained staff to serve as the gatekeeper to ensure drugs are safe and effective.[164] The FDA also has in-house economists for high-level policy analysis.[165] However, FDA's drug review team does not include economists or market analysts, whose expertise would be essential to analyze patient access and drug affordability. Therefore, even if Congress were to grant the FDA discretion to consider drug pricing, the FDA simply lacks the competence to contemplate the issue fully.[166]

The FDA should not act in a legislative role to address the growing problem of orphan drug affordability. FDA's role in orphan drug development is essential, but the role of other administrative agencies can be equally important. For example, the National Institute of Health (NIH) can provide research funding to encourage basic research in ultra-rare conditions.[167] The Center for Medicare and Medicaid Services (CMS) and the Health Resources and Services Administration (HRSA) can each address drug affordability through Medicare or the 340B Drug Pricing Program.[168] In addition, private players in the orphan drug community should not be ignored. Active patient groups for rare diseases play a central role in creating patient registries, advocacy groups, and funding resources, accelerating efforts to capture patient-reported outcomes and evidence generation.[169] Lastly, Congress should consider reforms that strike a more sustainable balance between the incentives for the orphan drug sponsor and affordability of the orphan drug for the

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information-patients-and-providers/makena-hydroxyprogesterone-caproate-injection-information (last visited Mar. 29, 2023).

[162] Sue Sutter, *Sarepta's Eteplirsen Approved After Contentious Internal FDA Debate,* PINK SHEET (Sept. 19, 2016), https://pink.pharmaintelligence.informa.com/PS119160/Sareptas-Eteplirsen-Approved-After-Contentious-Internal-FDA-Debate.

[163] *Orphan Drugs in the United States,* IQVIA INST. (Dec. 2019), https://rarediseases.org/wp-content/uploads/2021/03/orphan-drugs-in-the-united-states-NRD-2020.pdf. For example, orphan drugs have an average annual cost of $32,000, and more than a third of orphan drugs cost more than $100,000 annually. *Id.*

[164] *FDA's Drug Review Process: Continued,* U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-continued (last modified Aug. 24, 2015).

[165] *Office of Economics and Analysis,* U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/office-policy-legislation-and-international-affairs/office-economics-and-analysis (last modified Jan. 18, 2022).

[166] FDA could hire economists if Congress authorized FDA to consider drug pricing during the assessment of premarket approval. However, FDA's mission is to safeguard the safety and efficacy of drugs based on science, and the evaluation of drug affordability based on market may sometimes conflict with the safety and efficacy review. Therefore, Congress should consider tasking a separate agency other than FDA for drug affordability issues.

[167] *Rare Diseases,* NAT'L INST. HEALTH, https://www.nih.gov/about-nih/what-we-do/nih-turning-discovery-into-health/rare-diseases (last visited Mar. 29, 2023).

[168] *The Orphan Drug Act: Implementation and Impact*, OFFICE INSPECTOR GEN., OEI-09-00-00380 (May 2001), https://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf. (As the OIG report provides, orphan drug exclusion from the 340B Drug Pricing Program may provide significant financial incentives for manufactures to seek orphaned drug designation for drugs approved to treat common diseases or conditions. *Id.*

[169] Miller, *supra* note 147.

health system.[170] The issue of orphan drug development, coverage, pricing, and payment is complex, and the burden to fix the problem does not rest on the FDA's shoulders alone. Therefore, the FDA should not exceed its institutional competence to tackle such a complex issue alone.

D. The FDA Should Have Limited the Scope of Orphan Drug Designation, Not Repeatedly Ignored Court's Rulings Under the ODA.

The FDA should have learned the lessons from the courts' statutory interpretation in previous litigation relevant to orphan drug exclusivity. Specifically, the FDA should have reflected on how courts have previously interpreted the orphan drug exclusivity provisions.[171] Both in *Depomed* and *Eagle*, courts not only interpreted the provision using a plain language approach, but they also expressly rejected FDA's argument based on legislative history and purpose. [172] Courts considered § 360cc(a) as a "readily diagrammable formula" in the form of "if designation and approval, then exclusivity."[173] However, the FDA repeatedly ignored the courts' interpretation and insisted on imposing an extra-statutory interpretation of the exclusivity provision.[174] Had the FDA reflected on the *Depomed* and *Eagle* decisions, the Agency could have possibly avoided its statutory interpretation mistake in the *Catalyst* litigation.

The FDA could have avoided the *Catalyst* decision by fixing its regulation of orphan drug designation. Using its statutory authority, the FDA could have carefully designed the regulatory framework at the orphan drug designation stage to resolve issues relevant to the scope of the exclusivity. The FDA should not have, by default, designated an orphan drug for all patient populations. Instead, the FDA could consider any preliminary clinical data or real-world evidence available at the time of the designation request and determine whether the designation should be limited to specific patient subgroups. To implement the proposed regulation, the FDA could require the sponsors to provide evidence to establish at least a plausible medical hypothesis to determine whether the drug is indicated for all patient populations or a specific subgroup.

Limiting the scope of orphan drug designation based on preliminary evidence offers three benefits. First, it encourages applicants to consider patient diversity early in the drug development cycle. If an orphan drug is targeted at all patient populations, the FDA should require the applicant to submit a clinical trial plan involving different patient populations at the designation review phase. This requirement ensures that diverse patient populations will be enrolled during the clinical trials. In addition, this requirement will also help to ensure the scope of subsequent drug approval is consistent with the scope of the designation and thus avoid the *Catalyst* issue.

Second, limiting the scope of designation based on preliminary evidence helps to create healthier competition for orphan drug development. The FDA maintains an orphan drug database of designations and approvals that is accessible to the public,[175] which offers excellent transparency for the orphan drug research community. If a designation specifies the targeted patient populations, potential sponsors will allocate more resources to study

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[170] Caroline Pearson et al., *The Next Generation of Rare Disease Drug Policy: Ensuring Both Innovation and Affordability*, 11 J. COMPARATIVE EFFECTIVENESS RSCH. 999 (2022).
[171] *See supra* Part II.C.
[172] *Id.*
[173] Depomed, Inc. v. United States HHS, 66 F. Supp. 3d 217, 230 (D.D.C. 2014); Eagle Pharm., Inc. v. Azar, 952 F.3d 323, 327 (D.C. Cir. 2020).
[174] *See supra* Part IV.B.
[175] U.S. FOOD & DRUG ADMIN., *supra* note 51.

other patient populations that the existing designation has not covered. As a result, the proposal incentivizes potential sponsors to fill the gaps in orphan drug development.

Third, limiting the scope of designation based on preliminary evidence ultimately benefits more patients because it encourages population-specific treatments. Many orphan drugs reach patients at the early development stage through the Expanded Access program.[176] The program allows sponsors to collect preliminary safety data before submitting the orphan designation request. Specifying patient populations at the designation stage will encourage sponsors to have a heightened awareness of population-specific data even before the designation request, which helps to develop population-specific treatments that benefit the patients.

Limiting designation scope based on preliminary evidence benefits the patients and industry and resolves the FDA's concern about the *Catalyst* implications. The FDA raised three concerns addressing the impacts of *Catalyst* decisions,[177] and each can be resolved by limiting designation scope based on preliminary evidence. First, the FDA alleges that the *Catalyst* decision leaves the Agency no discretion to interpret the ODA. Consequently, some orphan drugs in late-stage development or that have undergone marketing review would be blocked from approval. However, if the FDA adopts the regulatory framework to limit the designation scope, other orphan drugs would not be blocked if they were designated for different patient populations.

Second, the FDA further maintains that the *Catalyst* decision undermines orphan drug development because sponsors could seek approval and exclusivity by focusing on the smallest, easiest-to-study populations without investing in the drug for all populations. Limiting the scope of designation can efficiently resolve this issue. Under the proposed approach, a sponsor no longer gets exclusivity for all populations by default. Instead, the scope of the exclusivity that the sponsor will receive is proportionate to the efforts the sponsor will invest in studying and developing the drug. Additionally, the proposed approach incentivizes other sponsors to fill the void by identifying potential treatment gaps based on the existing designation scope.

Third, the FDA blames the *Catalyst* decision for potentially delaying drug development for pediatric and later-studied populations.[178] Under the proposed regulation, the FDA may allow sponsors to submit supplements to an already granted designation in a mechanism similar to the post-approval supplements pathway.[179] If the sponsor intends to expand the clinical studies to later-studied populations, they can still do so later in drug development and submit a supplemental designation request accordingly to receive an expanded scope of designation.[180] Once the drug is approved for the expanded populations, the sponsor then receives exclusivity for the expanded populations. Treatment for pediatric populations will not be delayed because sponsors can provide pediatric safety data collected under the expanded access program to support a designation covering pediatric

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[176] *Expanded Access,* U.S. FOOD & DRUG ADMIN., https://www.fda.gov/news-events/public-health-focus/expanded-access (last modified Dec. 21, 2022).

[177] *FDA's Overview of Catalyst Pharms., Inc. v. Becerra,* U.S. FOOD & DRUG ADMIN., https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/fdas-overview-catalyst-pharms-inc-v-becerra (last modified Jan. 23, 2023).

[178] This claim is unjustified. Although Ruzurgi's approved indication is for pediatric patients, the approval is solely based on clinical data in adult patients. Catalyst Pharms., Inc. v. Becerra, 14 F.4th 1299, 1305 (11th Cir. 2021).

[179] 21 C.F.R. § 314.70 (outlining requirement of submitting supplements and other changes to an approved NDA).

[180] Under the proposed regulatory framework, sponsors may alternatively enter a clinical trial agreement with another sponsor to collaboratively explore or study the use of the drug in a different population.

populations. Alternatively, sponsors can submit additional clinical evidence through a supplemental designation request later in the drug development to receive an expanded designation.

CONCLUSION

In *Catalyst Pharms., Inc. v. Becerra*, the court held that the scope of orphan drug exclusivity applies to the disease or conditions for which the drug is designated because the plain language of the 21 U.S.C. § 360cc(a) is clear.[181] The decision is in contrast to the practice of the FDA to narrowly construe the exclusivity to apply only to the uses or indications for which the drug is approved.[182] The court correctly reached its holding using a plain language approach and rejected the FDA's argument based on legislative history and purpose.[183] The FDA has repeatedly ignored courts interpretations of the orphan drug exclusivity provision, persisting on an interpretation that is an overreach of its statutory authority.[184] The FDA does not have the institutional competence to address complex issues such as orphan drug pricing and affordability.[185] The FDA should not depend on a fractured Congress to codify its overreaching interpretations.[186] Instead, the FDA should implement regulations within its statutory authority and limit the scope of the orphan drug designation based on preliminary evidence.[187]

[181] *Catalyst Pharms., Inc.* 14 F.4th at 1304.
[182] *See supra* Part II.B.
[183] *See supra* Part IV.A.
[184] *See supra* Part IV.B.
[185] *See supra* Part IV.C.
[186] *See supra* Part IV.B.
[187] *See supra* Part IV.D.