United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued October 17, 2019 Decided March 13, 2020

No. 18-5207

EAGLE PHARMACEUTICALS, INC.,
APPELLEE

v.

ALEX MICHAEL AZAR, II, IN HIS OFFICIAL CAPACITY AS SECRETARY OF HEALTH AND HUMAN SERVICES, ET AL.,
APPELLEES

APOTEX, INC.,
APPELLANT

FRESENIUS KABI USA, LLC,
APPELLEE

Consolidated with 18-5254, 18-5255, 18-5292

Appeals from the United States District Court
for the District of Columbia
(No. 1:16-cv-00790)

Melissa N. Patterson, Attorney, U.S. Department of Justice, argued the cause for federal appellants. With her on the briefs was *Scott R. McIntosh*.

Steven E. Feldman, *Sherry L. Rollo*, *John K. Hsu*, and *Jeffrey D. Skinner* were on the briefs for intervenors-appellants Apotex, Inc, et al.

Gregory G. Garre argued the cause for plaintiff-appellee. With him on the brief were *Phillip J. Perry*, *Andrew D. Prins*, and *Benjamin W. Snyder*.

Before: HENDERSON and RAO, *Circuit Judges*, and WILLIAMS, *Senior Circuit Judge*.

Opinion for the Court filed by *Circuit Judge* HENDERSON.

Dissenting Opinion filed by *Senior Circuit Judge* WILLIAMS.

KAREN LECRAFT HENDERSON, *Circuit Judge*: In 2014, the United States Food and Drug Administration (FDA) designated a drug developed by Eagle Pharmaceuticals, Inc. (Eagle) as an "orphan drug" under the Orphan Drug Act (ODA), 21 U.S.C. §§ 360aa–360ee. In 2015, the FDA approved Eagle's drug for marketing but denied Eagle's request for a seven-year period of marketing exclusivity under 21 U.S.C. § 360cc(a), concluding that Eagle failed to prove its drug was clinically superior to a previously designated and approved version of the same drug. Eagle appealed, arguing that the ODA's plain language required the FDA to automatically grant Eagle marketing exclusivity upon designating its drug as an orphan drug and approving it for marketing. The district court agreed, granting summary judgment in Eagle's favor because the Congress's intent was clearly expressed in the unambiguous language of § 360cc(a). The FDA appeals. Because the text of § 360cc(a) unambiguously entitles a manufacturer to marketing exclusivity upon designation and approval, we affirm.

I. BACKGROUND

In 1983, the Congress enacted the ODA to address the problem of "orphan drugs." *See* Pub. L. No. 97-414, § 1, 96 Stat. 2049 (1983). An orphan drug is one that "is designed to treat a rare disease or condition that historically received little attention from pharmaceutical companies, and hence became 'orphaned' because the comparatively small demand for treatment left little motive for research and development."[1] *Spectrum Pharm., Inc. v. Burwell*, 824 F.3d 1062, 1064 (D.C. Cir. 2016) (citing § 1(b)). The ODA's goal is to "reduce the costs of developing" and "provide financial incentives to develop [orphan] drugs." § 1(b).

To accomplish this goal, the ODA allows the FDA to designate a drug, at its development stage, as an orphan drug. 21 U.S.C. § 360bb.[2] Designation as an "orphan drug" provides benefits designed to promote orphan drug development such as tax credits, assistance with investigations and the approval process and monetary grants to defray the costs of developing orphan drugs. *See* 26 U.S.C. § 45C; 21 U.S.C. §§ 360aa(a), 360ee. Before the sponsor of an orphan drug can sell its drug, it must obtain marketing approval from the FDA. Generally,

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[1] The ODA defines a "rare disease or condition" as one "which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug." 21 U.S.C. § 360bb(a)(2).

[2] The ODA gives various responsibilities to the Secretary of the United States Department of Health and Human Services (HHS) but the Secretary carries out these responsibilities through the FDA Commissioner. *See* 21 U.S.C. § 393(d)(2). We refer to the FDA, rather than the Secretary, throughout this opinion.

before any drug can be sold or marketed in interstate commerce, the FDA must "certify[ ] the drug's safety and efficacy." *Otsuka Pharm. Co. v. Price*, 869 F.3d 987, 989 (D.C. Cir. 2017) (citing 21 U.S.C. § 355(a), (b)).

After a sponsor's drug has been designated as an orphan drug and approved for marketing, the FDA provides the sponsor with a seven-year period of exclusive approval rights during which time the FDA may not approve another "such drug for such disease or condition" for marketing until the end of the seven-year exclusivity period. 21 U.S.C. § 360cc(a) (2012).[3] At the time of this case, § 360cc(a) provided that:

> Except as provided in subsection (b) of this section, if the Secretary-
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> (1) approves an application filed pursuant to section 355 of this title,
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> . . .
>
> 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 . . . for such drug for such disease or condition for a person who is not the holder of such approved application . . . until the expiration of seven

[3] Because this case involves § 360cc(a) as it was written before the 2017 amendments to the ODA, *see* Pub. L. No. 115-52, § 607, 131 Stat. 1005, 1049 (2017), we cite to the version that was in force at the time of Eagle's approval and the FDA's refusal to grant exclusivity. *See* 21 U.S.C. § 360cc(a) (2012). Thus, citations to § 360cc(a), unless otherwise noted, refer to § 360cc(a) (2012).

> years from the date of the approval of the approved application . . . .

Id. The Congress provided two exceptions to the seven-year exclusivity period: the FDA "may" approve another manufacturer's drug if the holder of the exclusive approval right (1) "cannot assure the availability of sufficient quantities of the drug" or (2) consents to the approval of "other applications . . . before the expiration of such seven-year period." *Id.* § 360cc(b).

The FDA has adopted regulations to implement the ODA that further define the requirements necessary to be designated and approved as an orphan drug. The ODA does not define "such drug" for the purpose of the seven-year exclusivity period—a key term because it defines the scope of the exclusivity. *See id.* § 360cc(a) ("[I]f the Secretary . . . approves an application . . . *for a drug* designated under section 360bb . . . the Secretary may not approve another application . . . for *such drug* . . ." (emphasis added)). The FDA has interpreted "such drug" to mean "same drug," 21 C.F.R. § 316.31(a), and has determined that a drug is the "same" as a previously approved drug if it shares the same "active moiety"—the same active ingredient—and "is intended for the same use," 21 C.F.R. § 316.3(b)(14)(i). The FDA has also determined, however, that, "if the subsequent drug can be shown to be clinically superior to the first drug"—despite having the same active moiety—"it will not be considered to be the same drug." *Id.* A drug is clinically superior if it "is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in one or more of the following ways: (i) [g]reater effectiveness . . . (ii) [g]reater safety . . . or (iii) [i]n unusual cases, . . . otherwise makes a major contribution to patient care." *Id.* § 316.3(b)(3).

Putting this all together, then, the FDA considers a drug the same as a previously-approved drug if it shares the same active moiety and is not otherwise clinically superior; it considers the drug to be different—and thus entitled to its own seven-year exclusivity period upon designation and approval—if it does not have the same active moiety or is clinically superior. The FDA applies this scheme not only when determining whether it can approve another drug for marketing during an orphan drug's seven-year exclusivity period but also in deciding whether to grant a subsequent drug its own period of exclusive approval after the seven years have expired. Put differently, "the FDA will not grant the Act's benefits to a drug if it has previously approved that same drug for a particular rare disease." *Eagle Pharm., Inc. v. Azar*, No. CV 16-790 (TJK), 2018 WL 3838265, at *1 (D.D.C. June 8, 2018).

The FDA applies its clinical superiority scheme differently at the two stages of the orphan drug process. At the designation stage, the sponsor of a drug that is otherwise the same—that is, with the same active moiety—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." 21 C.F.R. 316.20(a) (emphasis added). Later, after the drug has been approved for marketing, the FDA requires the manufacturer to "*demonstrate* . . . that the drug is clinically superior to the previously approved drug" in order to receive the seven-year exclusivity period. 21 C.F.R. § 316.34(c) (emphasis added).

The FDA imposed this heightened post-approval clinical superiority requirement because, in its view, "sponsors could otherwise: (1) [o]btain infinite, successive 7-year periods of exclusivity for the same drug for the same use when the previously approved drug had such exclusivity, known as

'evergreening,'[4] or (2) obtain an exclusivity period for a drug without providing any meaningful benefit to patients over previously approved therapies, when the previously approved drug did not have orphan exclusivity"—two results which the FDA views as being "at odds with the Orphan Drug Act." Orphan Drug Regulations, 78 Fed. Reg. 35,117, 35,127 (June 12, 2013). Thus, from the FDA's perspective, implementing a post-approval clinical-superiority requirement supports its long-held view that the ODA "accord[s] orphan exclusive approval only to the first drug approved for the disease or condition" because it allows a drug to receive the seven-year exclusivity period only if it is different (and thus an entirely new drug) from a previously approved drug—*i.e.*, it does not have the same active moiety or can prove that it is clinically superior. *Id.*

In 2012, a drug manufacturer alleged the FDA's post-approval clinical superiority requirement violated the ODA's plain language. *Depomed, Inc. v. United States Dep't of Health & Human Servs.*, 66 F. Supp. 3d 217, 220 (D.D.C. 2014). Depomed Inc. had developed a drug called Gralise to treat a rare condition. *Id.* It sought and obtained designation for Gralise as an orphan drug. *Id.* at 226. The FDA subsequently approved Gralise for marketing but it denied Depomed a seven-year exclusivity period, asserting that Depomed failed to prove that Gralise was clinically superior to a previously approved drug with the same active moiety.[5] *Id.* Depomed argued that

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[4] The FDA also uses the phrase "serial exclusivity" to refer to potential subsequent periods of market exclusivity for the same drug. *See* Appellant Brief at 2.

[5] At the time of *Depomed*, the FDA had not yet codified regulations for its clinical superiority requirement but it nevertheless interpreted and applied its exclusivity determinations in that manner. The FDA issued regulations codifying the requirement while *Depomed* was pending. *See* 78 Fed. Reg. at 35,118.

it was automatically entitled to market exclusivity under § 360cc(a) upon being designated and approved. *Id.* at 228. The FDA countered that under *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), the ODA was silent or ambiguous as to whether exclusivity must be recognized when a drug is designated and approved but is otherwise the same (same active moiety and not proven to be clinically superior) as a previously approved drug for the same disease or condition. *Depomed*, 66 F. Supp. 3d at 228–29. Thus, in the FDA's view, its clinical superiority requirement was a reasonable interpretation of the ODA and was entitled to deference. *Id.*

The district court, applying *Chevron*, held that the plain language of § 360cc(a) unambiguously required the FDA to grant marketing exclusivity when it had designated an orphan drug and approved that drug for marketing. *Id.* at 229–30. The district court concluded that the plain language of § 360cc(a) "employ[ed] the familiar and readily diagrammable formula 'if x and y, then z'"—if designation and approval, then exclusivity. *Id.* at 230. The district court held that there was no "gap" in the statute for the FDA to fill and rejected the FDA's argument that applying the plain language would lead to an absurd result. *Id.* at 231–35. The district court rejected the FDA's concern that interpreting the ODA in such a way could result in "serial exclusivity"—allowing drug manufactures to obtain successive periods of exclusivity by "simply tweak[ing] their formulation for that drug and resubmit[ting] applications for designation and approval" after the initial seven-year period expires—holding that "this result would only occur *if the FDA permitted it to happen*." *Id.* at 235. The district court explained that the "'serial exclusivity' problem would not arise at all if the FDA fashioned regulations to prevent such abuse in the context of the designation phase of the exclusivity process"—such as requiring a showing of

clinical superiority before granting orphan drug designation. *Id.*

The FDA initially appealed the *Depomed* decision but ultimately withdrew its appeal, *see Depomed Inc. v. U.S. Dep't of Health & Human Servs.*, No. 14-5271, 2014 WL 5838247, at *1 (D.C. Cir. Nov. 7, 2014), opting instead to nonacquiesce to the decision in future cases, *see* Policy on Orphan-Drug Exclusivity; Clarification, 79 Fed. Reg. 76,888 (Dec. 23, 2014). In other words, the FDA continued to require drugs with the same active moiety as a previously approved orphan drug, despite having been designated and approved, to also prove clinical superiority in order to receive market exclusivity.

On the facts of the case before us, in 2007 and 2008, the FDA designated a drug called Treanda as an orphan drug to treat two forms of cancer—chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin lymphoma (B-cell NHL). The FDA subsequently approved Treanda for marketing and granted Teva Pharmaceutical Industries, Ltd. (Teva)—the manufacturer of Treanda—seven years of exclusivity for its drug. Treanda's active ingredient is bendamustine. Teva's marketing exclusivity for Treanda ended in 2015.

In 2014, Eagle asked the FDA to designate its drug, Bendeka, as an orphan drug. Bendeka had the same active moiety as Treanda but was a different formulation—among other things, Treanda was a 500 mL solution and Bendeka was 50 mL. The FDA accepted Eagle's hypothesis for Bendeka's clinical superiority to Treanda and designated Bendeka an orphan drug in July 2014. In December 2015, the FDA

approved Bendeka for marketing.[6] Upon receiving approval for Bendeka, Eagle requested a seven-year period of market exclusivity, asserting that it was automatically entitled to market exclusivity under the plain language of § 360cc(a) and that, in the alternative, it had nevertheless proven that Bendeka was clinically superior to Treanda. Applying its post-approval clinical-superiority requirement, the FDA determined that Eagle had failed to prove clinical superiority to Treanda and, as a result, was not entitled to its own exclusivity period. The FDA also rejected Eagle's claim that it was automatically entitled to exclusivity under the ODA, asserting that *Depomed* was wrongly decided because it ignored the purposes and structure of the ODA in its *Chevron* analysis and "did not appreciate" the "absurd results" of its holding. Joint Appendix at 61–68.

Eagle then began this action in district court challenging the FDA's denial of exclusivity for Bendeka under the APA, 5 U.S.C. § 706.[7] The parties filed cross-motions for summary judgment. After the parties filed their respective cross-motions, two other drug manufacturers with pending applications for generic versions of Bendeka, Apotex, Inc.

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[6] In between Bendeka's designation and approval, Teva sued Eagle pursuant to the Food Drug and Cosmetic Act (FDCA)'s patent infringement provisions. *See* 21 U.S.C. § 355(b)(2). The parties settled and, as part of the settlement, Eagle permitted Teva to commercially market Bendeka and Teva waived its remaining orphan exclusivity with respect to Bendeka. The waiver allowed for the approval of Bendeka before the expiration of Treanda's exclusivity.

[7] Eagle sued the FDA along with HHS and the heads of both the FDA and HHS. We refer to the appellant defendants collectively as the FDA.

(Apotex) and Fresenius Kabi USA, LLC (Fresenius), intervened as defendants.[8]

The district court granted Eagle's motion for summary judgment and denied the FDA's cross-motion. *Eagle Pharm.,* 2018 WL 3838265, at *1. Applying *Chevron*, the district court concluded that the ODA "unambiguously require[d] the FDA to afford Bendeka the benefit of orphan-drug exclusivity." *Id.* at *5. Like the court in *Depomed*, the district court began with the text and held that the express language of § 360cc(a) requires the FDA to give a drug seven years of market exclusivity upon designating it as an orphan drug and approving it, leaving "no room for the FDA's imposition of the clinical-superiority requirement." *Id.* at *6. The district court rejected the FDA's attempts to show an ambiguity or silence in the text of the provision or elsewhere in the statute. *Id.* at *6–*7. It also rejected the FDA's purpose and structure arguments, concluding that the FDA's "broad" purpose argument could not override the text and that its points were essentially policy arguments. *Id.* at *7–*9. Like the *Depomed* court, the district court also recognized that the FDA could adjust the requirements for showing clinical superiority at the designation stage to avoid its concern about serial exclusivity. *Id.* at *7. The district court also rejected the FDA's reliance on legislative history as insufficient to override clear statutory text.[9] *Id.* at *9–*10.

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[8] The intervenors did not move for summary judgment.

[9] In 2017, while this case was in district court, the Congress amended the ODA to codify a clinical superiority requirement for exclusivity and supersede *Depomed*'s holding. *See* FDA Reauthorization Act of 2017, Pub. L. N. 115-52, § 607(a)(3), 131 Stat. 1005, 1049–50 (amending 21 U.S.C. § 360cc). The amendments, however, are not retroactive. *Id.* § 607(b) ("Nothing in the amendments made by subsection (a) shall affect any

The FDA and Intervenors now appeal the district court's summary judgment order.[10]

II. ANALYSIS

"We review *de novo* the District Court's rulings on summary judgment." *Am. Bankers Ass'n v. Nat'l Credit Union Admin.*, 934 F.3d 649, 662 (D.C. Cir. 2019). "We review the administrative record and give 'no particular deference' to the District Court's views." *Id.* (quoting *Oceana, Inc. v. Ross*, 920 F.3d 855, 860 (D.C. Cir. 2019)).

Here, the familiar *Chevron* doctrine—"a two-prong test for determining whether an agency 'has stayed within the bounds of its statutory authority' when issuing its action," *Am. Bankers Ass'n*, 934 F.3d at 662 (quoting *City of Arlington v. FCC*, 569 U.S. 290, 297 (2013))—guides our review of the FDA's interpretation of the pertinent provisions of the ODA and, in particular, § 360cc. *Chevron* step one requires us to "determine 'whether Congress has directly spoken to the precise question at issue,' and we 'give effect' to any 'unambiguously expressed intent.'" *Id.* (quoting *Chevron*, 467 U.S. at 842–43 & n.9). If we think the statute is ambiguous, "we turn to the second step and determine 'whether the agency's answer' to the question 'is based on a permissible

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determination under sections 526 and 527 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb, 360cc) made prior to the date of enactment of the FDA Reauthorization Act of 2017.").

[10] Intervenors also state that they are appealing the district court's denial of the FDA's motion to alter or amend the judgment under Federal Rule of Civil Procedure 59(e), *see Eagle Pharm., Inc. v. Azar*, No. CV 16-790 (TJK), 2018 WL 3838223, at *1 (D.D.C. Aug. 1, 2018), but they make no argument regarding that motion.

construction of the statute.'" *Id.* (quoting *Chevron*, 467 U.S. at 843).

A. CHEVRON STEP ONE

This case presents one central question: using the traditional tools of statutory interpretation under *Chevron* step one, is the Congress's intent in § 360cc(a) clear or is there an ambiguity, silence or gap that the Congress left for the FDA to fill?[11] Eagle agrees with the district court and *Depomed* that the language of § 360cc(a) is unambiguous. The FDA maintains that the Congress was silent on the issue of serial exclusivity—*i.e.*, whether subsequent drugs with the same active moiety could obtain their own successive exclusivity periods—and that § 360cc(a) must be read in light of the broader structure and purpose of the ODA.

At *Chevron* step one, "[w]e first ask whether the agency-administered statute is ambiguous on the 'precise question at issue.'" *Guedes v. Bureau of Alcohol, Tobacco, Firearms & Explosives*, 920 F.3d 1, 28 (D.C. Cir. 2019) (quoting *Chevron*, 467 U.S. at 842–43). "If the statute's meaning is unambiguous, then we need go no further." *Id.*; *see also Zuni Pub. Sch. Dist. No. 89 v. Dep't of Educ.*, 550 U.S. 81, 93 (2007) ("[I]f the intent of Congress is clear and unambiguously expressed by the statutory language at issue, that would be the end of our analysis."). "[W]e examine the [statute's] text, structure, purpose, and legislative history to determine if the Congress has expressed its intent unambiguously." *U.S. Sugar Corp. v. EPA*, 830 F.3d 579, 605 (D.C. Cir. 2016) (per curiam).

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[11] The district court did not reach the issue of *Chevron* step two and Eagle does not challenge the FDA's determination that Bendeka is not clinically superior.

1. The Text

"In addressing a question of statutory interpretation, we begin with the text." *City of Clarksville v. FERC*, 888 F.3d 477, 482 (D.C. Cir. 2018). Of the tools of statutory interpretation, "[t]he most traditional tool, of course, is to read the text." *Engine Mfrs. Ass'n v. EPA*, 88 F.3d 1075, 1088 (D.C. Cir. 1996). Indeed, "[t]he preeminent canon of statutory interpretation requires us to 'presume that [the] legislature says in a statute what it means and means in a statute what it says there.'" *Janko v. Gates*, 741 F.3d 136, 139–40 (D.C. Cir. 2014) (alteration in original) (quoting *BedRoc Ltd. v. United States*, 541 U.S. 176, 183 (2004) (plurality opinion of Rehnquist, C.J.)).

The relevant text in this case is § 360cc(a), which provides:

> [I]f the Secretary . . . *approves* an application . . . for a drug *designated* under section 360bb of this title for a rare disease or condition, the Secretary *may not approve another application* . . . for such drug for such disease or condition for a person who is not the holder of such approved application . . . until the expiration of seven years from the date of the approval of the approved application . . . .

21 U.S.C. § 360cc(a) (emphasis added). The district court in *Depomed* said it well when it described this provision as "employ[ing] the familiar and readily diagrammable formula, 'if x and y, then z'"—if designation and approval, then exclusivity. 66 F. Supp. 3d at 230. Under the plain language of this provision, the FDA is barred from approving another application for "such drug" for the same disease for seven years once it approves an orphan drug for marketing. Based on this

language, the seven-year marketing exclusivity period applies automatically—the text leaves no room for the FDA to place additional requirements on a drug that has been designated and approved before granting its manufacturer the right to exclusivity.

Despite § 360cc(a)'s plain language, the FDA argues that the provision is ambiguous because it is silent as to whether one or multiple manufacturers can win a period of exclusive approval for the same orphan drug for the same rare condition. The FDA is correct that the Congress did not specify whether the privilege of exclusive approval applies to one or multiple manufacturers but that fact does not create an ambiguity. If the text "clearly requires a particular outcome, then the mere fact that it does so implicitly rather than expressly does not mean that it is 'silent' in the *Chevron* sense." *Engine Mfrs. Ass'n*, 88 F.3d at 1088. Here, the particular outcome required by § 360cc(a) is that once a drug has been designated and approved, the FDA may not approve another "such drug" for seven years—regardless whether that drug is the first, second or third drug to receive that benefit. The fact that the Congress chose not to include an additional requirement, limitation or exception for successive or subsequent exclusivity holders does not make the provision ambiguous.

Attempting to find a textual hook, the FDA argues that the word "expiration" in § 360cc(a) is ambiguous because it could connote a permanent end, meaning that only the first drug to be designated and approved receives exclusivity.[12] The ODA

[12] Throughout its brief, Eagle asserts that several of the FDA's arguments about the interpretation of § 360cc(a) are barred by the doctrine of *SEC v. Chenery Corp.*, 318 U.S. 80, 87 (1943), because the FDA either failed to raise the argument in district court or changed its position. Although we note that it is not entirely clear that *Chenery* even applies at *Chevron* step one, *see Bank of Am., N.A.*

does not define "expiration" so we must give it its "ordinary meaning." *Petit v. U.S. Dep't of Educ.*, 675 F.3d 769, 781 (D.C. Cir. 2012). "Expiration" means "[t]he ending of a fixed period of time." *Expiration*, Black's Law Dictionary (11th ed. 2019). Read in context, "expiration" in § 360cc(a) is modified by the preposition "of seven years," which refers to the end of the seven-year period of exclusive approval guaranteed to the manufacturer of the drug that was designated and approved. The FDA's attempt to find ambiguity in this term stretches the term beyond its ordinary meaning. The provision does not say "expiration of the single seven-year period" or "expiration of the only exclusivity period"; rather, it simply refers to the end of the time period during which the FDA may not approve another application. It says nothing about the possibility of subsequent seven-year periods.[13]

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v. F.D.I.C., 244 F.3d 1309, 1320, 1322 (11th Cir. 2001) ("[I]t is ultimately the function of the judiciary, not the administrative agency, to decide whether Congress spoke directly to the issue in question" and, therefore, "*Chenery*'s prohibition on litigation-induced, post-hoc rationalizations does not apply" to *Chevron* step one); *see also Mozilla Corp. v. FCC*, No. 18-1051, 2019 WL 4777860, at *78 (D.C. Cir. Oct. 1, 2019) (Williams, J., concurring in part and dissenting in part) (*Chenery* "does not apply when the issue turns on a purely legal question, such as, here, 'our interpretation of [a statute] and binding Supreme Court precedent'" (alteration in original) (quoting *Sierra Club v. FERC*, 827 F.3d 36, 49 (D.C. Cir. 2016))), we need not decide this issue because even if we consider the FDA's arguments, we would nevertheless find § 360cc(a) unambiguous.

[13] The FDA makes one other textual appeal, arguing that we should apply the canon favoring a narrow interpretation of a statutory monopoly, presumably to construe § 360cc(a) to be limited to the first exclusivity holder only. We note that this canon has been invoked infrequently over the past century and its applicability to the statutory scheme at issue is not apparent. *See Louisville Bridge Co.*

2. Structure and Purpose

Having no luck with the text of § 360cc(a), the FDA turns to other provisions of § 360cc, other sections of the ODA and the overarching FDCA—the larger statute that the ODA amended—as well as the ODA's overall purpose to argue that § 360cc(a) is ambiguous. Granted, "court[s] must . . . interpret the statute 'as a symmetrical and coherent regulatory scheme,' and fit, 'if possible, all parts into an harmonious whole,'" *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000) (citation omitted) (first quoting *Gustafson v. Alloyd Co.*, 513 U.S. 561, 569 (1995); and then quoting *FTC v. Mandel Bros., Inc.*, 359 U.S. 385, 389 (1959)), but "[r]eliance on context and structure in statutory interpretation is a 'subtle business, calling for great wariness lest what professes to be mere rendering becomes creation and attempted interpretation of legislation becomes legislation itself,'" *King v. Burwell*, 135 S. Ct. 2480, 2495 (2015) (quoting *Palmer v. Massachusetts*, 308 U.S. 79, 83 (1939)).

Indeed, although it does not couch its argument this way on appeal, the FDA essentially argues that applying the district court's and Eagle's literal interpretation of § 360cc(a)'s text would lead to such odd results that we should look to other evidence beyond the text itself to determine the Congress's intent. In explaining the limitations of such an argument, we have held that "[t]he plain meaning of legislation should be

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v. United States, 242 U.S. 409, 417 (1917); *City of Paragould v. Ark. Utils. Co.*, 70 F.2d 530, 533 (8th Cir. 1934). To the extent the canon even applies here, however, it is only relevant to construing an ambiguous statute—something we find missing in this case. *See* 37 C.J.S. *Franchises* § 21 (2019) (explaining that rules for interpreting franchises conferred by the government "are to be applied only when doubt arises, for, when the meaning is clear, there is not room for construction").

conclusive, except in the 'rare cases [in which] the literal application of a statute will produce a result demonstrably at odds with the intentions of its drafters.'" *Engine Mfrs. Ass'n*, 88 F.3d at 1088 (alteration in original) (quoting *United States v. Ron Pair Enters., Inc.*, 489 U.S. 235, 242 (1989)). Although "literal interpretation need not rise to the level of 'absurdity' . . ., there must be evidence that Congress meant something other than what it literally said before a court can depart from plain meaning." *Id.* (quoting *Pub. Citizen v. U.S. Dep't of Justice*, 491 U.S. 440, 453 n.9 (1989)). Absent such evidence, we "cannot ignore the text by assuming that if the statute seems odd to us . . . it could be the product only of oversight, imprecision, or drafting error." *Id.* at 1088–89. It is not our "role . . . to 'correct' the text so that it better serves the statute's purpose, for it is the function of the political branches not only to define the goals but also to choose the means for reaching them." *Id.* at 1089 (quoting *Consol. Rail Corp. v. United States*, 896 F.2d 574, 579 (D.C. Cir. 1990)). Thus, for the FDA to avoid the literal interpretation of § 360cc(a) "at *Chevron* step one, it must show either that, as a matter of historical fact, Congress did not mean what it appears to have said, or that, as a matter of logic and statutory structure, it almost surely could not have meant it." *Id.* at 1089. The FDA fails to clear this high bar.

The FDA begins its structure argument by pointing to the two exceptions to exclusive approval in § 360cc(b). The FDA points out that the first exception—allowing the FDA to approve other drugs to ensure a sufficient quantity—directs it to consider only the *exclusivity holder's* capability to ensure sufficient quantities of the drug. The FDA argues that the exception's focus on the exclusivity holder's capability makes sense only in its single-exclusivity holder regime. Under the serial exclusivity regime contemplated by Eagle and the district court, the second drug manufacturer to receive exclusive

approval rights shares the market with the initial holder (creating a duopoly), the third drug shares the market the first and second holders (creating a triopoly) and so on. The FDA argues that under this serial scheme, it makes little sense for the Congress to focus solely on the exclusivity holder's ability to make sufficient quantities when other drug manufacturers would also be in the market.

Although the first exception may make more sense when applied to the initial exclusivity holder, it does not show definitively that the Congress intended a period of exclusive approval to apply only to the first manufacturer of a drug and it does not show a result so odd that it justifies overriding § 360cc(a)'s plain text. First, § 360cc(b) gives the FDA discretion to apply the exception. *See* § 360cc(b) ("[T]he Secretary *may* . . . approve another application . . . ." (emphasis added)). Thus, if the FDA thought that a current exclusivity holder could not meet demand but other manufacturers on the market were otherwise making sufficient quantities, it has discretion to find that there are sufficient quantities of the drug to meet the needs of persons with the disease for which the drug was designated. Moreover, if the FDA thought there was an insufficient quantity of one version of a drug it believed to be more beneficial (even if not clinically superior), it could at least theoretically use the exception to increase supply of that version of the drug: for example, if the FDA thought, despite the availability of Treanda, the supply of the different dosage version Bendeka (the current holder) was insufficient.

As for the second exception that allows the FDA to approve another application with the exclusivity holder's consent, the FDA argues that a serial exclusivity regime would allow the exception to be improperly manipulated. The FDA argues that the initial exclusivity holder could undercut future holders by consenting to numerous manufacturers or the initial

holder could agree with one manufacturer to effectively gain a fourteen-year period of exclusivity, as Teva did by entering a licensing agreement with Eagle to commercially market Bendeka. *See supra* note 6. First, as with the first exception, the FDA has discretion to approve or deny such a consent waiver. Moreover, the fact that the Congress chose to give the exclusivity holder, whether it be the first or a subsequent one, the ability to completely waive its right to exclusive approval does not speak to whether one or multiple drugs could enjoy the privilege of exclusivity. Indeed, an initial holder could waive its exclusivity period one month into its seven-year period or could wait to consent to the approval of other applications until the final month of its seven-year period. Plainly, the benefits of § 360cc(a)'s exclusive approval right decrease as more drugs are added to the market over time but that the first holder or first few holders enjoy more benefits and the ability to decide when to consent to other applications does not mean that the Congress meant for § 360cc(a) to apply only to the first holder against the provision's express language. Rather, the Congress specifically chose to leave this exception in the hands of the exclusivity holder subject to the FDA's discretion.

Next, the FDA fashions a structure and purpose argument based on the interplay between designation and exclusivity. The FDA argues that Eagle's (and the district court's) view will undermine the purposes of the ODA because, without a post-approval requirement of clinical superiority, it will be forced to grant exclusivity to drug manufacturers that merely tweak a drug's design to meet the plausible hypothesis standard at the designation stage—thus allowing drugs that may not end up being clinically superior to earlier versions of the same drug to obtain exclusivity. This result, the FDA argues, would lead to the problem of evergreening or serial exclusivity in which either the same manufacturers or multiple manufacturers can

obtain multiple periods of sequential exclusivity for the same drug to treat the same disease. In rejecting this argument, the district court explained that this result could occur only if the FDA allowed it to happen. The district court reasoned that because the FDA has "unchallenged statutory authority" to impose requirements for designation, it could raise the clinical superiority threshold at the designation stage. *Eagle Pharm.*, 2018 WL 3838265, at *7. The FDA asserts that the district court's view presents the FDA with a dilemma: either increase the requirements for designation—stifling drug development of clinically superior drugs—or leave the current requirements in place—allowing manufacturers to enjoy serial exclusivity for drugs that are only marginally different from earlier versions. The FDA argues that its post-approval clinical superiority requirement avoids these problems by harmonizing the designation and exclusivity provisions of § 360bb and § 360cc.[14]

Granted, the Congress's goal in enacting the ODA was to reduce the cost of and incentivize orphan drug development but 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. *See Baker Botts L.L.P. v. ASARCO LLC*, 135 S. Ct. 2158, 2169 (2015) ("Our job is to follow the text even if doing so will supposedly undercut a basic objective of the statute." (internal quotation marks omitted)); *Landstar Express Am., Inc. v. Fed. Mar. Comm'n*, 569 F.3d 493, 498 (D.C. Cir. 2009) ("[N]either courts nor federal agencies can rewrite a statute's plain text to correspond to its supposed purposes."). It is not

[14] Before diving into the FDA's structural arguments, it is important to note that, unlike § 360aa and § 360bb of the ODA, § 360cc contains no express delegation from the Congress to promulgate regulations under that section, further evidencing that it did not intend the FDA to alter the plain text requirements of § 360cc.

our job to say how the Congress should accomplish its goals; rather, we will ignore what the Congress has written only if we are so convinced by a conflict between the text and the purpose that we think the Congress "almost surely could not have meant" what it said. *Engine Mfrs. Ass'n*, 88 F.3d at 1089. Here, we are not so convinced.

To begin, the FDA fails to appreciate the significance of the plausible hypothesis requirement. It is not as if any drug with any "minor tweak" to its formulation can be designated. Rather, the drug's manufacturer must be able to show a plausible hypothesis of clinical superiority to be granted designation—a threshold that has some teeth. The plausible hypothesis requirement necessarily weeds out drugs that cannot provide at least some evidentiary basis for their claim of clinical superiority. *See* Def.'s Resp. to Mot. Summ. J. 11, ECF No. 19, *United Therapeutics Corp. v. HHS*, No. 17-cv-01577-ESH (D.D.C.) (Dec. 22, 2017) (noting FDA denied manufacturer's designation request for failure to show plausible hypothesis because FDA found that "convincing hypothesis of greater safety cannot be meaningfully entertained until at least some clinically-relevant evidence of comparable treatment effectiveness has been established").[15]

Moreover, the district court here (as well as the *Depomed* district court) was correct in holding that the FDA could further avoid its concern regarding serial exclusivity by changing its clinical superiority requirement at the designation stage. Indeed, the FDA can "by regulation promulgate procedures for the implementation of" the ODA's provisions regarding

[15] *United Therapeutics* is currently stayed in district court pending the outcome here. We do not weigh in on the merits of that case. We merely cite its background facts as an example of how the plausible hypothesis threshold is not an automatic greenlight to designation.

designation. 21 U.S.C. § 360bb(d). In doing so, the FDA has elected to require manufacturers to show a "plausible hypothesis" of clinical superiority to existing orphan drugs with the same active moiety before receiving designation. The FDA argues that the lower threshold—compared to *proving* clinical superiority—is necessary to allow drugs that are not yet developed or are still being developed to obtain designation and the benefits that come with that designation. But the fact that the FDA must balance the goals of drug development against the concern over serial exclusivity does not change the fact that it has the ability to control the definition of "such drug" and the evidentiary threshold of clinical superiority. For example, the FDA could require a more stringent threshold that requires a manufacturer to be further along in the development process if it wishes to be designated for a clinically superior drug. *See* 21 C.F.R. § 316.23(a) ("A sponsor may request orphan-drug designation at any time in its drug development process prior to the time that sponsor submits a marketing application for the drug for the same rare disease or condition.").

The FDA contends that raising the evidentiary threshold for designation would run counter to the purposes of the ODA by requiring a manufacturer to spend more money on the front end to develop a drug to the point of demonstrating clinical superiority. But whether such upfront costs would in fact discourage the development of orphan drugs is a question that we are not well-positioned to resolve. Indeed, the Congress could well have concluded that the guaranteed financial benefits of market exclusivity following designation and approval would outweigh concerns about upfront costs, as a manufacturer could likely recoup those costs during its seven-year period of exclusivity. In light of an unambiguous statutory directive, it is not our place to second-guess how the Congress

chose to effectuate the policy goals underlying the statute as a whole.

The FDA also points to a problem of "self-evergreening." It argues that a literal interpretation of § 360cc(a) will allow the first manufacturer of an orphan drug to extend its own exclusivity period indefinitely by continually seeking and obtaining approval for different formulations of the same drug while its current exclusivity period is in effect, as the provision prohibits the FDA from approving applications from "person[s]" who are "not the holder[s]" of the approved application only. 21 U.S.C. § 360cc(a). According to the FDA, the only way to combat the "infinite bar on approving others' applications" that could result from this interpretation would be to promulgate a regulation limiting the scope of a drug's exclusivity to the *precise* formulation approved—a result that would render the benefits of the exclusivity period "virtually meaningless" by permitting subsequent manufacturers to obtain exclusivity for any slight variation on the exclusivity holder's formulation while that exclusivity period is in effect. But this result assumes that the FDA's regulations for designation are correct and static.

Not so. The self-evergreening problem is within the FDA's power to manage and, if needed, alter. The ODA gave the FDA authority to promulgate regulations defining orphan drug designation. *See* 21 U.S.C. § 360bb(d). In doing so, it appears that the FDA may have created the self-evergreening problem itself. In practice, "[o]rphan drug designation is generally conferred to the active moiety rather than the product formulation; therefore, changes to the product formulation should not generally affect orphan drug designation status." FDA, *Frequently Asked Questions (FAQ) About Designating an Orphan Product*, https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/frequently-

asked-questions-faq-about-designating-orphan-product (last visited November 19, 2019). This means that a manufacturer can automatically receive designation for any later formulation of the same drug regardless whether the manufacturer presents a plausible hypothesis of clinical superiority, so long as the later drug contains the same active moiety as a previously approved one. Based on this definition where designation follows the active moiety, a manufacturer of a drug could potentially develop a new and only slightly different formulation of a previously designated and approved drug while its exclusivity period remains in effect—and rely on the same designation for its original drug to obtain infinite exclusivity periods upon approval of each formulation of the same drug.

But it was the FDA's decision to permit designation to be linked to an active moiety rather than a particular formulation. Were the FDA to change its regulations for designation to take into account both the active moiety and the formulation, for example, that would prevent a manufacturer from obtaining successive, automatic exclusivity periods for various formulations of the same drug simply by relying on its original designation.

Moreover, the FDA can use its plausible hypothesis of clinical superiority requirement to weed out incremental changes by requiring a manufacturer to show a plausible hypothesis of clinical superiority for every formulation of a drug, regardless whether the active moiety has previously been designated. And if the FDA is worried that the plausible hypothesis standard is too low, it is free to raise the standard.

In summary, the serial exclusivity and self-evergreening concerns do not result purely from a literal reading of the statutory text of § 360cc(a) but from the way the FDA has

decided to regulate its definitions for designation and the scope of exclusivity. That the FDA's current regulatory scheme for designation *could* result in some of these problems does not change its obligation to follow the plain text of § 360cc(a).[16]

Ultimately, the FDA's concerns do not come close to showing that the Congress could not have meant what it said when it wrote § 360cc(a). That the FDA's use of the post-approval clinical superiority requirement may be a more reasonable approach that, in its view, "harmonizes" the sections of the ODA does not mean that interpreting the text as written contravenes the statute's purpose. Although the FDA may believe that the addition of a post-approval clinical superiority requirement better accomplishes the ODA's goals, "under *Chevron*," an agency cannot "avoid the Congressional intent clearly expressed in the text simply by asserting that its preferred approach would be better policy." *Engine Mfrs. Ass'n*, 88 F.3d at 1089. Indeed, inherent in any sort of exclusivity period is a tradeoff between incentivizing research and development and promoting competition. In making that trade-off in the ODA, the Congress chose to authorize exclusive approval rights upon designation and approval without any qualification for the number of manufacturers that could enjoy that privilege or any other requirement. "Where a statute's language carries a plain meaning, the duty of an administrative agency is to follow its commands as written, not to supplant those commands with others it may prefer." *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1355 (2018).

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[16] Our dissenting colleague tags us with "reconstructive rulemaking." Dissent at 15. We do no such thing. Instead, we discuss various interpretations of the FDA's regulations to emphasize that its concerns stem from its regulations, not the statute. Its concerns, however, do not authorize it to depart from the statute's plain text.

Looking beyond the ODA, the FDA next turns to other provisions of the FDCA to argue that the Congress could not have meant for § 360cc(a) to apply to multiple manufacturers of the same drug. First, the FDA notes that the ODA's seven-year exclusivity period is one of the longest exclusivity periods in the FDCA, which it says indicates that the Congress could not have intended such a long period to continue by "mere tweaking" of a previously approved drug. We have already rejected the "mere tweaking" argument and, beyond that, the fact that § 360cc(a)'s period of exclusive approval is longer than other similar periods does not affect whether that exclusivity period is limited to one or multiple manufacturers under the provision's plain text.

Second, the FDA argues that other FDCA provisions that extend already existing exclusionary periods, *see* 21 U.S.C. §§ 355a(b), (c), § 355f, show that, if the Congress intended to allow multiple exclusivity periods, it would have said so. This argument fails because, in those provisions, the Congress *lengthens already existing exclusionary periods*; they have no bearing on the issue of other exclusionary periods after an earlier exclusivity period has ended.[17]

Third, the FDA looks to the Hatch-Waxman Act that amended the FDCA, *see* Pub. L. No. 98-417, 98 Stat. 1585 (1984), arguing that the Congress uses "unmistakable language" when it wishes to create a duopoly. The Act provides that a generic drug manufacturer has a 180-day exclusivity period during which time "no other generic can compete with the brand-name drug." *FTC v. Actavis, Inc.*, 570 U.S. 136, 143–44 (2013) (citing 21 U.S.C. § 355(j)). It is unclear how this amendment supports the FDA's argument

[17] It also matters not that § 355f refers to the extension of an "exclusivity period" as this phrase could refer to the first or to a subsequent exclusivity holder.

because a provision involving a generic drug automatically involves a duopoly—the generic and the name brand. Moreover, the amendment in fact supports Eagle's argument in that § 355(j)(5)(D) specifically states that, if the 180-day exclusivity period for a generic drug is forfeited by the first applicant to file, then no other generic can obtain it, showing that the Congress knows how to limit an exclusivity period to one manufacturer. In contrast, the Congress chose not to do so in § 360cc(a) and the FDA has given us no basis in the FDCA for overriding that choice.

Finally, the FDA argues that Eagle's categorical interpretation of § 360cc(a) would require the FDA to give and maintain drug exclusivity to sponsors even if the FDA discovered fraud or mistake within the designation process. Reading § 360cc(a) based on its plain language to prevent the FDA from approving other applications upon a drug's designation and approval, however, does not prevent the FDA from later revoking any designation or approval procured by fraud. The FDA's own regulations provide for this possibility. *See* 21 C.F.R. § 316.29. The FDA's ability to revoke designation or approval (and thus exclusivity) because of fraud or mistake does not run afoul of the language of § 360cc(a) in the same way that including an additional post-approval hurdle a manufacturer must clear before obtaining its right to exclusive approval would.

3. Legislative History

Finding no support in the text, structure or purpose, the FDA at last turns to legislative history. There is a reason that neither we nor the FDA begins our analysis with legislative history. As the Supreme Court has recognized, "[e]xtrinsic materials" such as legislative history, "have a role in statutory interpretation only to the extent they shed a reliable light on the

enacting Legislature's understanding of otherwise ambiguous terms." *Exxon Mobil Corp. v. Allapattah Servs., Inc.*, 545 U.S. 546, 568 (2005). Moreover, "legislative history in particular is vulnerable to two serious criticisms": it "is itself often murky, ambiguous, and contradictory[,]" having the "tendency to become . . . an exercise in 'looking over a crowd and picking out your friends'" and "judicial reliance on legislative materials like committee reports, which are not themselves subject to the requirements of Article I, may give unrepresentative committee members—or, worse yet, unelected staffers and lobbyists—both the power and the incentive to attempt strategic manipulations of legislative history to secure results they were unable to achieve through the statutory text." *Id.* (quoting Wald, *Some Observations on the Use of Legislative History in the 1981 Supreme Court Term*, 68 Iowa L. Rev. 195, 214 (1983)).

Although our precedent has instructed that we "exhaust the traditional tools of statutory construction, including examining the statute's legislative history to shed new light on congressional intent, notwithstanding statutory language that appears superficially clear[,]" *Sierra Club v. E.P.A.*, 551 F.3d 1019, 1027 (D.C. Cir. 2008) (quoting *Am. Bankers Ass'n v. Nat'l Credit Union Admin.*, 271 F.3d 262, 267 (D.C. Cir. 2001)), it has also held that if, after analyzing the text, structure and context, we conclude that the language is unambiguous, we need not resort to legislative history to decipher what the Congress intended. *See Nat'l Shooting Sports Found., Inc. v. Jones*, 716 F.3d 200, 212 (D.C. Cir. 2013). In other words, "we do not resort to legislative history to cloud a statutory text that is clear." *Id.* (quoting *Ratzlaf v. United States*, 510 U.S. 135, 147–48 (1994)). Here, what § 360cc(a) provides is clear: once a drug is designated and approved, it is entitled to a period of exclusive approval with no limits or qualifications other than the two express exceptions in § 360cc(b).

Even were we to consult legislative history in this case, the legislative history relied upon by the FDA would be particularly unhelpful for interpreting the statutory text. All of it was created *after* § 360cc(a) was originally drafted, *see Bruesewitz v. Wyeth LLC*, 562 U.S. 223, 242 (2011) ("Post-enactment legislative history (a contradiction in terms) is not a legitimate tool of statutory interpretation."), including several floor statements of individual legislators, *see N.L.R.B. v. SW Gen., Inc.*, 137 S. Ct. 929, 943 (2017) ("[F]loor statements by individual legislators rank among the least illuminating forms of legislative history.").

Although it is true that "[s]ubsequent *legislation* declaring the intent of an earlier statute is entitled to great weight in statutory construction," *Consumer Prod. Safety Comm'n v. GTE Sylvania, Inc.*, 447 U.S. 102, 118 n.13 (1980) (emphasis added), that is not what the FDA cites here. Rather, the FDA cites a report for a provision that was left out of the 1988 amendments to the ODA, a statement by the President explaining his pocket veto of a 1990 amendment to the ODA and a handful of comments by individual legislators during the debate and drafting of the 1990 bill. None of these sources is "legislation." Instead, they are less persuasive pieces of subsequent legislative history. *See id.* ("A mere statement in a conference report of such legislation as to what the Committee believes an earlier statute meant is obviously less weighty."). Finally, much like the other provisions of the ODA and the FDCA that the FDA points to, the legislative history on which it relies does not pass on the issue of subsequent or successive exclusivity periods after the initial seven-year period ends. For these reasons, the FDA's last-ditch reliance on legislative history fails to carry the day.

* * *

Our dissenting colleague thinks the text, structure and purpose of § 360cc(a) show that the Congress intended the exclusivity period afforded by that provision to be limited to the *first* manufacturer to secure designation and approval of its orphan drug. In his view, then, the FDA's additional clinical superiority requirement merely flows from the statute. Dissent at 6.

The problem with this interpretation is that it reads a limitation into the text that is not there. Nor is any such limitation required by the statute's structure or purpose. In the absence thereof, we cannot do the Congress's job for it by adding one. "To supply omissions transcends the judicial function." *Iselin v. United States*, 270 U.S. 245, 250–251 (1926).

Like our colleague, we could imagine a better statutory framework than what the Congress provided in § 360cc(a). But that is not our role. "Our role is to interpret the language of the statute enacted by Congress," *Barnhart v. Sigmon Coal Co.*, 534 U.S. 438, 461 (2002), "not to improve upon it." *Pavelic & LeFlore v. Marvel Entm't Grp.*, 493 U.S. 120, 126 (1989). As the Supreme Court has "stated time and again[,] . . . courts must presume that a legislature says in a statute what it means and means in a statute what it says there. When the words of a statute are unambiguous, then, this first canon is also the last: 'judicial inquiry is complete.'" *Barnhart*, 534 U.S. at 461–62 (quoting *Connecticut Nat. Bank v. Germain*, 503 U.S. 249, 253–254 (1992)).

The dissent claims that our approach reduces the role of judges to that of a computer that does nothing more than execute the Congress's script unguided by contextual common sense. To the extent our colleague implies that we

read § 360cc(a) in a vacuum, he is incorrect. We have considered the context of that provision within its larger statutory structure and in light of its purpose and we have found nothing in that context to convince us that the plain text of § 360cc(a) cannot mean what it says. To the extent he suggests that we follow the Congress's script without inputting our own policy preferences, we wholeheartedly agree.[18]

We conclude that the text of § 360cc(a) is unambiguous: if the FDA approves a previously-designated orphan drug, it cannot approve another such drug for the same condition for seven years. This language leaves no room for the FDA to add an after-the-fact requirement that a designated and approved drug prove clinical superiority before receiving that exclusive approval benefit. Nothing in the statute's text, structure or purpose limits this benefit to only one drug manufacturer.

The FDA has failed to show that this interpretation would lead to results that are so unreasonable or so bizarre that the Congress could not have meant what it said. *See Cent. Bank of Denver, N.A. v. First Interstate Bank of Denver, N.A.*, 511 U.S. 164, 188 (1994)); *Engine Mfrs. Ass'n*, 88 F.3d at 1089. Permitting successive exclusivity periods may produce results that we find odd or not the most effective way to achieve the goals of the ODA but our role is not to correct the text to better serve the statute's purpose. *See Engine Mfrs. Ass'n*, 88 F.3d at 1088–89. That responsibility is left to the Congress, who ultimately did amend § 360cc in 2017. Our task is to discern

[18] Speaking of policy preferences, the dissent, relying on an eleventh-hour letter filed by the FDA pursuant to Federal Rule of Appellate Procedure 28(j), decries the "long arm" of our decision. Dissent at 18. Its speculation regarding our holding's potential consequences is misplaced. Our task is to interpret the statute and decide the case on the facts before us, not surmise what parties may attempt to do in the future or opine on matters not before us.

whether the Congress clearly expressed its intent in § 360cc(a) at the time the FDA denied exclusivity to Eagle. We hold that it did. Therefore, the district court correctly determined at *Chevron* step one that the FDA's post-approval clinical superiority requirement was forbidden and that Eagle was automatically entitled to a seven-year period of exclusive approval when it approved Bendeka for marketing.

B. INTERVENORS' ARGUMENTS

We turn briefly to Intervenor Appellants Apotex's and Fresenius's arguments on appeal. As an initial matter, although Intervenor Appellants state in their brief that they are appealing the district court's denial of the FDA's motion to alter or amend the judgment, they make no argument as to the denial of that motion whatsoever. Thus, any challenge to that denial is waived. *See United States ex rel. Totten v. Bombardier Corp.*, 380 F.3d 488, 497 (D.C. Cir. 2004) ("Ordinarily, arguments that parties do not make on appeal are deemed to have been waived.").

Their main argument is that the district court's summary judgment grant to Eagle required the FDA to make a new determination by granting Eagle an exclusivity period and, therefore, that determination is controlled by the new 2017 amendment to § 360cc(a), which requires Eagle to prove clinical superiority in order to receive an exclusivity period. Their argument is based on section 607(b) of the 2017 amendments, which states that "[n]othing in the amendments made by subsection (a) shall affect any determination under sections 526 and 527 of the [FDCA] (21 U.S.C. 360bb, 360cc) made prior to the date of enactment of the FDA Reauthorization Act of 2017." § 607(b), 131 Stat. at 1050. In Intervenor Appellants' view, the FDA's previous denial of exclusivity was a determination under the unamended version

of the statute and implementing the district court's order is a new determination subject to the 2017 amendments.

Because they raise this argument for the first time on appeal, it is waived. *Salazar ex rel. Salazar v. D.C.*, 602 F.3d 431, 437 (D.C. Cir. 2010) ("[A]n argument not made in the trial court is forfeited and will not be considered absent 'exceptional circumstances.'" (quoting *Nemariam v. Federal Democratic Republic of Ethiopia*, 491 F.3d 470, 483 (D.C. Cir. 2007))). Intervenor Appellants make two arguments attempting to excuse their failure to raise this argument below. First, they argue that the FDA raised it for them. This is incorrect. The FDA never made this argument; rather, in discussing the 2017 amendments, the FDA asserted that they should be interpreted as ratifying the FDA's view of the earlier version of the statute. It made no argument about the effect of the 2017 amendments on the district's court's ruling.

Second, they argue the district court raised it for them. It is true that the general rule barring raising arguments for the first time on appeal does not apply if a district court nevertheless "addressed" or "passed upon" the issue. *See Blackmon-Malloy v. U.S. Capitol Police Bd.*, 575 F.3d 699, 707 (D.C. Cir. 2009). Here, however, the district court did not pass on the argument Intervenor Appellants now raise. It merely considered the 2017 amendments' effect on or relevance to the earlier version of the statute. It ultimately determined that the 2017 version of § 360cc(a) "by its own terms" was "irrelevant to the outcome here" and "[b]y the same token" its "opinion" had "no bearing on determinations made under the version of the statute currently in force."[19] *Eagle Pharmaceuticals*, 2018 WL 3838265, at *10. The district court did not pass on whether the 2017 amendments prevented it from ordering the FDA to

[19] We agree with the district court on this point and, as noted, we do not discuss the 2017 amendments in our analysis of § 360cc(a).

grant Eagle exclusivity because it would involve a "new determination." Thus, Intervenors Appellants' argument is not properly before us.[20]

For the foregoing reasons, the judgment of the district court is affirmed.

So ordered.

[20] Even if it were, the proposition that the district court's order somehow conflicts with, or requires the FDA to use, the 2017 amended version of § 360cc(a) is dubious at best. Based on its order, which we uphold, Eagle was automatically entitled to a period of exclusivity upon being approved. Thus, the district court order requires that the FDA give Eagle what Eagle was entitled to at the time its application for Bendeka was approved—prior to the enactment of the 2017 amendments.

WILLIAMS, *Senior Circuit Judge,* dissenting:

Four decades ago, Congress established a regulatory regime to incentivize medical research into rare diseases that might otherwise not attract much investment. The basic bargain: in exchange for conducting research into drugs for such diseases, pharmaceutical and biotech firms obtain "designation" for a drug, thereby triggering certain tax incentives; if the research leads the FDA to approve the drug for patients, firms also receive the added benefit of marketing exclusivity—in common parlance, a monopoly—for a period of seven years.

This bargain strikes a delicate balance, all with the goal of benefting patients. The scheme grants innovators enough of a monopoly to encourage them to research otherwise unprofitable orphan drugs—without enabling firms to extract more from the patients than Congress thought necessary to spur innovation benefitting those patients.

The question, as I see it, is whether Congress's intent, as codified in the Orphan Drug Act of 1983 (the "Act") and later amendments, was to give the seven-year exclusivity reward *only* to the first manufacturer to achieve both designation and approval for any given orphan drug, i.e., a manufacturer whose ingenuity and innovation yielded special benefits for patients; or, as the majority concludes, did Congress mean that multiple, successive manufacturers of the *same* drug should receive serial grants of exclusivity, indefinitely stretching out the era of higher drug prices—with no corresponding benefit to patients?

Because the majority's interpretation of the statute runs counter to the best reading of the congressional language, and because it fundamentally upsets the basic economic bargain that Congress so carefully struck, I respectfully dissent.

Before I begin, a warning: The interpretation that plaintiff proposes and the majority accepts contemplates successive holders of exclusivity on the same drug, but it understands the statute to allow all *prior* lawfully approved makers of the same drug to continue selling; they aren't elbowed out. So the market at any moment would consist of the reigning exclusivity holder *and* all prior holders. Such a use of the word "exclusivity" seems oxymoronic. Thus many sentences in this opinion and the majority's may make the reader squint. Given plaintiff's claim, that comes with the territory. Please bear with me.

* * *

The statutory scheme works as follows: In the first step, a manufacturer seeks designation for its proposed drug. According to the Act, FDA "shall" designate a drug whenever it determines that the proposed drug is "being or will be investigated for a rare disease or condition." 21 U.S.C. § 360bb(a)(1) (2012). The Act defines "rare disease or condition" to mean a disease or condition affecting fewer than 200,000 persons in the United States, or more than 200,000 persons if "there is no reasonable expectation that the cost of developing and making available" such a drug could be recovered from domestic sales. *Id.* § 360bb(a)(2). In short, FDA must "designate" a drug only if its anticipated market is so small that there would be, in Congress's view, a need for special incentives.

As directed by the Act, FDA promulgated regulations setting forth how firms apply for designation. Firms must provide FDA with a description of the drug, authorities establishing the prevalence of the disease or condition to be treated, and "the scientific rationale to establish a medically

plausible basis for the use of the drug for the rare disease or condition, including all relevant data." 21 C.F.R. § 316.20(b)(4). Essentially, FDA believed that before designating an as yet undeveloped drug, it would need reason to believe that the drug might work as intended to treat an orphan disease.

Moreover, if and only if another drug with "the same active moiety" and intended use has already been approved by FDA, a firm must also give FDA "an explanation of why [its] proposed variation may be clinically superior to the first drug" in order to receive designation. *Id.* § 316.20(b)(5). Put differently, if there's already another approved drug using the same active ingredient(s) to treat the same condition as the proposed drug, FDA needs reason to believe that the future drug could be significantly better before it will designate that future drug and thereby entitle its manufacturer to the statutory tax benefits that help defray the costs of the necessary clinical trials. *Id.*

In short, FDA has created a two-tiered system for designation: if no other approved drug uses the same active moiety, then a firm need only show a prospect that its drug will treat an orphan disease; but if there is already an approved drug using the same active moiety to treat a particular disease, then a firm must additionally demonstrate the prospect of its new drug working significantly better than the existing drug.

Once a firm has conducted clinical trials, it may then apply for approval, and if available, exclusivity. Approval of course is necessary to bring a drug to market. The statute grants the manufacturer "exclusivity" by barring FDA from approving *another* application for the same drug by a different manufacturer. Here's the relevant language:

> [I]f the Secretary [approves an application] for a drug designated under section 360bb of this title for a rare disease or condition, the Secretary may not approve another [drug application] for such drug for such disease or condition for a person who is not the holder of such approved [drug application] until the expiration of seven years from the date of the approval of the approved [drug application].

21 U.S.C. § 360cc(a) (2012).

What about a situation in which multiple firms compete to bring the same drug to market? If another drug using the same activity moiety to treat the same disease has already won approval, then a firm seeking its own exclusivity period must present data showing that its later-in-time drug is in fact clinically superior to the already-approved drug. According to FDA regulations, the later-approved drug using the same active moiety may qualify for its own exclusivity period if its maker can show the drug's clinical superiority; in that event the drug should not be considered "such drug," 21 U.S.C. § 360cc(a) (2012), i.e., the same as the earlier-approved drug. See 21 C.F.R. § 316.3(b)(3); 316.34(c).

Consider an example with some well-known medications (albeit not ones used to treat rare diseases): It is readily understandable that Advil (ibuprofen) and Tylenol (acetaminophen) are different drugs because they have different active moieties. But under the Orphan Drug Act regulations, FDA would not treat ibuprofen in pill form as "the same drug" as ibuprofen delivered intravenously, if the different mode of delivery deserved to be regarded as clinically superior to the one which came earlier. In this way, current

FDA regulations incentivize firms to continue innovating for the benefit of patients even after a particular active moiety has been approved for use in an orphan drug.

Thus, putting this all together, just as the prior-approval and grant of exclusivity to ibuprofen does not block the approval of acetaminophen because they have different active moieties and are therefore not the same drug, the prior-approval and grant of exclusivity to ibuprofen *in pill form* would not block the approval and grant of exclusivity to ibuprofen *in intravenous form*, if the intravenous route of administration were "clinically superior" in some way, meaning that it provided "a significant therapeutic advantage." *Id.* § 316.3(b)(3). For real examples, see FDA, *Clinical Superiority Findings*, https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings. See also FDA, Clinical Superiority Findings, Neurelis Pharmaceuticals, Inc. for Valtoco, www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings (finding nasal spray drug product clinically superior to rectally administered gel due to its easier route of administration).

* * *

In the majority's view, this whole scheme, as relevant here, is lawful, except that FDA may not deny exclusivity to a drug that has been designated and approved, even if it is no better than an already approved version of the same drug.

For example, if FDA were to designate ibuprofen for the treatment of an orphan disease and Firm A was developing ibuprofen in pill form using 100 mg tablets while Firm B was developing ibuprofen in pill form using 200 mg tablets, only

the first of these two firms to win approval would, under FDA's long-standing approach, receive the prize of exclusivity (assuming a tablet of one strength is not "clinically superior" to a tablet of the other strength). But whereas in FDA's practice the approval of Firm A's 100 mg tablet would block new market entrants for seven years, *with no additional exclusivity in the absence of clinical superiority*, under the majority's analysis the subsequent approval of Firm B's 200 mg tablet would block new market entrants for an additional seven years, for a total of fourteen years. And if Firm C had been simultaneously developing a 300 mg tablet, upon approval it too would be entitled to seven years exclusivity, for a total of twenty-one years. And so on—and on and on and on.

The majority believes this outcome to be compelled by what they see as the Act's formula: "if [designation] and [approval], then [exclusivity]," Maj. Op. 14 (quoting *Depomed, Inc. v. U.S. Dep't of Health & Human Servs.*, 66 F. Supp. 3d 217, 230 (D.D.C. 2014)). In particular, the majority believes that 21 U.S.C. § 360cc(a) precludes FDA from enforcing its requirement, stated at 21 C.F.R. § 316.34(c), that later-approved drugs secure exclusivity only on a showing of clinical superiority.

The upshot of the majority's view is that firms can successively receive designation and approval for an *identical* drug—for example, a drug with not only the same active moiety but also the exact same formulation (e.g., 100 mg tablet)—and yet can each be entitled to its own seven-year exclusivity (subject as noted above to any prior exclusivity holder's right to continue selling). I deal below with regulatory changes suggested by the majority for FDA to mitigate that result, changes that fall well short of solving the problem and that generate perverse results.

In my view, 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. As discussed in the next section, Congress clearly did not intend the same drug to enjoy multiple seven-year periods of exclusivity, so the FDA had to come up with a way to distinguish between drugs that are the "same" and ones that are different. In exercising its authority to draw that line, the FDA reasonably chose to define drugs that have different active moieties and/or are not intended for the same use as *not* the "same drug," and to define ones that have the same "active moiety" and are "intended for the same use" as a previously approved drug as being the "same drug," 21 C.F.R. § 316.3(14), *unless* the new drug is "clinically superior," i.e., it provides "a significant therapeutic advantage," see *id.*; see also *id*. § 316.3(b)(3).

The majority and I agree on one crucial fact: The Orphan Drug Act does not explicitly address the issue of serial repeatability at all. See Maj. Op. 15 ("Congress did not specify whether the privilege of exclusive approval applies to one or multiple manufacturers.") And this acknowledgment is clearly sound, because, again, here's all the key section of the statute says:

> [I]f the Secretary [approves an application] for a drug designated under section 360bb of this title for a rare disease or condition, the Secretary may not approve another [drug application] for such drug for such disease or condition for a person who is not the holder of such approved [drug application] until the expiration of seven years from the date of the approval of the approved [drug application].

21 U.S.C. § 360cc(a) (2012).

My view is that Congress meant to imply that this if-then statement—if designation and approval, then exclusivity—would cease to apply to that "same drug" at "the expiration of seven years." This is a natural reading of an if-then statement, no different from myriad other everyday uses. "If you paint my house, I will pay you $1,000" would in the usual context imply an offer for a single painting and a single reward of $1,000—not as many house paintings and as many thousands of dollars as an industrious painter might want to exchange. And who among us, upon reading "rinse, lather, repeat" on a shampoo bottle, would fail to grasp that the verb "repeat" operates only once, i.e., the instructions direct approximately two applications, not an infinite cycle? Indeed, the shampoo example is "an endless source of amusement for computer programmers," Jeffrey Elkner, 4.7 The While Statement, Beginning Python Programming for Aspiring Web Developers (March 2018), http://www.openbookproject.net/books/bpp4awd/ch04.html, among whom forgetting to expressly state a terminating condition is "a classic problem . . . , a small mistake [which] can lead to implementing a program that simply will not stop." David Grossman et al., 5.5 Infinite Loops, Computer Science Programing Basics in Ruby (April 2013), https://www.oreilly.com/library/view/computer-scienceprogramming/9781449356835/five dot5_infinite_loops.html. Judges, of course, can escape from infinite loops by simply assessing language in its context.

Because the drafters of § 360cc(a) failed to expressly close the infinite loop, we should look at how the statute might look if they had done so. In that case the statute might read something like:

> [I]f the Secretary [approves an application] for a drug designated under section 360bb of this title for a rare disease or condition, the Secretary may not approve another [drug application] for such drug for such disease or condition for a person who is not the holder of such approved [drug application] until the expiration of seven years from the date of the approval of the approved [drug application], ***after which seven-year period such drug for such disease or condition shall no longer be eligible for orphan drug exclusivity*.**

To give the statute the more unusual meaning that the majority believes is implied—infinite episodes of an if-then series—Congress might have said:

> "[I]f the Secretary [approves an application] for a drug designated under section 360bb of this title for a rare disease or condition, the Secretary may not approve another [drug application] for the same drug for the same disease or condition for a person who is not the holder of such approved [drug application] until the expiration of seven years from the date of the approval of the approved [drug application], ***regardless of whether such drug for such disease or condition has previously been granted orphan drug exclusivity***.

Congress didn't spell it out either way. This would seem to invite us to choose the interpretation most in line with Congress's apparent purpose, namely, that any given drug is entitled to a single seven-year period of exclusivity, not infinite periods. The majority would reduce our role as judges to nothing more than executing Congress's script like a computer

loaded with software having the classic infinite-loop mistake, unguided by contextual common sense.

And at bottom, the majority's only support for its interpretation is what it believes the statute implies but fails to state explicitly. Of course a statute *can* "clearly require[] a particular outcome . . . implicitly rather than expressly," Maj. Op. 15 (quoting *Engine Mfrs. Ass'n*, 88 F.3d at 1088)—but that's simply not what's happening here, at least not in the way the majority proposes. Given this acknowledged lack of explicit provision for endless periods of exclusivity, it makes sense to evaluate the probative value of other text in the statute before deciding what Congress meant to say by implication.

Indeed, the very next subsection of our statute, 21 U.S.C. § 360cc(b)(1), grants the Secretary the authority to cut short a drug's exclusivity period upon finding that the exclusivity-enjoying manufacturer "cannot ensure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated." As the majority recognizes, if the formula the majority draws from § 360cc(a) were endlessly repeatable, there would at times be other manufacturers supplying the same drug—the most recent entrant together with any and all previous holders of "exclusivity." But if Congress truly meant for the relevant market to consist simultaneously of both an "exclusive" drug and a string of predecessor exclusive drugs, then it would make little sense for Congress to direct the Secretary to make the necessary finding *only as to* the current "exclusivity" holder's production-capacity. The majority acknowledges the obvious discordance between its interpretation of § 360cc(a) and the directive in § 360cc(b)(1) but dismisses it as not "so odd" as to "definitively" show that Congress intended only one exclusivity period. Maj. Op. 19.

Nor, evidently, is the discordance enough to shake the majority's belief that the statute as a whole *unambiguously* requires FDA to grant successive producers of the same drug serial exclusivities. But giving some weight to the meaning of the § 360cc(b)(1) exception is not "overriding § 360cc(a)'s plain text," Maj. Op. 19; rather, it is the very task of statutory interpretation: calculating the probable meaning of the congressional language based on the information before us. And for us to assign some probative weight to the inconsistency between one reading of a statutory subsection and the obvious operation of an adjacent subsection does not require us to find complete incompatibility between the two sections, as the majority seems to require. Assessing these probative signs is what it means to read statutes as a "harmonious whole." *FDA v. Brown & Williamson*, 529 U.S. 120, 133 (2000) (quoting *FTC v. Mandel Brothers, Inc.*, 359 U.S. 385, 389 (1959)).

The most likely explanation, in my view, for why Congress did not specify in § 360cc(a) whether a drug's "exclusivity period" would or would not be repeatable (and shared with past market entrants), 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. The word "exclusive" means "not shared by others," Merriam-Webster's Dictionary of Law (2d ed. 2011), and Congress chose that word to describe this regime. See Pub. L. 112-144, 126 Stat. 993, 1077 (July 9, 2012) (amending 21 U.S.C. 355f) (referring to orphan drug act's "exclusivity period"). Moreover, of the many exclusivity periods established in the Food, Drug, and Cosmetic Act ("FDCA"), to which the Orphan Drug Act is an amendment, not one provides for repeatability. See Transcript 10:3-17; 21 U.S.C. § 355(j)(5)(F)(ii) (providing for a new chemical entity exclusivity period of five years); *id.* § 355(c)(3)(E)(iii)

(providing for a new clinical investigations exclusivity period of three years); *id.* § 355(j)(5)(B)(iv) (providing for a first generic drug exclusivity period of 180 days); *id.* § 355(j)(5)(B)(v) (providing for a competitive generic therapy exclusivity period of 180 days); *id.* § 355a (providing for pediatric drug exclusivity of six months); *id.* § 355f (providing for infectious disease exclusivity of five years); 42 U.S.C. § 262(k)(7)(A), (B) (providing for biologic product marketing exclusivity of twelve years and data exclusivity of four years, respectively).

Consider too that the idea of serial exclusivities—cumulating past holders into a steadily expanding oligopoly—which on the majority's view would be central to how the entire scheme operates, was neither raised directly nor even mentioned indirectly in the public comments to the agency's first rulemaking under the statute, in 1992. See generally Orphan Drug Regulations, 57 Fed Reg. 62,076 (Dec. 29, 1992); *id*. at 62,076 (noting receipt of 40 comments and fact of agency's responding to all, a discussion barren of any hint of serial exclusivity); see also Notice of Proposed Rulemaking, 56 Fed. Reg. 3330 (proposed Jan. 29, 1991). This case is a story of how creative lawyering can unseat settled, useful understandings, not how a court came to properly understand the true intent of Congress.

Thus, based on § 360cc(a)'s silence as to repeatability of exclusivity, the inconsistency between any such repeatability and the operation of § 360cc(b)(1), and the plain meaning of "exclusivity" both generally and in the FDCA specifically, this is not one of those "rare cases" in which we must set aside the "plain language" of the statute in order to avoid an "odd result"—as the majority suggests FDA moves us to do. Maj. Op. 18 (quoting *Engine Mfrs. Ass'n v. EPA*, 88 F.3d 1075, 1088

(D.C. Cir. 1996)). Congress may have expressed its provision for a unique exclusivity period per drug imperfectly, but it nonetheless did so unambiguously. If one were to move one step toward the majority's view, one might view the Orphan Drug Act as *ambiguous* on the point, so that if the other requirements of *Chevron* were met, namely, that Congress intended to "commit[] to the agency's care" the "reasonable accommodation of [these] conflicting policies," *Chevron, USA, Inc. v. Natural Resources Defense Council*, 467 U.S. 837, 845 (1984) (quoting *United States v. Shimer*, 367 U.S. 374, 382 (1961)), we would be obliged to accept FDA's interpretation. Least plausible, to me, is the majority's belief that the statute unambiguously compels a regime of serial exclusivity. At any rate, as both the majority and I think the statute clearly requires our differing interpretations, we need not address the applicability of *Chevron*.

I also note, however, that to industry specialists such as practitioners and Congressional committee members, in apparent contrast to some judges and other laypersons, describing today's decision as merely an "odd result" would likely be putting it charitably. Drug "exclusivity" has had a fixed meaning for nearly forty years; implicit in that meaning has always been that exclusivity is a one-time affair—to wit, "exclusive." Indeed, the Hatch-Waxman Act of 1984, which created the apparatus of regulatory exclusivity for new drugs (to supplement patent protection) upon which this industry rests, "[e]xpand[ed] upon [the] concept" of exclusivity first enacted in the Orphan Drug Act less than two years earlier. See Congressional Research Service, *The Hatch-Waxman Act: A Primer* at 9 (2016). The exclusivity provisions of both statutes operate similarly, by barring the FDA from approving other applications for a fixed number of years, after which any further

approvals of the same drug are non-exclusive.[1] Compare 21 U.S.C. § 355(j)(5)(F)(i)–(ii) with 21 U.S.C. § 360cc(a). It should set off alarms that the majority cannot point to anything suggesting that "serial exclusivity" was even an idea in the air at the time of these landmark statutes' enactment.

* * *

The majority then adds insult to injury when it suggests that FDA's own regulatory decisions are to blame for any excessive grants of "exclusivity" that may flow from our judgment. More important, the majority's proposals for possible FDA regulatory shifts to prevent serial exclusivities and other abuses are at best limited solutions for addressing this judge-created problem.

The majority first suggests that FDA could have defined "such drug" in § 360cc(a) "to take into account both the active moiety and the formulation," such that when FDA designates a drug, it is making a designation for only the specific combination of moiety and formulation. Maj. Op. 25. (As used here, formulation means the specific characteristics about a drug other than its active moiety, such as its dosage and strength, and its route of administration—characteristics that may change without necessarily offering any clinical superiority.) But this approach would make the resulting exclusivity absurdly narrow in scope—applying to only one formulation of a drug. A competitor would need only to make

[1] Under the Hatch-Waxman Act of 1984, however, the generic version of a drug may later qualify for exclusivity within the market for generics. See Pub. L. No. 98-417, § 101, 98 Stat. 1585, 1589–90 (1984).

a clinically insignificant change to its formulation, using the same active moiety, and presto—it would have circumvented exclusivity. The proposal would patently defeat Congress's intention to seriously reward only the first firm to develop a genuinely new solution.

Aware of this problem, the majority proposes a puzzling supplement to its solution. Each formulation could be subject to its own separate clinical superiority requirement *at the designation stage*. Under this regime, a competitor's formulation would have to be more than merely different in order to be designated, it would have to be at least plausibly superior to other formulations. Maj. Op. 23–25. But this additional requirement, as I understand the majority's proposal, would have the effect of barring approval (and thus patient access) to equivalent alternative formulations of drugs—proposed to FDA for approval effective on conclusion of the pioneer's exclusivity—that don't rise to the level of being plausibly clinically superior but which patients might otherwise prefer. Thus the majority's creative engineering would inflict a pointless injury on patient choice. (One example of just such a choice: Patients might prefer 50 mg dosages of a drug otherwise available only in 100 mg pills so that patients only taking 50 mg would not need to cut the 100 mg pill into two.)

Further, FDA points out that the majority's proposed beefing up of the criteria for designation flies in the face of the Act's strong implication that "[e]arly-stage designation is [] critical to the statute's function." Appellant's Br. 26. Designation "triggers subsidies for the clinical testing necessary to get a new drug approved," *id.* (citing 21 U.S.C. § 360ee(a), (b)(1)(B) (2012)) and "creates a clinical-testing tax credit," *id.* (citing 26 U.S.C. § 45C(b)(2) (Supp. III 2016)). Plus, the Act speaks clearly of FDA's obligation, at least in

some circumstances, to designate a drug even before a sponsor has begun investigating it. FDA is to designate a drug that "is being *or will be* investigated for a rare disease or condition." 21 U.S.C. § 360bb(a)(1) (2012) (emphasis added). So while FDA undoubtedly has the authority to specify the particulars of how the designation process works, see 21 U.S.C. § 360bb(d), it's not as if FDA can raise the standard for designation unboundedly, as the majority seems to suggest, Maj. Op. 22, without thwarting the role that Congress intended designation to play in facilitating the early stages of drug development.

Worse still, this rigmarole is at best a partial solution to the problem the majority creates. Before an active moiety has been approved for any given indication (i.e., a medical condition it can treat), a firm seeking designation of the active moiety for that indication need not show *any* form of clinical superiority (neither merely plausible nor actual). See Letter from Dr. Gayatri R. Rao, Director, Office of Orphan Products Development, FDA, to John R. Manthei, Latham & Watkins LLP at 5 (Mar. 24, 2016) ("If there is no such previously approved orphan drug at the time a sponsor seeks designation, the sponsor is not required to provide a plausible hypothesis of clinical superiority."). This is not really an FDA choice but simple common sense: until an active moiety has been shown to be effective for an indication, there's no benchmark for assessing whether a manufacturer's proposal represents an improvement. Accordingly, when there's no drug yet approved for an indication, manufacturers need only "establish a medically plausible basis for the use of the drug for the rare disease or condition." 21 C.F.R. § 316.20(b)(4). If one manufacturer can satisfy this, others can too. So even with the regulatory fix the majority envisions, whenever multiple manufacturers concurrently research a designated but not yet approved drug—*all* the manufacturers to *complete* the race

towards approval, not just the winner of that race, would be guaranteed their exclusivity periods, to take effect, apparently, in the sequence in which they receive approval. For this reason, FDA's "changing its clinical superiority requirement at the designation stage" would not, notwithstanding the majority's assertion, "avoid its concern regarding serial exclusivity." Maj. Op. 22. The majority thus falls short in its effort at reconstructive rulemaking.

And the majority's reading creates yet another problem: self-evergreening, i.e., the ability of an exclusivity holder to pile successive exclusivity periods on top of its original period, multiplying Congress's award for innovation. This results from today's decision because the statute only prohibits FDA from approving an application for the "same drug" by a "person who is not the holder of" the approved application. 21 U.S.C. § 360cc(a). The majority's decision invites abuse, enabling a manufacturer with an exclusive drug to make a minor change to that drug—a different strength or route of administration, for example—and despite the result's being the "same drug" (as FDA has hitherto defined the concept), the FDA would be obligated, under the majority's reading, to award that newly-tweaked drug a new exclusivity period of its own (remember: "if designation and approval, then exclusivity").

The majority's proposal for circumventing this ploy by the initial approval holder is a rulemaking adjustment we've already discussed: FDA could redefine "same drug" to encompass both the active moiety and the formulation. Maj. Op. 25. But, as we've also seen, this "solution" dilutes the statutorily provided exclusivity to a triviality, subjecting the first approved manufacturer to competition in the period of its supposed "exclusivity."

Under the FDA's long-standing implementation of the statute, self-evergreening has not been an issue because when a manufacturer makes a minor change to an exclusive drug, there were no additional periods of exclusivity to be awarded in the first place—exclusivity for any given drug was a one-time opportunity.

* * *

Congress, likely spurred by an earlier district court decision, *Depomed, Inc. v. U.S. Dep't of Health & Human Servs.*, 66 F. Supp. 3d 217 (D.D.C. 2014), discussed above, tried to limit the damage needlessly inflicted on the industry and patients by enacting an amendment in 2017 codifying the very regulatory scheme that the majority strikes down. As a result, only drugs designated and approved before the August 18, 2017 effective date of the amendment suffer the majority's transformation of single exclusivities into parades. See FDA Reauthorization Act of 2017, Pub. L. No. 115-52, sec. 607(a), § 527(c)–(d), 131 Stat. 1005, 1049–50 (amending 21 U.S.C. § 360cc). At oral argument FDA counsel reported that as of the 2017 amendment's effective date "at least 11 drugs" were designated and approved, but ultimately denied exclusivity (under the law preceding today's decision) for failure to demonstrate clinical superiority to an already approved drug. See Transcript 11:1–6. Counsel also referred to an "untold number" of generic drugs; today's creation of new exclusivities for brand name drugs will entitle the exclusivity holders to call on FDA to revoke the competing generics' approvals. See Transcript 11:6–9.

Just days ago FDA filed a letter indicating that the count of "at least 11 drugs" may have radically understated the impact of today's decision. See Letter dated March 2, 2020 under

FRAP Rule 28(j) ("FDA Letter"). That figure counted only those drugs which FDA actually determined were not clinically superior and therefore not entitled to exclusivity; it did not count drugs for which the sponsor never claimed clinical superiority. The FDA Letter informs us that a drug sponsor is now "asserting an automatic entitlement to an orphan-exclusivity period" because its once-designated drug recently received approval of a mere *supplemental* drug application, meaning the drug had already been approved for marketing but the sponsor sought and received the necessary approval to make minor changes in how its drugs is manufactured, labelled, and the like. The Orphan Drug Act does not on its face distinguish between the approval of new drug applications and the approval of supplemental drug applications; 21 U.S.C. § 360cc refers to approval "under section 355," which includes both new and supplemental applications. On the view taken by the majority, namely that "designation plus approval" *automatically* entails exclusivity, Maj. Op. 15, the sponsor of any designated drug receiving such a supplemental approval prior to the effective date of Congress's curative statute, August 18, 2017, would seemingly also be entitled to exclusivity (though perhaps only after waiting its turn after previously granted approvals that today's decision tranforms into exclusives).

The retroactive creation of exclusivity generated by today's decision sweeps with a long arm. The FDA Letter points out that if it truly mandates exclusivities based on designations followed by supplemental approvals, FDA will be forced to revoke approvals for drugs approved in the (hitherto) normal course and in conflict with these artificial exclusivities. Similar revocations will be in order for generics that FDA had approved with no apparent difficulty because no exclusivities—under the nearly 40-years' understanding of the law—were there to block its granting them.

As the FDA letter says, the resulting burst of new exclusivities "would lead to the market withdrawal of many currently marketed drugs, including many generics, which could significantly increase costs for patients with rare diseases due to only minor changes to approved drugs." FDA Letter at 2.

Eagle's counsel has responded to FDA with its own letter under Rule 28(j) dated March 4, 2020. The letter points out that FDA relies on only one party claiming exclusivity on the basis of its supplementary approval, and that FDA itself says it will oppose the claim. True enough. But the Eagle letter contains a conspicuous gap. Although Eagle's counsel framed precisely the statutory interpretation that the court embraces today, it offers not a hint as to how a court bound to follow that interpretation could reject the claim for exclusivity by holders of a supplemental approval issued before the effective date of Congress's 2017 remedial statute. Although the Eagle letter bemoans the supplemental approval holder's delay in raising the issue with FDA, it is hard to see why that is of any moment, given Eagle's and the court's view that designation plus approval automatically spell exclusivity. In sum, FDA's letter, updating figures presented at oral argument, shows how Eagle's interpretation of the Orphan Drug Act will likely result in outcomes even more bizarre than the parties originally depicted. Neither Eagle's response—nor the majority's, see Maj. Op. 32 n.18—does anything to dispel that likelihood.

* * *

Today's decision is quite extraordinary. The majority first ascribes to Congress a meaning of the statute that the full context precludes and that Congress surely did not intend. It

then supposes that FDA can undo the readily foreseeable harm by means of proposed regulatory fixes—all untested by experienced judgment or input from affected parties. The resulting disruption of the longstanding and relied-on application of the Orphan Drug Act will likely inflict needlessly higher costs on patients and their insurers, bringing benefit only to some drug companies that will receive exclusivity without having earned it, and to the lawyers litigating these senseless repercussions. I respectfully dissent.