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# The Orphan Drug Act and *Catalyst Pharmaceuticals, Inc., v. Becerra*

August 17, 2023

Congressional Research Service

<https://crsreports.congress.gov>

R47653



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## The Orphan Drug Act and *Catalyst Pharmaceuticals, Inc., v. Becerra*

Orphan drugs are used to treat rare diseases and conditions, but they can be costly to produce and are generally used to treat fewer than 200,000 people in the United States. In 1983, Congress enacted the Orphan Drug Act (ODA) as a way to incentivize the development and marketing of orphan drugs. Since that time, more than 500 orphan drugs have been developed in the United States. The Food and Drug Administration (FDA) oversees the designation and approval of orphan drugs.

The ODA incentivizes the production of orphan drugs through two main components: (1) orphan-drug designation and (2) orphan-drug exclusivity. A sponsor may apply for an orphan-drug designation at any time during the drug development process by filing an application with the FDA. Doing so entitles the sponsor to certain benefits, including tax credits, grant funding, and a waiver of the FDA User Fee. If the FDA approves an orphan drug for marketing, the sponsor is then entitled to a seven-year exclusivity period, during which time the FDA cannot approve the same drug for the same disease or condition for marketing.

The scope of the ODA's orphan-drug exclusivity periods has been extensively litigated over the last 40 years. The U.S. Court of Appeals for the Eleventh Circuit recently interpreted the meaning of the ODA provision "same drug for the same disease or condition" in *Catalyst Pharmaceuticals, Inc. v. Becerra*. The FDA argued that the ODA's phrasing of "same drug for the same disease or condition" was ambiguous and thus that the court should give deference to its regulations, which limit exclusivity to the "same drug" for the "same use or indication." Siding with a manufacturer, the court held that the FDA's interpretation of the ODA was not entitled to *Chevron* deference because the ODA's exclusivity provision was not ambiguous. The court held that the FDA should not have granted the marketing application for an orphan drug during the seven-year exclusivity period of the same orphan drug that is used to treat the same disease but is indicated for a different patient population.

The FDA complied with the 11th Circuit's order in *Catalyst*, but it issued a *Federal Register* notice in January 2023 announcing that it would continue to apply its existing regulations when reviewing marketing applications for orphan drugs. The decision created some uncertainty for orphan drug manufacturers. Several Members of Congress have similarly indicated their disagreement with the 11th Circuit ruling and support legislation to codify the FDA's existing regulation.

## Contents

The Orphan Drug Act and FDA Regulations: Setting the Stage for Ensuing Litigation.....	1
Orphan-Drug Designation.....	2
FDA’s Orphan-Drug Designation Process .....	3
Post-Designation Manufacturer Requirements .....	4
Orphan-Drug Exclusivity .....	5
Interpreting “Same Disease or Condition”: <i>Catalyst Pharmaceuticals, Inc. v. Becerra</i> .....	7
District Court Decision .....	8
Eleventh Circuit Reversal .....	9
FDA Non-Acquiescence in the Context of the ODA .....	11
Non-Acquiescence to <i>Catalyst</i> .....	11
FDA Non-Acquiescence Regarding Clinical Superiority and Congressional Response .....	12
Considerations for Congress.....	13

## Contacts

Author Information.....	16
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## The Orphan Drug Act and FDA Regulations: Setting the Stage for Ensuing Litigation

The cost and availability of prescription drugs have been of congressional interest, and expenditures related to the research and development of new drugs are a significant driver of drug costs.<sup>1</sup> A 2016 report by the Tufts Center for Drug Development estimated the pretax and preapproval cost of developing a Food and Drug Administration (FDA)-approved prescription drug was \$2.6 billion, while a 2016 Department of Health and Human Services (HHS) report estimated a range from \$1.2 billion to \$2.6 billion.<sup>2</sup> Given the extraordinary cost associated with development and marketing of a new drug, manufacturers aim to recover much of their research and development costs through drug sales.

Historically, drugs designed to treat rare diseases and conditions received little attention from U.S. drug manufacturers, given the high cost of development and lack of widespread use.<sup>3</sup> These drugs became known as “orphan drugs.”<sup>4</sup> In the 1970s, there was growing concern about the need for drugs to treat rare diseases; at that time, FDA established two committees to study the “inadequate motivation, and resources, for the development and distribution of drugs for rare diseases.”<sup>5</sup>

Congress began investigating and holding hearings on the development of drugs for rare diseases in June 1980.<sup>6</sup> As part of this effort, the House Subcommittee on Health and the Environment surveyed a number of federal agencies, universities, and pharmaceutical companies to gather information about various drug products used to treat rare diseases in the United States.<sup>7</sup> The results of the survey, published in 1982, showed that so-called orphan drugs were generally not profitable, many were not patentable, and it was difficult for drug sponsors to conduct clinical trials to demonstrate their safety and effectiveness—in part because of the small patient populations they were developed to treat.<sup>8</sup>

Given the high cost of drug development and approval in the United States, Congress found that “it is not financially feasible, except as a public service, for a pharmaceutical manufacturer to expend research and development funds” on orphan drugs, which are typically used only to treat small subsets of the population.<sup>9</sup> So in 1983, Congress enacted the Orphan Drug Act (ODA) as a way to “facilitate the development of drugs for rare diseases or conditions,”<sup>10</sup> primarily by

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<sup>1</sup> See generally, CRS Report R44832, *Frequently Asked Questions About Prescription Drug Pricing and Policy*, by Suzanne M. Kirchoff et al. (2021), at 3-6, and Appendix.

<sup>2</sup> *Id.* at 29. As discussed in the report, it is difficult to estimate an exact figure of the average research and development costs because detailed information about the cost of developing specific drugs is generally not available. As a contextual description for the litigation analyzed, this report describes different studies that estimate the average research and development costs, along with their varying methodologies.

<sup>3</sup> See James T. O’Reilly and Katherine A. Van Tassel, *Orphan Drug Act & Competition Among Drug Makers*, 13 FOOD AND DRUG ADMIN. 104, Fourth Ed. (Dec. 2022).

<sup>4</sup> *Id.*

<sup>5</sup> H.R. REP. 97-840, at 6, 1982 U.C.C.A.N. at 3579.

<sup>6</sup> *Id.*

<sup>7</sup> *Id.* at 7, 1982 U.C.C.A.N. at 3579.

<sup>8</sup> *Id.*

<sup>9</sup> H.R. REP. 97-840, at \*6.

<sup>10</sup> H.R. REP. NO. 97-840 (1982) at 5 (1982), as reprinted in 1982 U.S.C.C.A.N. 3577, 35577; Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. §§ 360aa-360ee). The ODA amended the Food, Drug and Cosmetic Act (FDCA).

establishing financial incentives—including tax credits, grant funding, and market exclusivity—to encourage pharmaceutical companies to develop and market orphan drugs in the United States.<sup>11</sup>

The FDA, a division of HHS, administers the ODA. The statute does not explicitly define “orphan drug,” but FDA has issued regulations to define the term as a drug “intended for use in a rare disease or condition,” which is consistent with the statute’s phrasing.<sup>12</sup> The ODA contains two main components: (1) orphan-drug designation, as described in Section 360bb, and (2) orphan-drug market exclusivity, as described in Section 360cc.<sup>13</sup> Drug manufacturers may apply to obtain an orphan-drug designation for drugs in development. If granted, orphan-drug designation enables a drug manufacturer to access financial assistance for drug research and development, including tax credits for clinical testing of the drug, grant funding to cover research costs, and a waiver of FDA’s Prescription Drug User Fee if it ultimately submits an application for FDA approval of the drug.<sup>14</sup> If a drug manufacturer receives FDA approval to market a drug designated as an orphan drug, the manufacturer is generally entitled to a seven-year exclusivity period. During the seven-year orphan-drug exclusivity period, the FDA cannot approve an application from a different drug manufacturer for approval<sup>15</sup> to market the same drug for the same disease or condition.<sup>16</sup> These statutory mechanisms of designation, approval, and exclusivity are intended to work together to promote the research and development of orphan drugs.<sup>17</sup>

## Orphan-Drug Designation

Orphan-drug designation allows drug manufacturers<sup>18</sup> and sponsors<sup>19</sup> to access financial benefits and incentives early in the drug development process, and it also assures orphan-drug exclusivity for a successfully marketed drug, which aids in the recoupage of the sizable upfront investment

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<sup>11</sup> *Id.* For more information, see Shashank Upadhye, *GENERIC PHARMACEUTICAL PATENT AND FDA LAW*, § 23:15 (2022 ed.). See also H.R. Rep. 97-840, at 8, 1982 U.C.C.A.N. at 3580–81 (explaining that Congress developed the orphan-drug designation process to “assure that the financial incentives and other regulatory provisions of the [FDCA] apply to drugs for rare diseases and conditions.”).

<sup>12</sup> 21 C.F.R. § 316.3(b)(10) (2023). Unless otherwise noted, this report uses “drugs” to include both “small-molecule” drugs products as well as biological products. For more information on the differences between small-molecule drugs and biological products, see CRS Report R45666, *Drug Pricing and Intellectual Property Law: A Legal Overview for the 116th Congress*, coordinated by Kevin J. Hickey (2019).

<sup>13</sup> 21 U.S.C. §§ 360bb (orphan-drug designation), 360cc (orphan-drug exclusivity).

<sup>14</sup> 21 U.S.C. § 360bb(a)(1); see also U.S. FOOD AND DRUG ADMIN., *Rare Diseases at FDA*, <https://www.fda.gov/patients/rare-diseases-fda> (last updated Dec. 13, 2022).

Congress first passed the Prescription Drug User Fee Act (PDUFA) in 1992, Pub. L. No. 102-571, which has since been reauthorized several times. PDUFA gives FDA authority to collect fees from the pharmaceutical industry and use the revenue to support “the process for the review of human drug applications.” For more information about the Prescription Drug User Fee Act, see CRS Report R44750, *FDA Human Medical Product User Fee Programs*, by Agata Bodie and Amanda K. Sarata (2021); see also U.S. FOOD AND DRUG ADMIN., *Financial Report to Congress: Prescription Drug User Fee Act of 1992, FY 2022*, at 7, <https://www.fda.gov/media/165427/download>.

<sup>15</sup> For purposes of this report, the term “approval” will be used to apply to both drugs and biologics.

<sup>16</sup> 21 U.S.C. §§ 360cc(a); 21 C.F.R. § 316.31(a); see also *Rare Diseases at FDA*, *supra* note 14.

<sup>17</sup> See CRS Report RS20971, *Orphan Drug Act: Background and Proposed Legislation in the 107th Congress*, by M. Angeles Villarreal (2001) (available to congressional clients upon request).

<sup>18</sup> The FDA defines a drug manufacturer as a person or agency that manufactures a drug or biologic that is “subject to investigation and approval.” 21 C.F.R. § 316.3(b)(8).

<sup>19</sup> The FDA defines a sponsor as “the entity that assumes responsibility for a clinical or nonclinical investigation of a drug,” and may be a person, corporation, government agency, or other entity. 21 C.F.R. § 316.3(b)(15).

in drug development.<sup>20</sup> A manufacturer or sponsor may apply for an orphan-drug designation at any time during the drug development process, so long as the request is submitted before submitting the application for FDA approval of the drug.<sup>21</sup> FDA regulations spell out the specific requirements for the content and format of orphan-drug designation requests,<sup>22</sup> discuss how the FDA verifies orphan-drug status<sup>23</sup> and alerts drug sponsors of deficiencies,<sup>24</sup> and stipulate the conditions under which the FDA may refuse to grant<sup>25</sup> or revoke a designation request.<sup>26</sup>

Manufacturers and sponsors may seek an orphan-drug designation if the drug is currently being investigated or will be investigated for a rare disease or condition and the approval or licensing of the drug would be for the “use for such disease or condition.”<sup>27</sup> For purposes of orphan-drug designation, a “rare disease or condition” is one that either (1) affects fewer than 200,000 people in the United States; or (2) affects more than 200,000 people in the United States but for which a manufacturer does not have a “reasonable expectation” of recovering its development costs from sales.<sup>28</sup> A manufacturer may seek orphan-drug designation for either a previously unapproved drug, or for a new use of a drug that is already FDA-approved.<sup>29</sup> Additionally, if the FDA has already designated and approved an orphan drug for a particular rare disease or condition, a sponsor may receive a subsequent designation for the same drug for the same disease or condition if it can present a “plausible hypothesis” that the second drug is clinically superior to the original.<sup>30</sup>

### **FDA’s Orphan-Drug Designation Process**

After a manufacturer files a designation request, the FDA determines whether the drug meets the definition of an orphan drug.<sup>31</sup> To enable the FDA to make this determination, sponsors must submit documentation showing either that (1) the prevalence of the rare disease or condition is fewer than 200,000 people, or (2) the sponsor does not reasonably anticipate recouping the costs of research and development of the drug through domestic sales.<sup>32</sup> For the first path, the sponsor must provide evidence of the estimated disease prevalence, and the FDA may request additional documentation, including the estimated prevalence of any other disease or condition for which the drug is being developed or was already approved.<sup>33</sup> The sponsor must also estimate the number of people who would receive the drug on a yearly basis.<sup>34</sup>

For the second path—demonstrating that developing the drug would not be cost effective—the sponsor must submit data on all costs incurred and expected to be incurred in the research and

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<sup>20</sup> Shashank Upadhye, *GENERIC PHARMACEUTICAL PATENT AND FDA LAW*, § 23:15 (2022 ed.).

<sup>21</sup> 21 U.S.C. § 360bb(a)(1); 21 C.F.R. § 316.23(a)–(b).

<sup>22</sup> 21 C.F.R. § 316.20.

<sup>23</sup> *Id.* § 316.21.

<sup>24</sup> *Id.* § 316.24.

<sup>25</sup> *Id.* § 316.25.

<sup>26</sup> *Id.* § 316.29.

<sup>27</sup> 21 U.S.C. § 360bb(a)(1)(A)–(B).

<sup>28</sup> *Id.* § 360bb(a)(2)(A)–(B).

<sup>29</sup> 21 C.F.R. § 316.20(a).

<sup>30</sup> *Id.* § 316.20(a).

<sup>31</sup> *Id.* § 316.21(a).

<sup>32</sup> 21 U.S.C. § 360bb(a)(2).

<sup>33</sup> 21 C.F.R. § 316.21(b)(1)–(2).

<sup>34</sup> *Id.* § 316.21(b)(3).

development of the drug, as well as a justification of the reasonableness of the cost data.<sup>35</sup> If a drug has already been approved and marketed for a different indication, or if the drug is being investigated for another indication, the sponsor must apportion the development cost data for each indication.<sup>36</sup> Sponsors are also required to estimate and justify the expected costs of marketing and production and the expected revenues from sales of the drug through seven years after marketing the drug.<sup>37</sup> Sponsors must also submit information about any other countries where the drug has already been approved and an independent accountant's certification of the request's data estimates and justifications.<sup>38</sup> (There are additional legal requirements for drugs developed either wholly or partially outside the United States.<sup>39</sup>)

If the FDA determines that a designation request is inaccurate or incomplete, it sends the sponsor a deficiency letter; the sponsor then has one year to either respond to the letter or withdraw the designation request.<sup>40</sup> The FDA denies a designation request if there is insufficient evidence that the drug will be used to treat fewer than 200,000 people or if a sponsor fails to demonstrate that there is no reasonable expectation that its costs could be recouped through domestic sales.<sup>41</sup> The FDA may also deny a designation request if the sponsor does not demonstrate a “medically plausible” theory showing that the drug will be effective in diagnosing, treating, or preventing a rare disease or condition.<sup>42</sup> Additionally, if the drug is the same as one that has already been approved and the sponsor has not demonstrated a “medically plausible hypothesis” of clinical superiority, or if the designation contains a false statement of material fact, the FDA may refuse to grant the designation.<sup>43</sup> The FDA grants a designation request when none of the reasons for refusing it apply.<sup>44</sup> The FDA updates a publicly available list of orphan designations every month.<sup>45</sup>

FDA may revoke an orphan-drug designation after it is granted if the agency determines that the designation request contained “an untrue statement of material fact,” omitted required material information, or was not actually eligible for designation at the time of the request.<sup>46</sup>

## **Post-Designation Manufacturer Requirements**

Certain requirements apply to manufacturers that receive orphan drug designation. During preclinical investigations before the drug is approved, the manufacturer must notify the FDA if it decides to discontinue its pursuit of FDA approval.<sup>47</sup> The FDA also requires manufacturers with an orphan drug designation to submit yearly progress reports to the FDA detailing the progress of drug development, including any clinical or preclinical studies, a yearly plan for investigation and any anticipated hurdles, and any changes that could affect the status of the product, including

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<sup>35</sup> *Id.* § 316.21(c)(1).

<sup>36</sup> *Id.* § 316.21(c)(3)–(4).

<sup>37</sup> *Id.* § 316.21(c)(5) – (6).

<sup>38</sup> *Id.* § 316.21(c)(7)–(8).

<sup>39</sup> *Id.* § 316.21(c)(2).

<sup>40</sup> *Id.* § 316.24(a).

<sup>41</sup> *Id.* § 316.25(a)(1).

<sup>42</sup> *Id.* § 316.25(a)(2).

<sup>43</sup> *Id.* § 316.25(a)(3), (b).

<sup>44</sup> *Id.* § 316.24(b).

<sup>45</sup> FOOD & DRUG ADMIN., *Search Orphan Drug Designations and Approvals*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/opdlisting/opd/> (last visited July 14, 2023).

<sup>46</sup> 21 C.F.R. § 316.29.

<sup>47</sup> *Id.* § 360bb(b)(2).

differences in market indications and designation indications.<sup>48</sup> If an orphan drug becomes FDA-approved, a manufacturer must notify the FDA if it chooses to halt production of the drug.<sup>49</sup>

## Orphan-Drug Exclusivity

Before the sponsor of a designated orphan drug may market the drug, the sponsor must seek FDA approval by applying under Section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA)<sup>50</sup> for drugs or Section 351 of the Public Health Service Act (PHSA)<sup>51</sup> (42 U.S.C. § 262) for biologics.<sup>52</sup> If the FDA approves a drug designated as an orphan drug, the drug sponsor is entitled to market exclusivity.<sup>53</sup> The ODA's exclusivity provision prohibits the FDA from approving another drug or licensing another biologic “for the same drug for the same disease or condition ... until the expiration of seven years from the date” of the original approval (or licensure, in the case of biologics).<sup>54</sup> This seven-year period is known as the “orphan-drug exclusivity” period.

In its implementing regulations, the FDA has interpreted the seven-year exclusivity period in a way that may limit its applicability. The regulations state that exclusivity “protects only the approved indication or use of a designated drug.”<sup>55</sup> Accordingly, if an orphan drug is approved for certain indications or uses for the rare disease or conditions, the regulations allow the FDA to “later approve the drug for additional indication(s) or use(s) within the rare disease or condition not protected by the exclusive approval.”<sup>56</sup>

In other words, the FDA treats orphan-drug exclusivity as specific to the designated use or indications for the drug rather than extending to any and all uses or indications for the rare disease or condition.<sup>57</sup> Thus, the FDA could designate an orphan drug for a particular indication, and then later designate the same drug for the same disease or condition but with a different indication.<sup>58</sup> Given the high cost of developing orphan drugs and the value of orphan-drug

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<sup>48</sup> 21 C.F.R. § 316.30.

<sup>49</sup> 21 U.S.C. § 360bb(b)(1).

<sup>50</sup> 21 U.S.C. § 355.

<sup>51</sup> 42 U.S.C. § 262.

<sup>52</sup> For more information about the FDA drug approval process for new drugs and generic drugs, see CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*, by Agata Bodie and Susan Thaul (2018).

<sup>53</sup> 21 U.S.C. § 360cc.

<sup>54</sup> *Id.* § 360cc(a).

<sup>55</sup> 21 C.F.R. § 316.31(b).

<sup>56</sup> *Id.* For example, in the case of *Catalyst Pharmaceuticals Inc. v. Becerra*, the FDA approved the same drug (amifampridine) which is used to treat the same disease (Lamberton-Eaton Myasthenic Syndrome), but which was *indicated* for use in different populations (i.e., adults vs. children). 14 F.4th 1299, 1304 (2021) (emphasis added).

<sup>57</sup> The FDA's regulations regarding labeling requirements for drugs distinguish a product's intended use and its indications for use. A product's “intended uses . . . refer to the objective intent of the persons legally responsible for the labeling of an article . . . . The intent may be shown by such persons' expressions, the design or composition of the article, or by the circumstances surrounding the distribution of the article.” 21 C.F.R. § 201.128. A product's “indications for use” are the conditions under which the product is used, including the population(s) for whom the drug is developed. U.S. Food & Drug Admin., *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format: Guidance for Industry* (July 2018).

<https://www.fda.gov/files/drugs/published/Indications-and-Usage-Section-of-Labeling-for-Human-Prescription-Drug-and-Biological-Products-%E2%80%94-Content-and-Format-Guidance-for-Industry.pdf>. In accordance with federal regulations, “all indications listed . . . must be supported by substantial evidence of effectiveness based on adequate and well controlled studies.” 21 C.F.R. §201.57(v)(2)(iv).

<sup>58</sup> *Id.* § 316.31(b).



exclusivity, the FDA's interpretation has generated controversy and litigation. As discussed below, a manufacturer recently challenged this interpretation, and questions remain about its validity.<sup>59</sup>

The statute provides two exceptions to the seven-year exclusivity period for orphan drugs, which allow the FDA to approve a competing orphan drug during the seven-year exclusivity period.<sup>60</sup> First, the FDA may approve another marketing application for “the same drug for the same disease or condition” if the FDA finds that the manufacturer of the original orphan drug cannot provide sufficient quantities of the drug to meet the demand for persons with the disease or condition.<sup>61</sup> Second, the FDA may override orphan-drug exclusivity with written consent of the holder of the approval or licensure.<sup>62</sup> The regulations provide two additional situations when the FDA may approve a sponsor's marketing application despite another manufacturer having received orphan-drug exclusivity: (1) if the FDA revokes the orphan-drug designation or the drug's approval; and (2) when the orphan drug's marketing application is withdrawn for any reason.<sup>63</sup>

Following uncertainty about the scope of the exclusivity for a subsequent sponsor of the same orphan drug for the same disease or condition, Congress created an additional requirement for orphan-designated drugs that enter the market when the same drug has already been approved for the same disease or condition.<sup>64</sup> In the FDA Reauthorization Act of 2017, Congress amended the exclusivity requirements of the ODA to create a “[c]ondition of clinical superiority” for sponsors that request orphan-drug exclusivity for a drug that the FDA has already approved to treat the same rare disease or condition.<sup>65</sup> The amendments clarify that a sponsor may obtain market exclusivity for an already approved orphan drug, but to do so, it must demonstrate that its drug is “clinically superior” to the previously approved drug.<sup>66</sup>

The statute defines a drug as being clinically superior when it “provides a significant therapeutic advantage over and above an already approved drug in terms of greater efficacy, greater safety, or

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<sup>59</sup> See *infra* at 7, “Interpreting “Same Disease or Condition”: Catalyst Pharmaceuticals, Inc. v. Becerra.”

<sup>60</sup> 21 U.S.C. § 360aa(b)(1)–(2).

<sup>61</sup> 42 U.S.C. § 300aa(b)(1).

<sup>62</sup> *Id.* § 300aa(b)(2).

<sup>63</sup> 21 C.F.R. 316.31(a)(1)–(4).

<sup>64</sup> The question of whether subsequent sponsors of the same orphan drug for the same disease or condition as an already marketed orphan drug are still entitled to receive orphan drug exclusivity for their drug, if approved, was first addressed in *Depomed, Inc. v. U.S. Dept of Health & Human Servs.*, 66 F. Supp. 3d. 217 (D.D.C. 2014). In *Depomed*, the U.S. District Court for the District of Columbia found that the scope of the seven-year orphan drug exclusivity was not limited to only the first manufacturer of an orphan drug for the treatment of a certain disease or condition. *Id.* at 230. The court observed that

although it is convenient to characterize orphan-drug marketing exclusivity as something in the nature of a benefit that the FDA confers or withholds . . . the text of section 360cc makes clear that the incentive Congress intended to create in the orphan drug context is not a thing to be ‘conveyed’ to drug manufacturers at all; rather, it is a restriction on the FDA’s ability to approve the marketing of other such drugs for the same rare disease or condition . . . when a drug that has been designated as an orphan drug is approved for marketing.

*Id.* After *Depomed* was decided, the FDA issued a notice in the *Federal Register* “to clarify its policy regarding certain aspects of orphan-drug exclusivity.” 79 Fed. Reg. 76,888 (Dec. 23, 2014). The FDA noted the “uncertainty” created by *Depomed* and characterized its holding as “limited.” *Id.* The agency stated that it “interprets section 527 of the [FDCA] and its regulations . . . to require the sponsor of a designated drug that is the ‘same’ as a previously approved drug to demonstrate that its drug is ‘clinically superior’ to that drug upon approval in order for the subsequently approved drug to be eligible for orphan-drug exclusivity.” *Id.* The agency also noted its intention to “continue to apply its existing regulations in part 316 to orphan-drug exclusivity matters.” *Id.*

<sup>65</sup> FDA Reauthorization Act of 2017, Pub. L. No. 115-52, § 607, 131 Stat. 1051 (amending 42 U.S.C. § 360cc); 21 U.S.C. § 360cc(c).

<sup>66</sup> *Id.* § 360cc(c)(1).

by providing a major contribution to patient care.”<sup>67</sup> To aid in the process of demonstrating clinical superiority, the FDA is required to notify sponsors of the basis for the orphan-drug designation, including “any plausible hypothesis” on which the FDA relies to find the drug clinically superior.<sup>68</sup> The FDA must also publish a summary of its clinical superiority findings after granting an application for exclusive approval or licensure of an orphan drug on the basis of clinical superiority.<sup>69</sup>

## Interpreting “Same Disease or Condition”: *Catalyst Pharmaceuticals, Inc. v. Becerra*

Since the ODA was enacted, courts have heard a number of cases addressing the scope of orphan-drug exclusivity.<sup>70</sup> A recent case, *Catalyst Pharmaceuticals, Inc. v. Becerra*, interpreted the meaning of the words “same disease or condition” with respect to the orphan-drug exclusivity.<sup>71</sup>

*Catalyst* arose after two different orphan-drug manufacturers received FDA approval to market amifampridine, which is used to treat Lambert-Eaton Myasthenic Syndrome (LEMS).<sup>72</sup> The FDA designated Catalyst’s drug Firdapse (a brand name for amifampridine) as an orphan drug for the treatment of LEMS in 2005; the FDA approved Firdapse for the treatment of LEMS in adults on November 28, 2018.<sup>73</sup>

A competing manufacturer, Jacobus, received an orphan-drug designation for Ruzurgi (the brand name for its version of amifampridine) in 1990.<sup>74</sup> The FDA approved Ruzurgi for the treatment of LEMS in *pediatric* patients on May 6, 2019.<sup>75</sup> Catalyst challenged the FDA’s approval of Ruzurgi, alleging that the approval of Ruzurgi violated Catalyst’s orphan-drug exclusivity for Firdapse.<sup>76</sup> The central issue in the case was whether the FDA could interpret the statutory phrase “same drug for the same disease or condition” so as to allow it to approve the same drug for the same disease but for a different indication (e.g., treating adults versus treating children).<sup>77</sup>

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<sup>67</sup> 42 U.S.C. § 360cc(c)(2).

<sup>68</sup> 21 U.S.C. § 360cc(e)(1).

<sup>69</sup> *Id.* § 360cc(e)(2).

<sup>70</sup> See, e.g., *Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141 (11th Cir. 2002); *Spectrum Pharms., Inc., v. Burwell*, 824 F.3d 1062 (D.C. Cir. 2016); *Eagle Pharms., Inc. v. Azar*, 952 F.3d 323 (11th Cir. 2020).

<sup>71</sup> *Catalyst Pharms., Inc. v. U.S. Food and Drug Admin.*, 2020 WL 5792595 (S.D. Fla. Sept. 29, 2020), *rev’d*, *Catalyst Pharms., Inc., v. Becerra*, 14 F.4th 1299 (11th Cir. 2021), *cert dismissed sub nom. Jacobus Pharm. Co. v. Catalyst Pharms.*, 142 S. Ct. 2904 (2022); see also 42 U.S.C. § 360cc(a).

<sup>72</sup> *Catalyst Pharms., Inc. v. Azar*, No. 19-cv-22425, 2020 WL 5514187, at \*1 (S.D. Fla. July 30, 2020), *report and recommendation adopted sub nom. Catalyst Pharms. v. U.S. Food & Drug Admin.*, No. 19-cv-22425, 2020 WL 5792595 (S.D. Fla. Sept. 29, 2020), *rev’d and remanded sub nom. Catalyst Pharms. v. Becerra*, 14 F.4th 1299 (11th Cir. 2021).

<sup>73</sup> *Id.* at \*2.

<sup>74</sup> *Id.* at \*3.

<sup>75</sup> *Catalyst Pharms.*, 14 F.4th at 1305.

<sup>76</sup> 2020 WL 5514187, at \*3.

<sup>77</sup> 2020 WL 5792595, at \*5.

## District Court Decision

On September 29, 2020, the U.S. District Court for the Southern District of Florida held that FDA had not violated the ODA or the Administrative Procedure Act (APA) in approving Ruzurgi.<sup>78</sup> Catalyst had argued that the FDA's approval of Ruzurgi infringed upon Catalyst's regulatory exclusivity for Firdapse.<sup>79</sup> Catalyst argued that the FDA's approval of Ruzurgi violated the plain language of the ODA, which prohibits the FDA from approving "the same drug for the same disease or condition" during Catalyst's exclusivity period.<sup>80</sup> In response, the FDA argued that the ODA's language was ambiguous and that therefore, under what is known as the *Chevron* doctrine, the court should defer to its interpretation of the ODA.<sup>81</sup> That interpretation, as discussed earlier, is embodied in the FDA regulation interpreting the phrase "same disease or condition" to refer to the drug's use as stated in the NDA, rather than the orphan-drug designation.<sup>82</sup>

When Congress gives an agency like the FDA regulatory authority, that authority is constrained by the statutes that authorize the FDA to carry out the delegated tasks.<sup>83</sup> The *Chevron* doctrine is a two-step framework of review used by federal courts that generally applies when Congress gives an agency the authority to make rules that have the force of law.<sup>84</sup> If a court determines that *Chevron* applies, at step one, the court will use traditional tools of statutory construction to determine whether Congress directly addressed the precise issue before the court.<sup>85</sup> If the statute is clear on its face, then the Court must implement Congress's stated intent.<sup>86</sup> If the court concludes that the statute is silent or ambiguous, it will proceed to *Chevron*'s second step.<sup>87</sup> Under step two, a court must defer to an agency's reasonable interpretation of the statute.<sup>88</sup>

Using a *Chevron* analysis, the district court first found the phrase "same disease or condition" ambiguous, stating "it is not clear whether the language 'disease or condition' in section 360cc refers to the *approved* disease or condition for which the sponsor applies in its [New Drug Application], or the disease or condition that was initially *designated* under section 360bb."<sup>89</sup>

In *Chevron*'s second step, the court found that the FDA's interpretation of the ambiguous statutory provision was reasonable, pointing to both the text of the statute as well as the greater statutory

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<sup>78</sup> 2020 WL 5792595. In its decision, the district court adopted the recommendations of an earlier magistrate judge's review of the parties' cross motions for summary judgment. *See* 2020 WL 5514187 (S.D. Fla. July 30, 2020). The district court refers to the magistrate judge's findings at various places throughout its opinion, and thus this report cites to both the magistrate judge's recommendation and the district court's opinion.

<sup>79</sup> 2020 WL 5514187 at \*3. A second legal issue presented to the district court was whether Ruzurgi's label was false or misleading. *See* 2020 WL 5792595, at \*5. This report focuses only on the first issue regarding the orphan-drug exclusivity.

<sup>80</sup> 2020 WL 5514187 at \*4; *see also* 21 U.S.C. § 360cc(a).

<sup>81</sup> 2020 WL 5514187 at \*4.

<sup>82</sup> 2020 WL 5514187 at \*5. The FDA's reading narrows the scope of the orphan drug's market exclusivity because the NDA may be limited to specific to subgroups or subpopulations whereas an orphan-drug designation is generally broader. *Id.*

<sup>83</sup> *See* 5 U.S.C. § 706(2)(A).

<sup>84</sup> *Chevron U.S.A., Inc. v. Nat. Res. Def. Council, Inc.*, 467 U.S. 837 (1984). For more information about the *Chevron* doctrine, *see* CRS Report R44954, *Chevron Deference: A Primer*, by Benjamin M. Barczewski (2023). For more information about how *Chevron* has been applied specifically by federal appeals courts, *see* CRS Legal Sidebar LSB10976, *Chevron Deference in the Courts of Appeals*, by Benjamin M. Barczewski (2023).

<sup>85</sup> *Id.* at 842.

<sup>86</sup> *Id.* at 842-43.

<sup>87</sup> *Id.* at 843.

<sup>88</sup> *Id.*

<sup>89</sup> 2020 WL 5792595, at \*6.

scheme.<sup>90</sup> The court reasoned that because Section 360cc referred back to Section 355 of the FDCA (which concerns drug approvals), more than one interpretation was reasonable.<sup>91</sup> The court observed that “Congress could have, but did not, omit reference to section 355, or make clear that the term ‘same disease or condition’ refers only to the disease or condition *as designated* in section 360bb.”<sup>92</sup> In other words, because the relevant provision of the statute refers to the NDA process in Section 355, and an NDA is specific to certain uses or indications for a drug, it was reasonable for the FDA to approve two orphan-drug applications for the same drug when those two drugs were approved for different indications. The court conceded that Catalyst’s interpretation of the statute “was not necessarily *wrong*, but it is not the only reasonable way to interpret the plain language of the statute.”<sup>93</sup>

## Eleventh Circuit Reversal

Catalyst appealed the district court’s ruling to the U.S. Court of Appeals for the Eleventh Circuit (the 11th Circuit).<sup>94</sup> On September 30, 2021, the 11th Circuit reversed the district court, holding that the ODA’s use of “same disease or condition” was not ambiguous, and thus that the FDA violated Catalyst’s seven-year orphan-drug exclusivity when it approved Ruzurgi.<sup>95</sup>

The 11th Circuit began with the statutory text. After reviewing various definitions of the term “same,” the court concluded that “[t]he ordinary and plain meaning of ‘same disease or condition’ read in the context of [the statute] yields only one result—the term unambiguously refers to the ‘rare disease or condition’ designated under § 360bb.”<sup>96</sup> The 11th Circuit disagreed with the district court’s conclusion that the statute’s earlier reference to Section 355 (the NDA provisions) made the phrase “same disease or condition” ambiguous, finding it unsupported by the statutory text.<sup>97</sup> The court observed that Section 355 contains “more limited language” than the “broader” language used in Section 360cc, and thus inferred that Congress must have meant to exclude these more specific terms.<sup>98</sup> The court stated that “if Congress wanted to make the ‘use or indication’ inquiry relevant to a holder’s market exclusivity for an orphan drug, it could have done so by including such language in § 360cc(a). The fact that Congress did not include that language counsels against an interpretation that finds an ambiguity in § 360cc(a)’s language.”<sup>99</sup>

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<sup>90</sup> 2020 WL 5792595, at \*8.

<sup>91</sup> *Id.* at \*8. Section 355 concerns the submission and approval process for NDAs. *See* 21 U.S.C. § 355.

<sup>92</sup> 2020 WL 5792595, at \*8.

<sup>93</sup> *Id.* at \*9 (emphasis in original). As for Catalyst’s argument that Ruzurgi’s labeling was false or misleading for implying an unapproved indication for the treatment of LEMS in children, the court was not persuaded. *Id.* The FDA-approved label for Ruzurgi stated that the drug was indicated for the treatment of LEMS “in patients 6 to less than 17 years of age,” but drug trials were only performed in adults. *Id.* The court agreed with the magistrate’s recommendation to defer to the FDA’s review of the drug label; the magistrate pointed to several places in the record where the “FDA applied its judgment and expertise to the data in the new drug application and made determinations about what to include and what to exclude.” *Id.* at \*10; 2020 WL 5514187 at \*8.

<sup>94</sup> Notice of Appeal, *Catalyst Pharms., Inc. v. Becerra*, No. 20-13922 (11th Cir. Oct. 19, 2020), ECF No. 1.

<sup>95</sup> *Catalyst Pharms., Inc. v. Becerra*, 14 F.4th 1299 (11th Cir. 2021), *cert dismissed sub nom.* *Jacobus Pharm Co. v. Catalyst Pharms.*, 142 S. Ct. 2904 (2022).

<sup>96</sup> *Id.* at 1307.

<sup>97</sup> *Id.* at 1308.

<sup>98</sup> *Id.* at 1309. The court also observed that, in addition to § 355’s NDA provision, § 360cc(a) also referenced § 262 of the Public Health Service Act, which concerns the licensing of biological products. *Id.* These references were significant, the court said, only insofar as they refer to “what must occur to trigger market exclusivity . . . and what the FDA is prohibited from doing once both the designation and approval conditions are met.” *Id.* In other words, the 11th Circuit did not find the ODA’s references to either § 355 or 42 U.S.C. § 262 made the ODA provision ambiguous. *Id.*

<sup>99</sup> 14 F.4th at 1309.

The court also pointed to other cases interpreting the ODA's market exclusivity provision with respect to a drug's use or indication. The court found that reading these cases as supportive of the FDA's position was to take their holdings out of context.<sup>100</sup> One such case was *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, in which the Fourth Circuit interpreted the ODA market exclusivity provisions in the context of generic drug production.<sup>101</sup> In *Sigma-Tau*, a manufacturer received a seven-year orphan drug exclusivity for a drug known as levocarnitine, which was used to treat carnitine deficiency in patients with certain metabolic disorders.<sup>102</sup> Shortly after the exclusivity period ended, the manufacturer obtained another orphan-drug exclusivity for the same drug to treat carnitine deficiency in patients with end-stage renal disease (ESRD).<sup>103</sup> During the second exclusivity period for levocarnitine, the FDA approved a generic form of the drug for patients with metabolic disorders, and Sigma-Tau sued, arguing that the FDA's approval of the generic violated its market exclusivity because the generic could be prescribed off-label to treat carnitine deficiency for ESRD patients, the condition for which it still held exclusivity.<sup>104</sup> The Fourth Circuit disagreed, finding the plain language of the ODA<sup>105</sup> unambiguous; the court stated that "Congress made clear its intention that § 360cc(a) was to be disease-specific, not drug-specific. In other words, the statute as written protects uses, not drugs for any and all uses."<sup>106</sup> Accordingly, FDA could approve a generic version of the same drug for a different disease than the one entitled to exclusivity.

In *Catalyst*, the 11th Circuit distinguished *Sigma Tau* on the basis that it concerned orphan-drug exclusivity for two different diseases. It declined to extend the Fourth Circuit's ruling to a situation in which the same drug was being used to treat the same condition but with two different indications.<sup>107</sup> Because the court found that the ODA's phrase "same disease or condition" was unambiguous, it concluded that the FDA's interpretation was not entitled to *Chevron* deference.<sup>108</sup> The court held that "the FDA's interpretation of [the ODA] is contrary to the clear statutory language enacted by Congress."<sup>109</sup> The court set aside the FDA's approval of Ruzurgi and

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<sup>100</sup> *Id.* 1311.

<sup>101</sup> *Id.* at 1311; *Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002). The 11th Circuit also distinguished the D.C. Circuit's ruling in *Spectrum Pharms., Inc. v. Burwell*, 824 F.3d 1062 (D.C. Cir. 2016), which addressed off-label use in the context of the exclusivity provisions in § 360cc(a). In that case, the D.C. Circuit affirmed a grant of summary judgment against Spectrum, finding that a competing manufacturer could market a generic drug that could be used off-label to treat a different condition for which Spectrum held market exclusivity. 824 F.3d at 1064. Citing the Fourth Circuit's ruling in *Sigma-Tau*, the D.C. Circuit agreed that Congress's intention was to make § 360cc "disease specific, not drug specific," noting that "the rest of the statutory language [in § 360cc] focuses on protecting approved indications, not intended off-label uses." *Id.* at 1067. *Catalyst* declined to extend this holding to situations in which the exclusivity covered different indications for the same disease or condition. 14 F.4th at 1311.

<sup>102</sup> 288 F.3d at 143.

<sup>103</sup> *Id.*

<sup>104</sup> *Id.* at 143.

<sup>105</sup> It should be noted that *Sigma-Tau* was decided in 2002, prior to the 2017 ODA amendments, in which Congress changed the prohibition language in § 360cc(a) from "such drug for such disease or condition," to the language used now (i.e., "same drug for the same disease or condition"). See FDA Reauthorization Act of 2017, Pub. L. No. 115-52, § 607, 131 Stat. 1051, § 607 (amending 42 U.S.C. § 360cc).

<sup>106</sup> 288 F.3d at 145.

<sup>107</sup> 14 F.4th at 1311. In other words, *Catalyst* concerns orphan-drug exclusivity for a drug used to treat the same disease but with two different indications, but *Sigma-Tau* addressed orphan-drug exclusivity for a different disease.

<sup>108</sup> *Id.* at 1312.

<sup>109</sup> *Id.*

remanded the case to the district court, which granted Catalyst’s motion for summary judgment.<sup>110</sup> The FDA’s motion for rehearing en banc was denied.<sup>111</sup>

## FDA Non-Acquiescence in the Context of the ODA

### Non-Acquiescence to *Catalyst*

Within the field of administrative law, the practice of agency non-acquiescence is defined as “[t]he selective refusal of administrative agencies to conduct their internal proceedings consistently with adverse rulings of the courts of appeals.”<sup>112</sup> Federal agencies, including the FDA, occasionally engage in this practice, which has “persisted without either legitimation or interdiction by Congress or the Supreme Court” since at least the 1940s.<sup>113</sup> While some courts and scholars have questioned the constitutionality of the practice of agency non-acquiescence, others have insisted that it remains an essential component of administrative law.<sup>114</sup> As discussed in this report, within the context of orphan-drug exclusivities, the FDA has non-acquiesced to federal court rulings on a few occasions.<sup>115</sup>

In the months after *Catalyst* was decided, stakeholders debated its impact on orphan drug development. Some went so far as to claim that the decision “undoubtedly increases the value of orphan-drug exclusivity to include the entire disease or condition,” while others were less certain, saying only that the decision created “uncertainty,” and that orphan-drug sponsors would need to monitor the FDA’s reaction to the ruling “to evaluate the potential impact for their rare disease products.”<sup>116</sup> On January 24, 2023, the FDA issued a Federal Register Notice (FRN) announcing that, although it had complied with the 11th Circuit’s order in *Catalyst* and rescinded Jacobus’s approval for Ruzurgi, the “FDA intends to continue to apply its regulations tying the scope of orphan-drug exclusivity to the uses or indications for which a drug is approved.”<sup>117</sup>

To explain its reasoning, the FDA referenced its regulatory definition of “orphan-drug exclusive approval,” which states that it will not extend exclusivity to a subsequent sponsor that requests

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<sup>110</sup> *Id.* at 1313. Order Upon Remand, *Catalyst Pharms, Inc. v. U.S. Food and Drug Admin.*, No. 19-22425 (S.D.FL., Jan. 31, 2022). The Eleventh Circuit’s order did not overturn the FDA regulation at 21 C.F.R. § 316.31(b).

<sup>111</sup> Order Denying Petition for Rehearing en Banc, *Catalyst Pharms., Inc. v. Becerra*, No. 20-13922 (11th Cir., Jan. 7, 2022).

<sup>112</sup> Samuel Estreicher & Richard L. Revesz, *Nonacquiescence by Federal Administrative Agencies*, 88 YALE LAW J. 679-772 (Feb., 1989).

<sup>113</sup> *Id.* at 681.

<sup>114</sup> *Id.* at 718 (citing *Lopez v. Heckler*, 713 F. 2d 1432, 1431 (9th Cir. 1983); *Allegheny Gen. Hosp. v. NLRB*, 608 F.2d 965, 967 (3rd Cir. 1979); *Stieberger v. Heckler*, 615 F. Supp. 1315, 1365-66 (S.D. N.Y. 1985) (*vacated by Stieberger v. Bowen*, 801 F.2d 29 (2nd Cir. 1986)).

<sup>115</sup> *See, e.g.*, Clarification of Orphan-Drug Exclusivity Following *Catalyst Pharms., Inc. v. Becerra*, 88 Fed. Reg. 4068 (Jan. 24, 2023).

<sup>116</sup> Sara W. Koblitz, *Catalyst Pharms, Inc. v. Becerra: Why It Made the List*, FOOD AND DRUG LAW INST., <https://www.fdli.org/2022/06/catalyst-pharmaceuticals-inc-v-becerra/> (last visited July 14, 2023); George A. O’Brien, *Catalyst Pharms v. Becerra: Did the Eleventh Circuit Broaden the Scope of Orphan Exclusivity*, MAYER BROWN (Aug. 18, 2022), <https://www.mayerbrown.com/en/perspectives-events/publications/2022/08/catalyst-pharms-v-becerra-did-the-eleventh-circuit-broaden-the-scope-of-orphan-exclusivity>.

<sup>117</sup> Clarification of Orphan-Drug Exclusivity Following *Catalyst Pharms., Inc. v. Becerra*, 88 Fed. Reg. 4068 (Jan. 24, 2023). The FDA did not specifically state whether it intends to continue applying its interpretation of 21 C.F.R. § 316.31(b) in the 11th Circuit.

approval for the same drug for the same *use or indication*.<sup>118</sup> The FDA also pointed to its regulations on the scope of orphan-drug exclusivity, stating that “orphan-drug exclusive approval protects only the approved *indication or use* of a designated drug.”<sup>119</sup>

The FDA provided several reasons for continuing to tie exclusivity to an orphan drug’s use or indication. First, contrary to the 11th Circuit’s holding in *Catalyst*, the FDA reasserted its position that the statutory text in Section 360cc(a) is ambiguous.<sup>120</sup> Second, the FDA asserted that its interpretation of the statute “best advances the [ODA]’s purposes, appropriately balancing the need to incentivize the development of drugs for rare diseases . . . with the need to provide patient access to orphan drugs.”<sup>121</sup> The FDA pointed out that limiting the scope of exclusivity to the drug’s use or indication leaves room for other sponsors to continue to innovate. In addition, other sponsors may be incentivized by the continued availability of exclusivity to pursue other indications for the same drug and same disease or condition that are not covered by the approved drug’s exclusivity.<sup>122</sup> In this way, the regulations “incentivize sponsors to continue to develop a drug for use in all persons affected by a rare disease or condition.”<sup>123</sup> For these reasons, the agency has decided to “continue to apply its longstanding regulations” regarding the scope of orphan-drug exclusivity.<sup>124</sup>

## FDA Non-Acquiescence Regarding Clinical Superiority and Congressional Response

The FDA’s January 2023 FRN is not the first time that the agency has chosen not to adopt a court’s reasoning for future approvals regarding the scope of exclusivity in the ODA. In the 2014 case *Depomed, Inc. v. U.S. Department of Health & Human Services*, the D.C. District Court ruled against the FDA’s requirement that a subsequent sponsor of the same orphan drug for the same disease or condition demonstrate clinical superiority to receive marketing exclusivity. The court concluded that the plain language of the ODA required that any sponsor of a designated orphan drug receive seven years of exclusivity following approval, regardless of whether the same drug had already been approved for the same disease or condition.<sup>125</sup> The FDA initially appealed the ruling to the D.C. Circuit but later withdrew its appeal, instead opting to publish an FRN stating its non-acquiescence to the decision.<sup>126</sup> The FRN summarized the FDA’s policy of requiring subsequent manufacturers of the same orphan drug for the same disease or condition to

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<sup>118</sup> *Id.* at 4068 (emphasis added) (“[N]o approval will be given to a subsequent sponsor of the same drug for the same use or indication for 7 years, except as otherwise provided by law or in this part. A designated drug will receive orphan-drug exclusive approval only if the same drug has not already been approved for the same use or indication.” (quoting 21 C.F.R. § 316.3(b)(12)).

<sup>119</sup> 88 Fed. Reg. at 4086 (emphasis added) (citing 21 C.F.R. § 316.31(b)). The regulations go on to state that if “such approval is limited to only particular indication(s) or uses(s) [sic] 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.” 21 C.F.R. § 316.31(b).

<sup>120</sup> 88 Fed. Reg. at 4087.

<sup>121</sup> *Id.*

<sup>122</sup> *Id.*

<sup>123</sup> *Id.*

<sup>124</sup> *Id.* Were a similar issue to come up again in the 11th Circuit, a district court would be bound to follow the 11th Circuit’s ruling in *Catalyst*. If a future case were to be appealed to the 11th Circuit, the court would be bound to apply *Catalyst*’s reasoning unless the full 11th Circuit revisits the decision in a rehearing en banc.

<sup>125</sup> *Depomed, Inc. v. U.S. Dept. of Health & Human Servs.*, 66 F. Supp. 3d 217, 220 (D.D.C. 2014). At the time that *Depomed* was decided, Congress had not yet added § 360cc(c) to the ODA, which codified the FDA’s clinical superiority requirements. Congress added this section in 2017 via the FDA Reauthorization Act. See *supra* note 53.

<sup>126</sup> Policy on Orphan-Drug Exclusivity; Clarification, 79 Fed. Reg. 76,888 (Dec. 23, 2014).

demonstrate clinical superiority in order for the drug to receive seven years of market exclusivity.<sup>127</sup> Similar to the aftermath of *Catalyst*, the FDA stated its intention to “continue to apply its existing regulations . . . to orphan-drug exclusivity matters,” and that it interpreted the ODA “to require the sponsor of a designated drug that is the same as a previously approved drug to demonstrate that its drug is clinically superior to that drug upon approval” to receive market exclusivity.<sup>128</sup>

Less than four years later, *Eagle Pharmaceuticals, Inc. v. Azar* presented the same legal question of whether the ODA permitted the FDA to require subsequent manufacturers of the same orphan drug to demonstrate clinical superiority prior to receiving exclusivity.<sup>129</sup> While *Eagle* was being litigated, Congress passed the FDA Reauthorization Act of 2017, amending Section 360cc of the ODA to codify the FDA’s clinical superiority requirement for market exclusivity, thus superseding *Depomed*.<sup>130</sup> Because Congress did not retroactively apply these changes to the ODA, however, the district court applied the earlier text of the ODA to hold that the FDA lacked the authority to apply the clinical superiority requirements when granting orphan-drug approvals prior to the statutory change.<sup>131</sup> The D.C. Circuit affirmed the district court’s decision on appeal, unpersuaded by the FDA’s arguments that the absence of a clinical superiority requirement would create “serial exclusivity.”<sup>132</sup>

## Considerations for Congress

A 2020 HHS drug pricing report to Congress showed that drug spending is increasing across federal health care programs, and Congress is consistently concerned about rising prescription drug costs.<sup>133</sup> The ODA attempts to balance the competing needs and interests of pharmaceutical companies and patients with rare diseases by incentivizing the development and marketing of

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<sup>127</sup> *Id.*; see also 78 Fed. Reg. 35,117 (final rule explaining FDA’s policy of clinical superiority for orphan-drug exclusivity and amending existing regulation in 21 C.F.R. part 316).

<sup>128</sup> 79 Fed. Reg. at 76,888 (internal punctuation omitted).

<sup>129</sup> *Eagle Pharm., Inc. v. Azar*, No. 16-790, 2018 WL 3838265 (D.D.C. June 8, 2018).

<sup>130</sup> FDA Reauthorization Act of 2017, Pub. L. No. 115-52, § 607, 131 Stat. 1051, § 607 (amending 42 U.S.C. § 360cc).

<sup>131</sup> 2018 WL 3838265, at \*6 (“The Court thus agrees with the conclusion in *Depomed* that this language [in the pre-amendment ODA] leaves no room for the FDA’s imposition of its clinical-superiority requirement after an orphan drug has been designated and approved.”)

<sup>132</sup> *Eagle Pharms., Inc. v. Azar*, 952 F.3d 323 (D.C. Cir. 2020). The majority found that both the text and structure of the ODA failed to support the FDA’s argument market exclusivity was not automatic and that the statute left enough room for FDA’s clinical superiority requirement. *Id.* at 331. The majority was similarly unpersuaded by the FDA’s argument that the statute’s structure and purpose supported such a requirement, finding that although “Congress’s goal in enacting the ODA was to reduce the cost of and incentivize orphan drug development . . . the fact that following the text of a statute may conflict with the statute’s larger purpose alone does not warrant departing from the text.” *Id.* at 355.

One judge dissented, arguing that the majority’s interpretation of the statute could result in “endless exclusivity,” and finding that “FDA’s decision to condition exclusivity on a showing of clinical superiority over already-approved drugs using the same active moiety flows from the Act’s plain language and basic structure.” *Id.* at 344–45 (Williams, J., dissenting). According to the dissent, “[t]he most likely explanation . . . for why Congress did not specify in § 360cc(a) whether a drug’s exclusivity period would or would not be repeatable . . . is that such a notion would have been so far afield from what Congress was contemplating at the time that it would not have occurred to any member of Congress as something in need of clarification.” *Id.* at 347.

<sup>133</sup> Stephanie Armour & Liz Essley Whyte, *Something Congress Might Agree on: Tackling Drug Costs*, WALL STREET J. (May 8, 2023), <https://www.wsj.com/articles/something-congress-might-agree-on-tackling-drug-costs-39f6574d>. U.S. DEPT. OF HEALTH & HUMAN SERVS., OFFICE OF THE ASST. SEC. FOR PLANNING & EVAL., Report to Congress: Prescription Drug Pricing (May 20, 2020), [https://aspe.hhs.gov/sites/default/files/migrated\\_legacy\\_files//194881/2020-drug-pricing-report-congress-final.pdf](https://aspe.hhs.gov/sites/default/files/migrated_legacy_files//194881/2020-drug-pricing-report-congress-final.pdf).



orphan drugs.<sup>134</sup> Between the act's passage in 1983 and 2018, the FDA has approved more than 500 orphan drugs,<sup>135</sup> and more recently, between 2017 and 2021, orphan drugs made up about half of the FDA's drug approvals.<sup>136</sup> At the same time, the median treatment cost for an orphan drug upon market entry was more than \$218,000, compared to the median cost of a non-orphan drug at \$12,798.<sup>137</sup>

Since its creation, the ODA has been criticized by some stakeholders for giving drug companies too much power to monopolize and profit from lifesaving medications.<sup>138</sup> Others argue that the law is outdated and does not take into account more recent advances in science, whose increased focus on genetic research tied to specific patient subpopulations makes it more likely that new therapies will qualify as orphan drugs.<sup>139</sup> Some critics of the law highlight that the ODA's seven-year exclusivity has often been abused, in their view, and that the exclusivity makes it more difficult for patients to afford their medications.<sup>140</sup> Others have praised the law for encouraging manufacturers to invest in research and development for otherwise unprofitable drugs, highlighting that without it, many lifesaving therapies would likely be unavailable.<sup>141</sup> Stakeholders have also disagreed about whether the ODA should take into account drug-pricing practices, as the ODA does not give the FDA authority to directly regulate drug prices or to consider the impact of orphan-drug status on pricing.<sup>142</sup>

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<sup>134</sup> See, e.g., Orphan Drug Regulations, 56 Fed. Reg. 3338 (Jan. 29, 1991) (proposed ODA regulations). FDA states, "The main purpose of the Orphan Drug Act is to stimulate innovation in developing treatments for patients with rare diseases and conditions and to foster the prompt availability of therapeutically superior drugs. These proposed regulations attempt to ensure that improved therapies will always be marketable, and that orphan drug exclusive approval does not preclude significant improvements in treating rare diseases." See also Orphan Drug Regulations, 57 Fed. Reg. 62,076, 62,077 ("Some comments argued that the proposed regulations go too far in protecting exclusive marketing rights, while other[s] . . . argued that they do not go far enough . . . FDA believes the final rule achieves the best balance possible between protecting exclusive marketing rights and fostering competition.").

<sup>135</sup> Shailin Thomas and Arthur Caplan, *The Orphan Drug Act Revisited*, 321 JAMA 833-34 (2019).

<sup>136</sup> Hana Althobaiti, et al., *Disentangling the Cost of Orphan Drugs Marketed in the United States*, 11 HEALTHCARE 4 (Feb. 13, 2023), <https://www.mdpi.com/2227-9032/11/4/558>.

<sup>137</sup> *Id.*

<sup>138</sup> For example, in 2011 the FDA approved KV Pharmaceuticals' drug Makena as an orphan drug to prevent preterm labor, resulting in a large price increase for the drug, which had previously been available at compound pharmacies at low cost. The price increase generated concern from Congress, with several members asking the Federal Trade Commission to investigate potential pricing abuses. See, e.g., Press Release, Sen. Sherrod Brown Statement on Makena Repricing, <https://www.brown.senate.gov/newsroom/press/release/brown-statement-on-makena-repricing> (April 1, 2011). The FDA later released a statement that it would not take enforcement action against pharmacies that compound the generic version of the drug. See Andrew Zajac, *Drug Maker Lowers Price of Makena Pregnancy Drug to \$690 per Dose*, L.A. TIMES (April 1, 2011), <https://www.latimes.com/health/la-xpm-2011-apr-01-la-pn-makena-price-cut-fda-20110401-story.html>.

<sup>139</sup> Thomas and Caplan, *supra* note 118.

<sup>140</sup> Jake Stump, *WVU Research Shows How Much Pharmaceutical Companies are Capitalizing on Rare Drug Incentives*, WVUTODAY (June 12, 2023), <https://wvutoday.wvu.edu/stories/2023/06/12/wvu-research-shows-how-much-pharmaceutical-companies-are-capitalizing-on-rare-drug-incentives>; see also, Orphan Drug Regulations, FOOD & DRUG ADMIN., 57 Fed. Reg. 62076, 62077, where FDA addressed comments on the proposed ODA Regulations. FDA noted, "Some comments argued that the proposed regulations go too far in protecting exclusive marketing rights, while other[s] . . . argued that they do not go far enough . . . FDA believes the final rule achieves the best balance possible between protecting exclusive marketing rights and fostering competition.").

<sup>141</sup> Abbey S. Meyers, *Orphan Drug Tax Credits Save Lives*, ABBEYSMEYERS.COM (December 10, 2017), <https://www.abbeymeyers.com/memories/45-orphan-drug-tax-credits-save-lives>; Gary A. Pulsinelli, *The Orphan Drug Act: What's Right with It*, 15 SANTA CLARA COMP. & HIGH TECH. L. J. 299 (1999).

<sup>142</sup> 57 Fed. Reg. at 62079 ("Although FDA understandings that costs can indeed have a major impact on access to a drug, FDA has no authority over drug pricing or any authority to consider it in drug approval.")

The Government Accountability Office (GAO) evaluated the FDA's orphan-drug processes, including how the FDA has addressed the increase in demand for orphan-drug designations and how FDA has addressed orphan-drug development challenges.<sup>143</sup> The study was conducted by analyzing FDA data, templates for orphan-drug designation applications, and interviews with patient advocates, manufacturers, industry experts, and others.<sup>144</sup> In its report, the GAO highlighted competing views regarding the profitability of orphan drugs and the need for further incentives for manufacturers to develop orphan-drug therapies.<sup>145</sup> The report similarly commented that much of the recent action FDA has taken to increase efficiency in its review of orphan-drug designation applications does not address the wider disagreements about the unmet need for rare disease treatments, the need for orphan-drug incentives, and the high cost of orphan drugs, including the effects of these costs on patients.<sup>146</sup>

To address these and other concerns, Members of the 118<sup>th</sup> Congress have proposed various amendments to the ODA, including changes to address the potential for uncertainty caused by the 11th Circuit's decision in *Catalyst*.<sup>147</sup> The Retaining Access and Restoring Exclusivity (RARE) Act, proposed in both the 117th and 118th Congresses, would amend the ODA to mirror the FDA's interpretation of the scope of the exclusivity provision for approved or licensed orphan drugs.<sup>148</sup> Specifically, the RARE Act would codify the FDA's interpretation of the "same drug for the same disease or condition" language to read, "the same drug for the same *approved use or indication within such* rare disease or condition."<sup>149</sup> Such a change would codify the FDA's regulations regarding the scope of orphan-drug approvals.<sup>150</sup> More than 80 stakeholder groups, including the National Organization for Rare Disorders and various foundations and associations dedicated to the study of rare diseases, sent a letter to the leadership of the Senate Committee on Health, Education, Labor and Pensions, urging the 117th Congress to enact the legislation.<sup>151</sup>

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<sup>143</sup> GOV'T ACCT. OFFICE, *Orphan Drugs: FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue*, Nov. 2018, <https://www.gao.gov/assets/gao-19-83.pdf>, at 1.

<sup>144</sup> *Id.*

<sup>145</sup> *Id.* at 1, 30.

<sup>146</sup> *Id.* at 39-40.

<sup>147</sup> Other proposals, such as the Fairness in Orphan Drug Exclusivity Act (FODEA), would limit market exclusivity for drugs that receive an orphan-drug designation on the basis that the sponsor has no reasonable expectation of recovering the costs of developing and distributing the drug. H.R. 456, 118th Cong. (2023). As part of a request to designate an orphan drug, a sponsor must demonstrate an inability to recover research and development costs if the drug will be used for a disease affecting more than 200,000 people. 21 U.S.C. § 360bb(a)(2)(B). FODEA would extend the requirement of demonstrating cost-prohibitive status to the drug approval process as well, such that in order to be entitled to the seven-year exclusivity, a manufacturer would have to demonstrate an inability to recover costs of the drug as of the date the drug is approved. *See* H.R. 456, § 2(f)(1). A press release from Rep. Carter, the sponsor of the bill, states that the proposal is intended to "close a loophole that allows drug manufacturers to block new treatment[] options for rare diseases from coming to the market." Press Release, Carter Introduces Bill to Close Loophole Blocking Rare Disease Treatments from Market, Jan. 24, 2023, available at <https://buddycarter.house.gov/news/documentsingle.aspx?DocumentID=10861>.

Another proposal, introduced as Cameron's Law, proposes an amendment to the Internal Revenue Code to increase the amount of the orphan drug tax credit from 25% to 50%. H.R. 1350, Cameron's Law, March 3, 2023 (118th Cong., 1st Session).

<sup>148</sup> S. 4185, 117th Cong. (2022); S. 1214, 118th Cong. (2023). The two bills contain the same text.

<sup>149</sup> *Id.* § 2(a)(1)–(2) (emphasis added).

<sup>150</sup> 21 C.F.R. § 316.31(b).

<sup>151</sup> Letter from National Organization for Rare Disorders to Sen. Patty Murray and Sen. Richard Burr, Senate HELP Committee (June 3, 2022), available at <https://rarediseases.org/wp-content/uploads/2022/08/NORD-2022-ODE-Letter-to-HELP.pdf>.

Alternatively, Congress could also enact legislation codifying the 11th Circuit’s broader definition, or choose to take no action.

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