

No. 26-2165

IN THE UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

ASTRAZENECA PHARMACEUTICALS LP; ASTRAZENECA AB;
ASTRAZENECA UK LTD,

Plaintiffs-Appellants,

v.

ROBERT F. KENNEDY, JR., in his official capacity as Secretary of the
U.S. Department of Health and Human Services; UNITED STATES
DEPARTMENT OF HEALTH & HUMAN SERVICES; MEHMET C. OZ,
in his official capacity as Administrator of the Centers for Medicare and
Medicaid Services; CENTERS FOR MEDICARE AND MEDICAID
SERVICES,

Defendants-Appellees.

On Appeal from the United States District Court for
the District of Maryland
The Honorable Matthew J. Maddox, Jr. (No. 1:25-cv-4212)

PLAINTIFFS'-APPELLANTS' OPENING BRIEF

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CORPORATE DISCLOSURE STATEMENT

Pursuant to Fed. R. App. P. 26.1, Plaintiffs-Appellants, by and through undersigned counsel, hereby submits the following disclosure statement.

1. AstraZeneca Pharmaceuticals LP—a limited partnership organized under the laws of the State of Delaware with its principal place of business in Wilmington, Delaware—is a biopharmaceutical company focusing on the discovery, development, manufacturing and commercialization of medicines. AstraZeneca Pharmaceuticals LP declares that it is an indirectly wholly owned subsidiary of AstraZeneca plc, which is a public company organized under the laws of England and Wales and is publicly traded. Upon information and belief, no other publicly held company owns 10% or more of the voting interest in AstraZeneca Pharmaceuticals LP.

2. AstraZeneca AB—a private company operating and existing under the laws of Sweden, with its principal place of business at S-151 85 Södertälje, Sweden—is the corporate parent of AstraZeneca Pharmaceuticals LP. AstraZeneca AB declares that it is an indirectly wholly owned subsidiary of AstraZeneca plc, which is a public company organized under the laws of England and Wales and is publicly traded. Upon information and belief, no

other publicly held company owns 10% or more of the voting interest in AstraZeneca AB.

3. AstraZeneca UK Ltd.—a private company operating and existing under the laws of the United Kingdom, with its principal place of business at 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge CB2 0AA, United Kingdom—is an indirect shareholder of AstraZeneca Pharmaceuticals LP. AstraZeneca UK Ltd. declares that it is an indirectly wholly owned subsidiary of AstraZeneca plc, which is a public company organized under the laws of England and Wales and is publicly traded. Upon information and belief, no other publicly held company owns 10% or more of the voting interest in AstraZeneca UK Ltd.

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INTRODUCTION

Pharmaceutical development in the United States has long occurred under a market-based system that encourages innovation. Developers of certain innovative drugs are statutorily eligible for a period of market exclusivity, meaning their products are protected from generic competition for a specified amount of time. Because developing new drugs is exceedingly expensive, risky, and time-consuming, market pricing and exclusivity provide crucial incentives for the development of novel products for patients.

In 2022, Congress enacted the Inflation Reduction Act (IRA), which imposes price controls on certain prescription drugs, while also seeking to preserve market-based pricing and exclusivity as incentives. The statute directs the Secretary of Health and Human Services to establish a “Drug Price Negotiation Program,” which allows the Centers for Medicare and Medicaid Services (CMS) to establish prices for a limited set of drugs with the highest Medicare expenditures. 42 U.S.C. § 1320f(a). At the same time, the IRA attempts to safeguard innovation, by limiting this novel price-fixing regime to a specified number of drugs that have already been on the market for a significant period. For what the IRA refers to as “initial price applicability year 2027,” the statute limits CMS’s price-setting authority to fifteen

“qualifying single source drugs” that meet certain statutory criteria. *Id.* § 1320f-1(a)(2), (e)(1)(A)(i)-(iii).

This case turns on the definition of “qualifying single source drug”—referred to here as “Qualifying Drug” or “QSSD.” The IRA defines these qualifying drugs by reference to the well-established legal framework for the approval of pharmaceutical products by FDA, the cornerstone of which is the “New Drug Application” or “NDA.”

To receive FDA approval, each “new drug” requires an NDA, meaning that the manufacturer must submit “full reports of investigations” into the drug’s safety and effectiveness. 21 U.S.C. § 355(a), (b)(1)(A)(i). Obtaining approval for a new drug thus involves a “long, comprehensive, and costly testing process” to determine whether the drug will be safe and effective in treating identified conditions in a specific patient population. *FTC v. Actavis, Inc.*, 570 U.S. 136, 142 (2013). Once a drug is deemed safe and effective, it receives “marketing approval” from FDA and is listed in the agency’s so-called “Orange Book.” The drug can then receive a limited period of statutory exclusivity—*i.e.*, a right to sell without competition—based on the date of the drug’s NDA approval. *See id.* at 142-44.

The IRA expressly incorporates this NDA-approval framework in defining a Qualifying Drug. Under the statutory definition, each such drug must have been approved pursuant to its own distinct NDA. In other words: one Qualifying Drug; one NDA. Each part of the definition, codified at 42 U.S.C. § 1320f-1(e)(1)(i)-(iii), confirms that reading:

Romanette (i): First, a Qualifying Drug must be “approved under Section 355(c) of Title 21 and . . . marketed pursuant to such approval.” 42 U.S.C. § 1320f-1(e)(1)(i). Section 355(c) is the statute governing NDA approval. And a brand-name drug is “marketed” pursuant to the approval of its NDA. So when the Qualifying Drug definition says “*such* approval,” it means approval of the drug’s NDA.

Romanette (ii): Second, “at least 7 years [must] have elapsed since the date of such approval.” *Id.* § 1320f-1(e)(1)(ii). Each approval of a Qualifying Drug’s NDA (“*such* approval”) accordingly must have occurred on a specific date (“*the* date”) at least seven years earlier. As a result, a single Qualifying Drug cannot have *multiple* NDA “approvals” on *different* “dates.”

Romanette (iii): Finally, a drug that would otherwise be a Qualifying Drug is nevertheless exempt if it becomes “the listed drug” (*i.e.*, the brand-name drug) for a generic version. *Id.* § 1320f-1(e)(1)(iii). A branded drug, in turn, is “listed” by NDA number.

These provisions thus make clear—each on its own, but especially when read together—that each Qualifying Drug has a single NDA.

CMS has refused to follow Congress’s instructions. Instead, CMS has issued “guidance” reinterpreting the term Qualifying Drug to include any *group* of drugs that share the same “active moiety,” even when these products have “different NDAs.” CMS, *Medicare Drug Price Negotiation Program: Final Guidance*, 167-68 (Oct. 2, 2024) (*Guidance*), <https://perma.cc/RH4T-B3PX>. Where a new drug approved under a new NDA shares an “active moiety” with a different drug that was approved years earlier under a different NDA, CMS will group both of them together as *one* Qualifying Drug subject to a *single* price cap under the IRA. Indeed, CMS will lump together as many different drugs as share the same active moiety.

The consequences of CMS’s “active moiety” approach to grouping drugs are remarkable. When combining two or more different drugs with different NDAs into a single Qualifying Drug, CMS treats the relevant approval date as the “earliest date” of the drugs’ various NDA approvals. *Id.* at 170. As a result, a drug can be subject to price controls less than seven years after its NDA approval—possibly even as soon as it is approved. And since multiple products can be grouped together if they share an active moiety, more than fifteen

drugs can be subject to price caps, even if none of their individual Medicare expenditures would meet the eligibility threshold.

CMS's redefinition of Qualifying Drug to encompass multiple products with "different NDAs" contravenes the IRA's plain language, which clearly adopts a one-drug, one-NDA framework. Yet even if a Qualifying Drug could somehow span multiple products with separate NDAs, the Guidance would *still* conflict with the IRA, because there is no justification whatsoever for CMS's active moiety-based definition. While Congress has used the term "active moiety" in numerous *other* federal statutes, the IRA does not use it even once in more than 270 pages of text. If Congress had wanted eligibility for price caps under the IRA to turn on a technical concept like active moiety, it would at least have *mentioned* the term somewhere in the law.

In addition to being atextual, CMS's "active moiety" definition would undermine the IRA's goal of maintaining a reasonable period of exclusivity for innovative drugs. Manufacturers expend immense time and resources developing new drugs (requiring new NDAs) to treat distinct conditions and patient populations, sometimes by developing new products that derive from existing active moieties. For example, a pill to prevent organ rejection after transplants (Prograf) shares an active moiety with an eczema ointment

(Protopic); a treatment for hypertension (Catapres) shares an active moiety with an ADHD treatment for children and adolescents (Kapvay); and so on. The IRA preserves the incentives to develop distinct drugs using existing moieties. CMS's statutory rewrite undercuts them. The Court should reverse.

JURISDICTIONAL STATEMENT

The district court had subject-matter jurisdiction under 28 U.S.C. § 1331 and entered judgment on August 19, 2026. JA1, JA22. AstraZeneca appealed on August 21. JA61. This Court has jurisdiction under 28 U.S.C. § 1291.

ISSUE PRESENTED FOR REVIEW

Whether CMS's Guidance exceeds the agency's authority under the IRA by redefining "qualifying single source drug."

PERTINENT STATUTES AND REGULATIONS

Pertinent statutes and regulations are reproduced in the Addendum to this brief.

STATEMENT OF THE CASE

A. Factual Background

1. Congress Created an Exclusivity Framework to Facilitate Innovation

The American pharmaceutical industry thrives on innovation. Manufacturers like AstraZeneca expend substantial time and resources identifying, testing, and developing new medicines—with the average cost of successfully bringing a drug to market now reaching \$2.23 billion.¹ Despite immense R&D costs, however, only one compound in 5,000 that enters preclinical testing achieves FDA approval, a failure rate of 99.98%.² Of the therapies approved for patient use, only one-third recover their costs of development, much less provide an economic return significant enough to allow for continued investment and innovation in new medicines.³ And even when an innovative drug reaches the market, it cannot hope to compete with generic versions, which “are not required to repeat the costly clinical trials of

¹ See Deloitte, *Be Brave, Be Bold: Measuring the Return from Pharmaceutical Innovation* 6 (Mar. 2025), <https://perma.cc/7KFW-49ZG>.

² See Sandra Kraljevic et al., *Accelerating Drug Discovery*, 5 EMBO Reps. 837, 837 (2004).

³ See John A. Vernon & Joseph H. Golec, *Pharmaceutical Price Regulation: Public Perceptions, Economic Realities, and Empirical Evidence* 7 (2008).

new drugs and generally do not [need] costly advertising, marketing, and promotion.”⁴

Given the challenges of developing new drugs and the relative ease of producing generic versions, the system depends on providing legal protections for the relatively few drug-development efforts that *do* succeed. Namely, “the prospect of patent protection and exclusivity can motivate innovators to invest in the development of novel products and new treatment options for patients.” U.S. Pat. & Trademark Off., *Drug Patent and Exclusivity Study* 7 (June 2024) (*Drug Patent and Exclusivity*), <https://perma.cc/2Z8D-HZAU>.

The modern legal framework stems from the Hatch-Waxman Act.⁵ By rewarding innovation, that framework benefits patients globally. But it helps Americans most. Manufacturers generally launch new drugs here first, so American patients are often the first to receive lifesaving and life-sustaining medicines. Nearly 80% of medicines approved by FDA in 2021 were available in the United States before any other country. *See* FDA, *Advancing Health*

⁴ FDA, *Facts About Generic Drugs* 3 (2020), <https://perma.cc/AM26-XADC>.

⁵ Formally, the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417, 98 Stat. 1585.

Through Innovation: New Drug Therapy Approvals 2021 21 (Jan. 2022), <https://perma.cc/8SHW-QZMB>.

To obtain the benefits of exclusivity for a new drug—and hence a market-based return on its investment—a manufacturer must subject its drug to a rigorous vetting process. “In the United States, new drugs generally cannot be legally marketed for human use without FDA approval.” *Drug Patent and Exclusivity* at 8. The cornerstone of the approval process is the New Drug Application. 21 U.S.C. § 355(a)-(b). “Applicants seeking to market a novel new drug must file a New Drug Application (NDA) with the FDA and provide enough information to permit the FDA to determine whether the drug is safe and effective for its intended use (i.e., that the benefits of the drug outweigh the risks for its intended use).” *Drug Patent and Exclusivity* at 8. No brand-name manufacturer may “introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such drug.” 21 U.S.C. § 355(a).

Approval of an NDA involves a “long, comprehensive, and costly testing process.” *Actavis*, 570 U.S. at 142. The manufacturer must submit “full reports of investigations” into the drug’s safety and efficacy; “a full list of the articles used as components”; and a “full description” of how the drug is manufactured,

processed, and packed. 21 U.S.C. § 355(b)(1)(A). If FDA is persuaded of the drug's safety and efficacy, the manufacturer receives "marketing approval," *id.* § 355(d), and the NDA is assigned its own number, *see* FDA, *Manual of Policies & Procedures, NDA Classification Codes* (Dec. 8, 2022), <https://perma.cc/S66V-NL4R>. The date that the NDA's approval "shall be made effective" is fixed by statute according to specified criteria. 21 U.S.C. § 355(c)(3).

After an NDA has been approved, the manufacturer generally may not make changes to the drug without notifying FDA. *Id.* § 356a; 21 C.F.R. § 314.70(a)(1)(i). For some relatively modest changes, sponsors must obtain approval for a "supplement" to the original NDA. 21 C.F.R. § 314.70(b). Changes to a drug approved through a supplement, however, are still considered part of the *existing* NDA. *Id.* § 314.3(b) (NDA includes "all ... supplements"). Thus, a supplement is approved under the existing NDA's number and is not assigned a new NDA number. *Id.* § 314.50(a)(1).

Changes so significant that they result in a "new drug," by contrast, require the sponsor to submit a separate, original NDA. 21 U.S.C. § 355(a). FDA guidance addresses the circumstances in which alterations to a drug should be submitted under an original NDA, versus through a supplement to

an existing NDA. See FDA, *Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (Dec. 2004) (*Separate Marketing Applications Guidance*), <https://perma.cc/8Z7R-CHQD>. For instance, some changes to a drug's dosage form⁶ or strength can be approved through a supplement, whereas others are so significant that they result in an entirely new drug and “should be included in separate original applications”—that is, in new NDAs. *Id.* at 3-4.

“[U]pon marketing approval,” a new drug can be “eligible for a period of exclusivity under the U.S. statutory framework . . . before lower cost generic competitors can be approved or licensed.” *Drug Patent and Exclusivity* at 7. The relevant period of exclusivity varies depending on circumstances. See, e.g., 21 U.S.C. § 360cc (seven-year period for so-called “orphan drugs”); *id.* § 355(c)(3)(E)(iii)-(iv), (F)(iii)-(iv) (three years for new clinical investigations); *id.* § 355(c)(3)(E)(ii), (F)(ii) (five years for new chemical entity, potentially extendable to seven-and-a-half years); see also 21 C.F.R. § 316.31 (orphan drugs); *id.* § 314.108(b)(4) (new clinical investigations); *id.* § 314.108(b)(2) (new chemical entity). Exclusivity generally runs from the date FDA “approves”

⁶ “Dosage form” refers to a drug’s physical features, such as tablets, capsules, or injectables. See FDA, *Drugs@FDA Glossary of Terms* (Nov. 14, 2017), <https://perma.cc/8DPJ-JSAW>.

the qualifying NDA; depending on that approval date, the exclusivity periods can overlap with each other or run consecutively. *See, e.g.*, 21 U.S.C. § 360cc(a) (“seven years from the date of the approval”). Likewise, drugs can receive patent protection, serving a “critical role in incentivizing and protecting the investments essential for bringing life-saving and life-altering drugs to market.” *Drug Patent and Exclusivity* at 2.

FDA is required to periodically publish a “list” of brand-name drugs approved under original NDAs, including their exclusivity and patent information. 21 U.S.C. § 355(j)(7). That list appears in FDA’s “Orange Book” of Approved Drug Products, so-called because the print version has an orange cover. *See* FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations | Orange Book* (2026), <https://perma.cc/A34F-CZG9>.

Once an NDA-approved drug’s regulatory exclusivity and patent-protection periods have expired, generic competitors are eligible to enter the market. A generic manufacturer can obtain approval by filing an Abbreviated New Drug Application. *See* 21 U.S.C. § 355(j). In general, to obtain approval for a generic drug, an applicant first must identify the previously approved product it seeks to duplicate—often referred to as the “listed drug” because of its listing in the Orange Book. *See* FDA, *Referencing Approved Drug Products*

in *ANDA Submissions: Guidance for Industry* 2 (Oct. 2020), <https://perma.cc/YHQ3-4LWT>. An applicant must attest “that the generic has the ‘same active ingredients as,’ and is ‘biologically equivalent’ to, the already-approved brand-name drug.” *Actavis*, 570 U.S. at 142 (cleaned up); see 21 U.S.C. § 355(j)(2)(A)(ii), (iv); 21 C.F.R. § 314.92.

This “statutory framework” for the approval of brand and generic drugs—which allows manufacturers of novel drugs to receive market-based returns *before* facing generic competition—is crucial to innovation. *Drug Patent and Exclusivity* at 7. “Innovator companies bear the expense and risk of developing life-saving drug products” based on the promise that the law will “protect[] those inventions for a limited period of time.” *Id.* By the same token, “the generic industry relies on innovator companies taking substantial initial risks during [drug] development, which must occur before lower cost versions of innovator products can be brought to market.” *Id.* at 7-8.

2. The IRA Exempts a Limited Set of Drugs from Market Pricing

Medicare is a federal program that provides health insurance coverage for individuals over 65 and patients with certain disabilities and medical conditions. It includes two major prescription drug programs. Part B covers medically necessary and preventive healthcare services, including drugs

administered by a physician. 42 U.S.C. §§ 1395k(a)(1), 1395x(s)(2)(A). Part D covers self-administered prescription drugs. *Id.* § 1395w-102. For decades, prices in Medicare Parts B and D have been dictated by the market. Indeed, Congress has long prohibited the Secretary of Health and Human Services from “interfer[ing]” with market-based pricing for Medicare drugs. *Id.* § 1395w-111(i)(1) (Part D); *see id.* § 1395w-3a (Part B).

The IRA removes a specified number of drugs from the standard market-based pricing model. It directs the Secretary to establish a “Drug Price Negotiation Program,” under which CMS will set new prices for drugs that meet strict eligibility requirements and have been on the market for at least seven years. 42 U.S.C. §§ 1320f(a), 1320f-1(e)(1)(A)(ii). The Program is limited to Medicare Part D drugs for the first two annual cycles, after which CMS “selects” Part B drugs as well. *Id.* § 1320f-1(b). Although the IRA is designed to reduce drug prices, it also seeks to preserve incentives for innovation, by limiting which drugs qualify for price caps based on the amount of time since their approval.

Here is how the Program works. Each applicable year, CMS must “publish a list of selected drugs” that will be subject to what the statute calls “maximum fair prices.” *Id.* § 1320f(a). The IRA then directs the agency to

“negotiate” with manufacturers and “enter into agreements” setting the price. *Id.* § 1320f-2(a)(1)-(3). While the IRA calls this process a “negotiation,” it functionally allows CMS to dictate the price for each “selected” drug and compel the manufacturer to “agree” to that price. *Id.* § 1320f-3(c). With one minor exception not applicable here, the statute does not limit how *low* a price the agency can demand. *See id.* § 1320f-3(b)(2)(F). But it does place a “ceiling” on how *high* the ultimate price can be, requiring a minimum discount of 25% to 60%. *Id.* § 1320f-3(b)(2)(F), (c)(1)(C). Below that “ceiling,” the agency must “consider” various “factors,” but it ultimately must “achieve the lowest maximum fair price for each selected drug.” *Id.* § 1320f-3(b)(1), (e).

The statute then requires CMS to “compute and apply the maximum fair price across different strengths and dosage forms of a selected drug.” *Id.* § 1320f-5(a)(2). Once CMS has imposed a new price for a selected drug, the manufacturer must provide “access to such price to” more than 70 million Medicare “eligible individuals,” millions of private providers, and thousands of private pharmacies. *Id.* § 1320f-2(a)(1)-(3).

3. The IRA Expressly Limits the Set of Drugs Eligible for Price Caps

To preserve the marketing exclusivity and patent protections that provide crucial incentives for innovation, the IRA strictly limits the drugs that

can qualify for price caps each year. The statute effectuates these limits through a three-step process.

Step One: Qualifying Drug. Whether a drug can qualify for price caps under the Program depends on the timing of its NDA approval. The IRA directs CMS to begin the price-setting process by identifying each “qualifying single source drug”—also known as a “QSSD” or “Qualifying Drug.” The QSSD definition comprises three romanettes, which specify that a Qualifying Drug is “a covered part D drug”⁷:

- i. “that is approved under section 355(c) of Title 21 and is marketed pursuant to such approval;”
- ii. “for which . . . at least 7 years will have elapsed since the date of such approval; and”
- iii. “that is not the listed drug for any drug that is approved and marketed under section 355(j) of [Title 21].”

42 U.S.C. § 1320f-1(e)(1)(A)(i)-(iii).⁸

⁷ The definition also includes certain “drug[s] or biological product[s]” payable under Part B, but Part B is not included in the Program for 2027. 42 U.S.C. § 1320f-1(a)(2).

⁸ The IRA excludes certain drugs from the Qualifying Drug definition, including “[c]ertain orphan drugs,” “[l]ow spend medicare drugs,” and “[p]lasma-derived products.” 42 U.S.C. § 1320f-1(e)(3).

Each of these romanettes thus links a particular Qualifying Drug to its specific NDA⁹:

- Romanette (i) confirms that each Qualifying Drug must be “marketed pursuant to” an NDA, because “Section 355(c) of Title 21” is the statutory provision that governs FDA approval, and the only “approval” “pursuant to” which a drug can be “marketed” is its NDA approval.
- Romanette (ii) confirms that at least 7 years must have elapsed “since the date of *such* approval,” again referring to the NDA approval.
- Romanette (iii) provides that a Qualifying Drug cannot be “the listed drug” for a generic version, which is a reference to the generic approval process of showing equivalency to a drug that is “listed”—by its individual NDA number—in FDA’s Orange Book.

Step Two: Negotiation Eligibility. After identifying Qualifying Drugs based on the timing of their NDA approval and the existence of any generic competitor, CMS must determine which Qualifying Drugs are “negotiation-eligible drug[s].” *Id.* § 1320f-1(d). To do so, CMS must rank Qualifying Drugs based on each drug’s total expenditures under Medicare Part D or Part B over the previous year. *Id.* § 1320f-1(d)(1). Because only Part D drugs can be selected during the first two cycles, the ranking for those initial cycles includes only Part D expenditures. *Id.* § 1320f-1(a)(1), (2). A Qualifying Drug must be

⁹ A similar definition applies with respect to “biological product[s],” which are approved under “biologics license application[s].” 42 U.S.C. § 1320f-1(e)(1)(B). But no biological products are at issue in “initial price applicability year 2027,” which is the subject of the Guidance at issue here. *Id.* § 1320f-1(a)(2).

among the top 50 highest-expenditure Part D drugs to be deemed “negotiation-eligible.” *Id.* § 1320f-1(d).

In determining whether a Qualifying Drug ranks as negotiation-eligible, the IRA instructs CMS to “use data that is aggregated across dosage forms and strengths of the drug, including new formulations of the drug, such as an extended release formulation.” *Id.* § 1320f-1(d)(3)(B). Thus, after CMS has identified a Qualifying Drug by its NDA approval, this provision requires the agency to assess its negotiation-eligibility in light of its total expenditures, across all of the dosage forms and strengths approved via the original NDA and any supplements to that NDA.

Step Three: Selection. The IRA then directs CMS to “select” a specified number of the highest-ranked negotiation-eligible drugs for the Program each year. *Id.* § 1320f-1(a)-(b). CMS was required to select ten Part D drugs during the first annual cycle, and price caps took effect in 2026. *Id.* § 1320f-1(a)(1). For the second cycle—at issue here—the IRA directs CMS to select fifteen additional drugs, with price caps scheduled to take effect in 2027. *Id.* § 1320f-1(a)(2).¹⁰

¹⁰ For the third cycle, the statute directs CMS to select fifteen Part B or D drugs for price caps taking effect in 2028. 42 U.S.C. § 1320f-1(a)(3). The statute

Once chosen, a drug remains selected until a defined period after the agency determines that a generic version of the drug has been “approved” by FDA and marketed “pursuant to such approval.” *Id.* § 1320f-1(c)(1)(B). Thus, the IRA also uses the FDA-approval framework—including approval of a generic version of a “listed drug”—to determine when a drug *no longer* qualifies as a “selected drug.” *Id.* § 1320f-1(c)(1)(A)(i).

4. CMS’s Program Guidance

On October 2, 2024, CMS promulgated the Guidance at issue in this case. The Guidance sets forth the agency’s plan for implementing the Program during “initial price applicability year 2027,” *Guidance* at 1, for which the IRA directs CMS to select fifteen Part D drugs for price caps.

Section 30 of the Guidance articulates CMS’s approach to “the requirements governing the identification of qualifying single source drugs” (*i.e.*, Qualifying Drugs). *Id.* at 165. Key here is the following instruction:

CMS will identify a potential qualifying single source drug using . . . all dosage forms and strengths of the drug with the same *active moiety* and the same holder of a New Drug Application (NDA), *inclusive of products that are marketed pursuant to different NDAs*.

instructs CMS to select twenty more Part B or D drugs for the fourth cycle and for each cycle thereafter. *Id.* § 1320f-1(a)(4).

Id. at 167 (emphases added) (footnotes omitted). In other words, when drugs approved under “different NDAs” share an “active moiety,” CMS will treat them as a single Qualifying Drug.

The term “active moiety” does not appear in the IRA. An “active moiety” is not itself a drug, but is the “molecule or ion ... responsible for the physiological or pharmacological action of the drug substance.” 21 C.F.R. § 314.3. Distinct drugs may share an active moiety, yet still may be different enough that they require separate NDAs. For example, here is a list of some of the drugs that share an active moiety but treat distinct conditions:

Drug 1 (Indication)	Drug 2 (Indication)	Active Moiety
Daliresp (chronic obstructive pulmonary disease)	Zoryve (plaque psoriasis)	<i>Roflumilast</i>
Prograf (organ rejection after transplants)	Protopic (eczema)	<i>Tacrolimus</i>
Loniten (severe/resistant hypertension)	Rogaine (androgenic alopecia)	<i>Minoxidil</i>
Catapres (hypertension)	Kapvay (ADHD in children and adolescents)	<i>Clonidine</i>

Indeed, drugs that share the same active *moiety* may nevertheless still have different active *ingredients*. When that happens, FDA instructs that each such drug “should be submitted in a separate original application”—that is, under its own separate NDA. *Separate Marketing Applications Guidance* at 3 & n.7.

Under CMS’s Guidance, therefore, two or more distinct drugs with different active ingredients—drugs whose distinct NDAs have been separately approved by FDA at different times based on different safety and efficacy data—could nevertheless be treated collectively as a *single* Qualifying Drug. For example, two of AstraZeneca’s drugs share an active moiety but have different active ingredients and are indicated for different patient populations. JA37, JA40.

As noted, the IRA’s definition of Qualifying Drug requires “at least 7 years [to] have elapsed since the date of such approval.” 42 U.S.C. § 1320f-1(e)(1)(A). To implement this requirement where two or more products with the same active moiety were approved under different NDAs at different times, CMS has elected to start the seven-year eligibility countdown from the “earliest date of approval or licensure of the initial FDA application.” *Guidance* at 170. As a result, a new product could be subject to a price cap under the Program *immediately* after its FDA approval, so long as it shares an active moiety with a different product with an older approval date.

B. Procedural History

AstraZeneca filed a complaint seeking to set aside CMS’s Guidance under the Administrative Procedure Act. JA15, JA22, JA56-58. AstraZeneca

contends that, by defining Qualifying Drug to mean any group of products that share the same “active moiety”—even though they were approved under “different NDAs”—the Guidance exceeds CMS’s authority under the IRA. *Guidance* at 167.

The parties cross-moved for summary judgment, and the Government also moved to dismiss based on the IRA’s bar on reviewing certain of CMS’s drug-specific “determination[s].” 42 U.S.C. § 1320f-7. After oral argument, the district court ruled from the bench, denying AstraZeneca’s motion for summary judgment; denying the Government’s motion to dismiss; and granting the Government’s cross-motion for summary judgment.

First, the court held that the IRA’s judicial-review provision, 42 U.S.C. § 1320f-7, does not apply to AstraZeneca’s APA claims. The court explained that “there is a strong presumption that Congress intends judicial review of administrative action,” JA99, and that AstraZeneca is not challenging any of CMS’s drug-specific findings. “The complaint instead attacks the guidance and the interpretation of the IRA reflected in that guidance,” which is not a topic that the provision shields from review. JA167.

Second, the district court denied AstraZeneca’s motion for summary judgment and granted summary judgment to the Government. The court

concluded that a Qualifying Drug, as defined in the IRA, *can* encompass multiple different products approved under separate NDAs. It reasoned that “[n]othing in [the Qualifying Drug definition] draws a line at the edge of an NDA.” JA169. Further, the court concluded that CMS’s “active moiety” definition reflects “the best interpretation” of the Qualifying Drug definition, JA170, even though “Congress did not use the term ‘active moiety’ at all in the IRA,” JA170. In reaching that conclusion, the court relied on the D.C. Circuit’s decision in *Teva Pharmaceuticals USA, Inc. v. Kennedy*, 187 F.4th 587 (D.C. Cir. 2026), in which CMS’s Qualifying Drug definition was one of several issues presented.

SUMMARY OF ARGUMENT

CMS’s Guidance exceeds the agency’s authority under the IRA by redefining Qualifying Drug to encompass multiple drugs approved under “different NDAs.” The Guidance also independently contravenes the IRA by redefining Qualifying Drug in terms of products that share an “active moiety,” a term that does not appear anywhere in the statute.

I. The IRA ties each Qualifying Drug to a single NDA.

A. The text of the Qualifying Drug definition requires a one-drug, one-NDA approach. Romanette (i) requires a Qualifying Drug to be “approved

under Section 355(c)” and “marketed pursuant to *such* approval.” That necessarily refers to approval of the drug’s NDA, because that is the only approval pursuant to which a brand-name drug *can* be “marketed.” Romanette (ii) then requires “at least 7 years” to have elapsed “since *the* date of *such* approval,” confirming that each Qualifying Drug has a single NDA approval that occurred on a single date. And romanette (iii), which exempts a Qualifying Drug that is “the listed drug” for a generic competitor, similarly presupposes that each Qualifying Drug corresponds to an NDA. One Qualifying Drug; one NDA.

B. The IRA’s structure and function confirm this interpretation. Congress designed the Qualifying Drug definition to preserve market exclusivity as an innovation incentive, shielding newly approved drugs from price controls for the first seven years after their NDA approval. Only an approach that sets a new exclusivity clock based on a drug’s NDA-approval date serves that purpose.

II. CMS’s Guidance improperly redefines Qualifying Drug to encompass multiple different products “marketed pursuant to different NDAs,” so long as they share the same “active moiety.”

A. CMS’s approach is inconsistent with the IRA’s text. It contravenes the requirement that “at least 7 years . . . have elapsed since *the* date of *such* approval,” which can refer only to a single NDA approval on a single date. CMS’s approach of redefining “such approval” to mean the “earliest” approval date among the grouped drugs is invented from whole cloth. Defining Qualifying Drug to encompass multiple drugs with separate NDAs would also undermine the IRA’s central purpose: CMS’s approach would prematurely strip drugs of their access to market pricing—possibly even from the moment they are approved—making it much riskier for manufacturers to invest in research to develop novel treatments using existing active moieties, since the manufacturers may never be able to recoup their investments. Congress never intended for new drugs with separate NDAs to be merged into one Qualifying Drug.

B. CMS bases its interpretation on three ancillary IRA provisions that apply at steps two and three of the IRA—that is, *after* a Qualifying Drug has already been identified at step one. None of those provisions purports to define what a Qualifying Drug is; each applies only after a Qualifying Drug has already been identified by its NDA. And regardless, all three provisions are perfectly consistent with a Qualifying Drug having a single NDA.

C. Even if a Qualifying Drug could somehow span distinct products with multiple NDAs, CMS’s “active moiety” definition would still be invalid. The term has no connection to the IRA and appears nowhere in the statute—even though Congress has used the term elsewhere in the U.S. Code. If Congress had wanted eligibility for the Program to turn on “active moiety,” it surely would have said so.

STANDARD OF REVIEW

The Administrative Procedure Act requires courts to “hold unlawful and set aside” agency action that is “not in accordance with law” or is “in excess of statutory jurisdiction, authority, or limitations.” 5 U.S.C. § 706(2)(A), (C). This Court “review[s] de novo the district court’s evaluation of a challenged agency action under the APA.” *Ren v. USCIS*, 60 F.4th 89, 93 (4th Cir. 2023). Summary judgment is appropriate where “the movant is entitled to judgment as a matter of law.” Fed. R. Civ. P. 56(a).

ARGUMENT

“[T]he duty of an administrative agency is to follow [a statute] as written, not to supplant [the statute’s] commands with others it may prefer.” *SAS Inst., Inc. v. Iancu*, 584 U.S. 357, 363 (2018). The only “permissible” reading of a statute is the “best” one, which is the interpretation the court would adopt “if

no agency were involved.” *Loper Bright Enters. v. Raimondo*, 603 U.S. 369, 400 (2024). CMS’s Guidance does not reflect the “best” interpretation—or even a plausible interpretation—of the IRA.

I. EACH QUALIFYING DRUG HAS ITS OWN NDA

The IRA defines “qualifying single source drug”—also called “Qualifying Drug” or “QSSD”—as a drug marketed pursuant to an NDA that was approved at least seven years earlier. Each Qualifying Drug has its own NDA, which literally constitutes the approval of a “new drug.” Each approval of an NDA starts the seven-year clock for that particular drug. CMS’s Guidance, by instead redefining Qualifying Drug to encompass *multiple* products with distinct NDAs, contravenes the statute.

A. The IRA Is Clear That a Qualifying Drug Has a Single NDA

The Qualifying Drug definition has three parts. Romanettes (i) and (ii) specify the requirements for being a Qualifying Drug; romanette (iii) describes an exemption for a product that would otherwise satisfy the definition. Separately and together, these provisions confirm that each Qualifying Drug is identified by its specific NDA—and accordingly cannot have more than one NDA. Consider each romanette in turn:

i. “[A covered part D drug] that is approved under section 355(c) of Title 21 and is marketed pursuant to such approval”

First, a Qualifying Drug must be “a covered part D drug ... that is approved under Section 355(c) of Title 21.” 42 U.S.C. § 1320f-1(e)(1)(A)(i). Section 355(c) is the provision that governs FDA approval and specifies the date on which the approval “shall be made effective.” 21 U.S.C. § 355(c)(3). So the IRA starts by tying the Qualifying Drug definition to the FDA-approval framework: A Qualifying Drug must be “approved under” that framework.

Next, the Qualifying Drug must be “marketed pursuant to *such* approval.” 42 U.S.C. § 1320f-1(e)(1)(A)(i) (emphasis added). As the Supreme Court has explained, “the word ‘such’ usually refers to something that has already been ‘described,’” especially where there is a “clear referent.” *Slack Techs., LLC v. Pirani*, 598 U.S. 759, 766 (2023) (citation omitted). Here, “such approval” clearly refers to the aforementioned “approv[al] under Section 355(c)” —that is, to FDA’s approval.

Crucially, romanette (i) can only be read to mean that “such approval” refers specifically to the drug’s NDA. That is because the NDA is the *only* FDA “approval” “pursuant to” which a brand-name drug *can be* “marketed.” At its core, an NDA is “an application for marketing approval of a drug.” 21 U.S.C. § 355(d). “Applicants seeking to market a novel new drug must file a

New Drug Application,” *Drug Patent and Exclusivity* at 8, and no brand-name manufacturer may “introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an [NDA] is effective with respect to such drug,” 21 U.S.C. § 355(a).¹¹ The drug’s NDA number is listed in FDA’s “Orange Book,” which indicates that the drug has been “approved by FDA for marketing.” FDA, *National Drug Code Database Background Information*, <https://perma.cc/W85S-K7HQ>.

In short, a brand-name drug is “marketed pursuant to” its NDA. When the IRA says a Qualifying Drug must be “approved under Section 355(c) of Title 21 and ... marketed pursuant to such approval,” therefore, “such approval” necessarily refers to the approval of the drug’s NDA.

ii. “for which ... at least 7 years will have elapsed since the date of such approval”

The second romanette reinforces the one-drug, one-NDA reading of the Qualifying Drug definition: “at least 7 years [must] have elapsed since *the* date of *such* approval.” 42 U.S.C. § 1320f-1(e)(1)(A)(ii) (emphases added). “[S]uch

¹¹ See 21 C.F.R. § 314.81(d) (noting that FDA’s “withdraw[ing] approval of the application ... prohibit[s] continued marketing of the drug”); FDA, *New Drug Application (NDA)* (“The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S.”), <https://perma.cc/VRB9-WN7P>. For generic drugs, an Abbreviated New Drug Application is required.

approval” again refers to the approval “under Section 355(c),” which is the approval “pursuant to” which the drug is “marketed.” *See Slack*, 598 U.S. at 766. That is, “such approval” again means the approval of the drug’s NDA. And importantly, seven years must have elapsed since “*the* date” that the drug’s NDA was approved.

That timing instruction can *only* be read to mean that each Qualifying Drug has its own, singular NDA. When Congress “us[es] a definite article with a singular noun,” it refers to “a discrete thing.” *Niz-Chavez v. Garland*, 593 U.S. 155, 166 (2021). The IRA pairs the definite article (“*the* date”) with a singular NDA approval (“*such* approval”). *The* date of *such* approval is the NDA-approval date for the prospective Qualifying Drug. *See* 21 U.S.C. § 355(c)(3) (specifying the “date” on which an NDA approval “shall be made effective”). Each Qualifying Drug thus has a particular NDA approval that occurred on a specific date, and that approval starts the seven-year clock. It is accordingly impossible for a Qualifying Drug to somehow have multiple NDA “approval[s],” or else starting the clock on “*the* date of *such* approval” would be an incoherent concept.

iii. “that is not the listed drug for any drug that is approved and marketed under section 355(j) of [Title 21]”

Finally, a drug that would otherwise be a Qualifying Drug is nevertheless exempt if it is “the listed drug” for a generic version of the drug—that is, a version “approved and marketed under section 355(j).” All FDA-approved drugs appear on a “list” published periodically by the Secretary in FDA’s Orange Book, which is the source of the term “listed drug.” 21 U.S.C. § 355(j)(7). Each brand-name drug is “listed” by its individual NDA number. *See* 21 C.F.R. § 314.3. Generic drugs, in turn, gain approval by showing equivalency to a specific “listed drug.” *See* 21 U.S.C. § 355(j)(2)(A)(i), (j)(7). So when the IRA discusses the possibility of a Qualifying Drug becoming “the listed drug” for a generic version, it presupposes what the preceding romanettes make clear: Each Qualifying Drug has its *own* NDA.

* * *

In sum, the IRA’s Qualifying Drug definition defines a particular Qualifying Drug by its specific NDA. First, CMS must identify individual drugs by their distinct NDAs (the “approval” “pursuant to” which each drug is “marketed”). Then, CMS must determine whether each drug’s NDA approval (“*such* approval”) occurred on a specific date (“*the* date”) at least seven years earlier. If so—and if there is no generic version of a brand drug

“listed” by its NDA—then the drug is a Qualifying Drug. Otherwise, it is not.

In other words: one Qualifying Drug; one NDA.

B. The IRA’s Structure and Function Confirm That Each Qualifying Drug Is Linked to a Single NDA

Congress had good reasons for tying each drug’s potential IRA eligibility to its NDA, as opposed to using a definition that would encompass *multiple* products with *distinct* NDAs. The availability of market pricing and the prospect of market exclusivity are key incentives for innovation. *See* pp. 7-13, *supra*. Because the vast majority of drugs never reach the market, the relatively few drugs that receive FDA approval after the lengthy and costly testing and approval processes must be able to generate enough revenue to support the manufacturer’s entire pipeline.

Because generic manufacturers “are not required to repeat the [brand-name drug’s] costly clinical trials,” however, immediate generic entry would prevent brand-name drugs from competing at all. FDA, *Facts About Generic Drugs* 3, <https://perma.cc/AM26-XADC>. Patent protection and marketing-exclusivity laws thus ensure that new drugs benefit from a period of market pricing before generic competition is allowed. *See, e.g.*, 42 U.S.C. § 1395w-111(i)(1) (Part D); *id.* § 1395w-3a (Part B). And such “[e]xclusivity attaches

upon approval” of an NDA. FDA, *Frequently Asked Questions on Patents and Exclusivity* (2020), <https://perma.cc/3MHN-JCJX>.

Congress was well aware of the importance of market pricing and exclusivity when it enacted the IRA. Indeed, the Program is a narrow exception to the longstanding rule *preventing* the Secretary from “interfer[ing]” with market pricing. 42 U.S.C. § 1395w-111(i). That is why a drug does not become eligible for a price cap under the IRA until “at least 7 years will have elapsed since the date of [its NDA] approval.” *Id.* § 1320f-1(e)(1)(A)(ii). As one Congressman put it in endorsing the IRA: “We don’t negotiate during [a drug’s] initial exclusivity period.” House Rules, *Rules Committee Meeting on H.R. 5376* at 34:20 (YouTube, Nov. 3, 2021), <https://perma.cc/GFJ9-L3KZ>. The IRA prevents that outcome by linking each Qualifying Drug to its NDA approval—*i.e.*, to the “approval” “pursuant to” which the drug is “marketed”—and by insulating the drug from IRA pricing until “7 years ... have elapsed since the date of such approval.” 42 U.S.C. § 1320f-1(e)(1)(A)(i)-(ii). The resulting seven-year period of market pricing for new drugs thus preserves key incentives for innovation.

II. CMS'S GUIDANCE CONFLICTS WITH THE STATUTE

Instead of following the IRA's definition of Qualifying Drug—which links each drug to its own NDA—CMS's Guidance redefines Qualifying Drug to include any *group* of products “with the same *active moiety*,” even when those products “are marketed pursuant to *different NDAs*.” *Guidance* at 167 (emphases added) (footnote omitted). Nothing in the text supports this approach. But even if a single Qualifying Drug could somehow have multiple NDAs, the Guidance *still* exceeds the agency's statutory authority: It impermissibly groups together drugs based on whether they share an “active moiety,” a term (and concept) that does not appear anywhere in the IRA. That error independently requires reversal.

A. CMS's Guidance Improperly Defines Qualifying Drug to Include Multiple Drugs with Different NDAs

1. CMS's Guidance Contravenes the IRA's Text

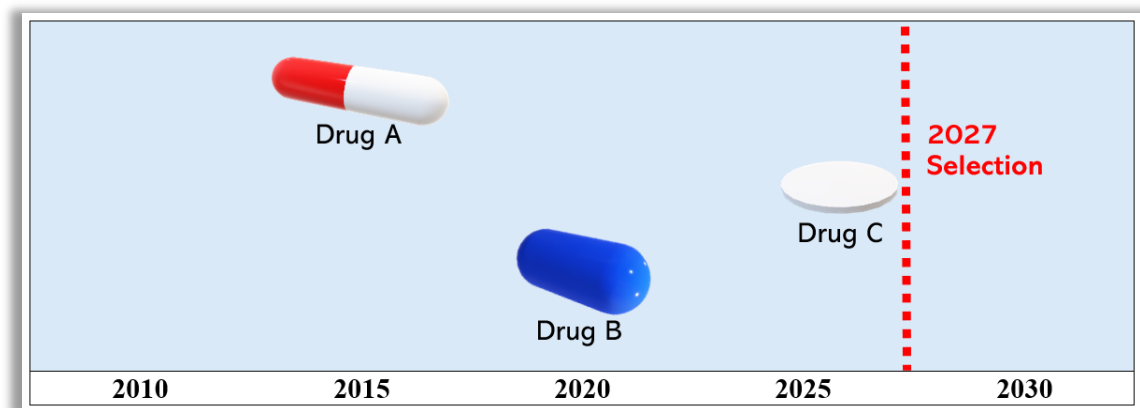
Section 30 of CMS's Guidance articulates CMS's interpretation of the Qualifying Drug definition. According to the Guidance, that definition requires CMS to:

identify a potential qualifying single source drug using ... all dosage forms and strengths of the drug with the same *active moiety* and the same holder of a New Drug Application (NDA), *inclusive of products that are marketed pursuant to different NDAs*.

Id. (emphases added) (footnotes omitted). In other words, CMS defines Qualifying Drug as any *collection* of drugs, even if approved under “different NDAs,” so long as they share an “active moiety” and NDA-“holder.” *Id.* This approach is not even close to the “best” interpretation of the statute. *Loper Bright*, 603 U.S. at 400.

As discussed, the IRA defines a Qualifying Drug as having a single NDA approved on a specific date—namely, the “date” on which the NDA approval “shall be made effective.” 21 U.S.C. § 355(c)(3). Each Qualifying Drug must be “approved”; must be “marketed pursuant to *such* approval” (meaning approval of its NDA); and must be “at least 7 years [removed from] *the* date of *such* approval.” 42 U.S.C. § 1320f-1(e)(1)(A)(i)-(ii) (emphases added). Each “such approval” is singular, occurring at a singular point in time (“the date”), which is when the seven-year clock starts. A Qualifying Drug cannot somehow have multiple “different” approval dates. *Guidance* at 167.

Indeed, if a single Qualifying Drug *could* span multiple products marketed pursuant to different NDAs, then the statute would create an unanswered question: Which date starts the seven-year clock? Imagine three drugs that share an active moiety but were approved under different NDAs:



Combining the three together into a single Qualifying Drug, despite their separately approved NDAs, would require choosing between their approval dates. Yet the statute provides no guidance about how to decide in this situation whether “7 years will have elapsed since the date of *such* approval.” 42 U.S.C. § 1320f-1(e)(1)(A)(ii) (emphasis added). That lacuna is a clear sign that Congress did not contemplate this scenario at all. *See Stern v. Marshall*, 564 U.S. 462, 476 (2011) (rejecting interpretation under which statute “provides no guidance on” necessary implementation decision).

In fact, CMS itself recognizes that starting eligibility “7 years [after] the date of such approval” would make no sense if a Qualifying Drug could have multiple “approvals.” So in its Guidance, CMS has added a requirement that appears nowhere in the IRA: “CMS will use the *earliest* date of approval” to start the seven-year clock. *Guidance* at 170 (emphasis added). Why the earliest date, as opposed to the latest date (or some other date)? Maybe

because it maximizes the number of drugs subject to IRA pricing. In the example above, Drugs B and C would be eligible for selection in 2027—not because seven years have elapsed since *they* were approved, but because seven years have elapsed since *Drug A* was approved.

But the IRA does not say “7 years since the *earliest* date of approval,” even though Congress easily could have written the statute that way. *Cf.* 5 U.S.C. § 9003(d) (requiring the Office of Personnel Management to contract with long-term-care insurers “for a term of 7 years,” with “the 7-year period beginning on the earliest date as of which any long-term care insurance coverage under this chapter becomes effective”). Nor can CMS explain why Congress started the seven-year countdown from “the” date of “such” approval, if it actually meant for the clock to start from the “earliest” date of multiple different “approvals.”

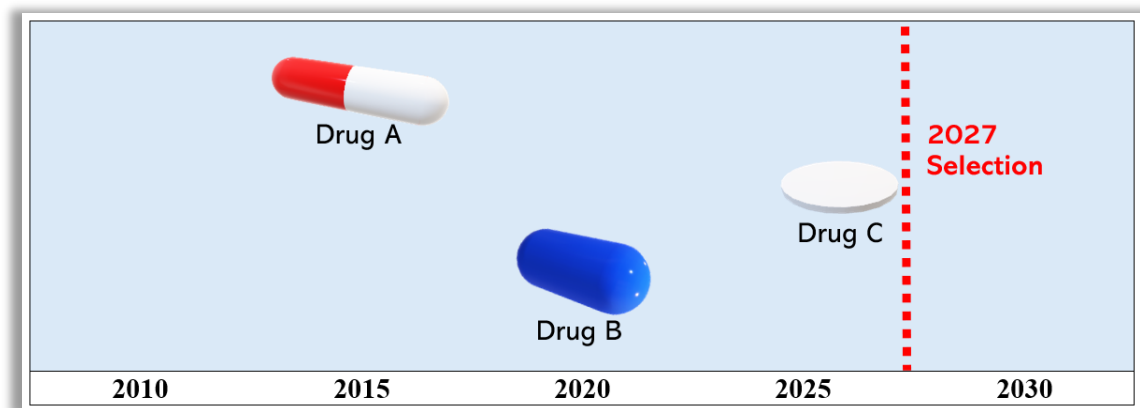
The district court’s explanation fares no better. The court accepted CMS’s “earliest-approval” theory on the premise that “the seven-year requirement imposed in the QSSD definition measures the age of the drug once it has been identified,” and “[t]he IRA does not require each NDA to be treated as a separate statutory drug.” JA169. But that explanation simply disregards the text: The seven-year requirement is not an independent

“measure[ment]” that occurs only “once [a Qualifying Drug] has been identified.” Rather, it is *part of* the Qualifying Drug definition—the second of three parts. So unless “at least 7 years have elapsed since the date of such approval,” a product simply *is not* a Qualifying Drug in the first place.

In any event, the district court’s argument fails on its own terms. Even if it were true (contrary to the text) that “the seven-year requirement imposed in the QSSD definition measures the age of the drug once it has been identified,” that still would not explain why CMS has read “*such* approval” as a reference to the earliest date of multiple NDAs, as opposed to some other date. The only way to make the timing instruction work is if “such approval” refers to a single, identifiable point at which the seven-year clock starts. The one-drug, one-NDA approach satisfies that condition; CMS’s multiple-NDA approach does not.

2. CMS’s Guidance Flouts the IRA’s Purposes

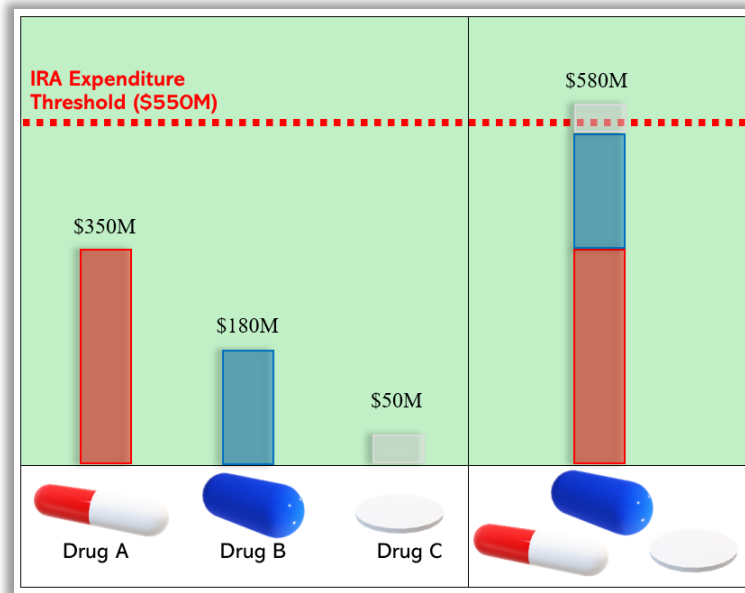
CMS’s “earliest” approval rule also undermines the IRA’s purposes. Starting the seven-year countdown from the “earliest” NDA of a multi-drug group would mean that newly approved drugs could be subject to IRA pricing *during* their initial exclusivity period. Again, consider the example in which Drug C was approved in 2026:



If Drug C were lumped in with Drug A based on the date of Drug A’s NDA approval, then Drug C would have only a single year of exclusivity between reaching the market in 2026 and being subject to a price cap under the IRA in 2027. Indeed, an otherwise profitable drug could be subject to price caps *immediately* upon approval, simply because it shares an “active moiety” with an old drug.

Further, if a new drug could be lumped together with an old drug for purposes of IRA-eligibility, the new drug’s Medicare expenditures would be added to the old drug’s expenditures, increasing the likelihood that *both* drugs would qualify for the Program. *See* 42 U.S.C. § 1320f-1(d)(1). In this example, even if expenditures for Drugs A, B, and C would not independently cross the top-50 threshold to qualify as negotiation-eligible, their *combined* expenditures might. When Drug C reaches the market in 2026, it could push *all three* drugs over the IRA threshold for 2027.

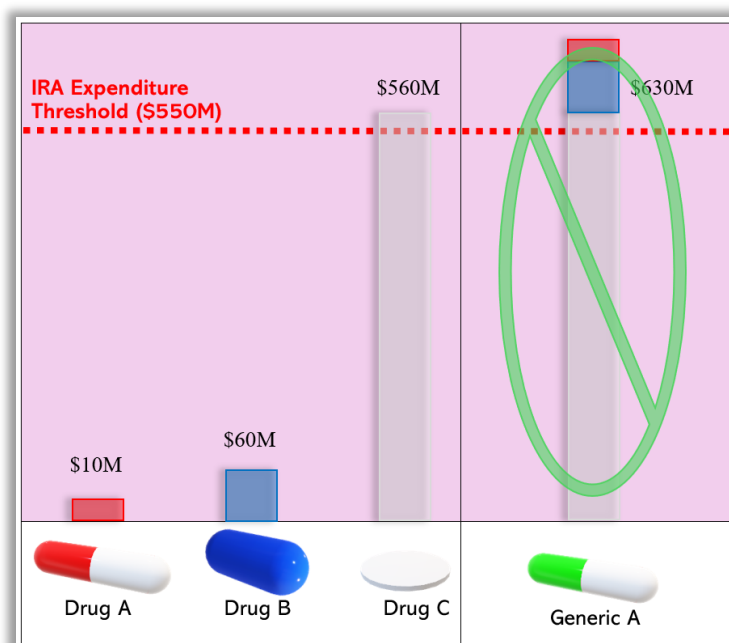
For example, imagine that the expenditure threshold for 2027 is \$550M. Introduction of Drug C, with expenditures of \$50M, could push Drug A (\$350M) and Drug B (\$180M) over the line:



In other words, developing a new drug (Drug C) would risk not only a price cap for *that* drug, but might also expose *earlier-approved* drugs (Drugs A and B) to price caps that they would otherwise be ineligible to receive. In that case, pursuing novel treatments using existing active moieties would actually be financially *counterproductive* for the manufacturer, undermining incentives for the further study of existing active moieties. *See, e.g.*, 21 C.F.R. § 314.108 (providing “new clinical investigation” exclusivity for certain drugs “that contain[] an active moiety that has been previously approved in another NDA”) (emphasis added). Such an anti-innovation approach, which could lead

to fewer new breakthroughs for patients, is hardly what Congress intended in the IRA.

The Qualifying Drug definition in CMS's Guidance also undermines the IRA's goal of lowering prices for the highest expenditure drugs. Recall that generic competition leads to the *deselection* of a drug. *Id.* § 1320f-1(c)(1)(B), (c)(2). But what about a scenario where there is a generic competitor for only *one* of several drugs that have been grouped together under CMS's approach? For instance, FDA might approve a generic version of Drug A, but *not* of Drugs B or C. In that scenario, the question arises: Would competition from Generic A disqualify *all three* brand-name drugs from IRA pricing—even if, say, *Drug C* accounts for virtually all of the total Medicare expenditures?



Under CMS’s interpretation, the high-expenditure drug (Drug C) would be excluded from the Program simply because it shares an active moiety with a *low-expenditure* drug (Drug A) that has a generic competitor (Generic A). Again, this result would conflict with Congress’s purposes in enacting the IRA. At minimum, the statute’s utter silence on this issue is a strong sign that Congress never intended for multiple drugs to be lumped together in the first place. *See Stern*, 564 U.S. at 476 (rejecting statutory interpretation that would mean “Congress failed to provide any framework for identifying or adjudicating [an important] category”).

B. CMS’s Attempts to Justify Its Multi-NDA Approach Are Unpersuasive

To defend CMS’s interpretation of the IRA’s Qualifying Drug definition, the Guidance invokes language from three *different* provisions of the IRA: the “Use of Data” provision, 42 U.S.C. § 1320f-1(d)(3)(B); the “Compute and Apply” provision, *id.* § 1320f-5(a)(2); and the “Applications and Approvals” provision, *id.* § 1320f-3(e)(1)(D). But those provisions do not define Qualifying Drug. As the district court acknowledged, they “govern different decisions made at different points in the negotiation program.” JA171.

CMS’s attempt to redefine Qualifying Drug based on provisions *outside* the statutory definition is a flashing warning sign. “When Congress takes the

trouble to define the terms it uses”—as it did in the Qualifying Drug definition—“a court must respect its definitions as virtually conclusive.” *Dep’t of Agric. Rural Dev. Rural Hous. Serv. v. Kirtz*, 601 U.S. 42, 59 (2024) (cleaned up). Indeed, it would be highly peculiar for Congress to have defined Qualifying Drug in such intricate detail in 42 U.S.C. § 1320f-1(e)(1)(A)(i)-(iii), only to have altered a key feature of the definition by implication based on non-definitional provisions that operate at *later* stages of the price-setting process.

Regardless, the ancillary provisions on which CMS relies in its Guidance are perfectly consistent with the proper interpretation of the Qualifying Drug definition. Once CMS has identified a Qualifying Drug by its single NDA, those separate provisions simply instruct the agency to make product-selection and pricing decisions using information concerning various “dosage forms and strengths” that include approvals *both* under the drug’s original NDA *and* under any supplemental applications linked to that specific NDA. None of those ancillary provisions is inconsistent with a one-drug, one-NDA approach.

1. Use of Data: 42 U.S.C. § 1320f-1(d)(3)(B)

Recall that in step one, the IRA instructs CMS *first* to identify Qualifying Drugs using FDA’s approval framework. *See* 42 U.S.C. § 1320f-

1(e); *see also* pp. 16-17, 27-32, *supra*. The “Use of Data” provision is part of the IRA’s *second* step—that is, the process for determining whether a particular Qualifying Drug counts as a “negotiation-eligible drug.” It instructs:

In determining whether a qualifying single source drug satisfies any of the criteria described in paragraph (1) or (2) [(i.e., the criteria for a negotiation-eligible drug)], the Secretary shall use data that is aggregated across dosage forms and strengths of the drug, including new formulations of the drug, such as an extended release formulation, and not based on the specific formulation or package size or package type of the drug.

Id. § 1320f-1(d)(3)(B) (emphases added).

In other words, once a Qualifying Drug has already been identified, this *separate* subsection instructs CMS to determine whether that Qualifying Drug is eligible for “negotiation,” a step that involves aggregating data “across [its] dosage forms and strengths.” The aggregation instruction thus applies at step two, where it is used “[i]n determining whether a qualifying single source drug satisfies any of the criteria” for negotiation eligibility.

The district court acknowledged that the IRA’s “aggregation provision operates after CMS identifies a qualifying single source drug,” but nevertheless insisted the provision should not be “read . . . in isolation.” JA168-169. The court observed that the Qualifying Drug definition “supplies the conditions for qualification[,] while [the Use of Data provision] tells CMS what

formulations belong to the drug, whose expenditures it must calculate.” JA169. According to the court, “[n]othing in either provision draws a line at the edge of an NDA.” JA169.

The district court’s argument misreads the Use of Data provision, which expressly states that it applies “[i]n determining whether a qualifying single source drug satisfies any of the criteria [regarding negotiation-eligibility] described in paragraph (1) or (2).” AstraZeneca is not asking the Court to read the Qualifying Drug definition and Use of Data provision in isolation; it is simply asking the Court to read them in order.

Regardless, the district court’s argument fails on its own terms, because the Qualifying Drug definition *does* “draw[] a line at the edge of an NDA.” It says that each Qualifying Drug must be “marketed pursuant to” a particular “approval,” and that “*the* date” of “*such* approval” starts the seven-year countdown. Even if the Use of Data provision could be reverse-interpreted into the Qualifying Drug definition, therefore, it could not override or explain away those requirements.

According to CMS’s Guidance, the Use of Data provision “necessarily establish[es] that the statutory negotiation procedures apply more broadly than to a distinct NDA,” because it requires “identify[ing] a potential

qualifying single source drug” using “all dosage forms and strengths of the drug.” *Guidance* at 12-14. CMS’s argument rests on the premise that a single NDA cannot encompass multiple dosage forms and strengths, such that the aggregation instruction in the Use of Data provision is inconsistent with a one-drug, one-NDA interpretation of the Qualifying Drug definition. But that premise is demonstrably incorrect.

As discussed, “changes to dosage forms, strengths, and formulations *may be encompassed within a single NDA.*” JA26 (emphasis added); *see* JA25-28. In particular, a single Qualifying Drug with a single NDA can have multiple *supplemental* approvals that reflect “changes in the qualitative or quantitative formulation of the drug product.” JA25 (citations omitted); *see* 21 C.F.R. § 314.3(b) (an NDA includes “all . . . supplements”). The Government agrees: It has stated that “a drug . . . with multiple dosage forms and strengths may have been approved in a single NDA.” Dist. Ct. Dkt. 40 at 17. In fact, FDA’s guidance often *requires* different dosage forms and strengths of a product “[to] be submitted” in connection with the same “original application.” *Separate Marketing Applications Guidance* at 3-4.

The upshot is that a single NDA can (and sometimes must) include multiple products—approved under supplemental applications tied to the

same original NDA—that differ in terms of dosage form and strength. So the Use of Data provision provides a clarifying instruction: Once a Qualifying Drug has been identified by its NDA in step one, CMS must determine the drug’s negotiation-eligibility in step two by using data about *all* of that Qualifying Drug’s dosage forms and strengths, including those approved through supplemental applications. But since all the supplemental applications are still tied to the original NDA, that data-aggregation instruction poses no problem for a one-drug, one-NDA interpretation of Qualifying Drug.

The D.C. Circuit in *Teva*, although it endorsed CMS’s approach, did not dispute that the Use of Data provision is compatible with a one-drug, one-NDA interpretation. Instead, it relied on a superfluity argument: “If CMS could consider only one NDA, Congress’s instruction to account for ... ‘new formulations of the drug’ ... would add little to the expenditure calculation,” because “any formulation approved through a supplement would already fall within the NDA-defined drug.” 187 F.4th at 608.

But Congress had good reason for adding that instruction. As discussed, the IRA expressly defines each Qualifying Drug by reference to the “approval” of its *original* NDA, which can (and sometimes must) include multiple products that differ in terms of their dosage forms and strengths.

Congress accordingly had ample reason to “remove doubt” about how the agency should aggregate data in that scenario—*i.e.*, when multiple dosage forms and strengths are included under a single NDA via supplemental approvals. *Marx v. Gen. Revenue Corp.*, 568 U.S. 371, 385 (2013). Otherwise, manufacturers might have argued for the exclusion of sales data based on dosage forms and strengths that were not included in the original NDA.

Regardless, “the canon against surplusage assists only where a competing interpretation gives effect to every clause and word of a statute.” *Id.* (quotation marks omitted). CMS’s position—that each Qualifying Drug can encompass multiple NDAs—would create the very same surplusage issue it purports to avoid: If CMS were right that the statute groups together all products that share an active moiety, then each Qualifying Drug would *already* encompass all “applications and approvals” of products with that shared active moiety, making the Use of Data provision just as superfluous. *See* 42 U.S.C. § 1320f-3(e)(1)(D).

In other words, any surplusage problem would exist regardless of whether the Court reads Qualifying Drug to include only products approved under a single NDA (AstraZeneca’s approach), or multiple products grouped

together by active moiety (CMS's approach). And only the former reading is consistent with the Qualifying Drug definition itself.

2. Compute and Apply: 42 U.S.C. § 1320f-5(a)(2)

Similarly unpersuasive is the Guidance's reliance on the Compute and Apply provision, which provides:

For purposes of section 1320f(a)(4) of this title, the administrative duties described in this section are the following:

....

(2) The establishment of procedures to compute and apply the maximum fair price *across different strengths and dosage forms of a selected drug* and not based on the specific formulation or package size or package type of such drug.

42 U.S.C. § 1320f-5(a)(2) (emphases added). Like the Use of Data provision, the Compute and Apply provision applies *after* a Qualifying Drug has been identified. Indeed, it applies “[f]or purposes of section 1320(f)(a)(4),” which is the provision that instructs CMS to “carry out [its] publication and administrative duties and compliance monitoring” for manufacturers whose drugs have been selected for negotiation and subjected to price caps.

The Compute and Apply provision thus applies *after* step three—that is, after CMS has identified all Qualifying Drugs; determined which of them are negotiation-eligible; and selected some of them for “negotiation.” Only then, once CMS has set a maximum price for all selected drugs, does the statute

instruct CMS to “compute and apply” each drug’s maximum price across the different dosage forms and strengths of the selected drug. The Compute and Apply provision thus has no bearing on whether a product is a Qualifying Drug in the first place. Indeed, it is not even codified in the same statutory *section* as the Qualifying Drug definition.

In any event, much like the Use of Data provision, the Compute and Apply provision *does not* imply that a single Qualifying Drug can have multiple NDAs. As noted, different dosage forms and strengths of a product can (and sometimes must) be approved under a single NDA through supplements to that original NDA. So, like the Use of Data provision, the Compute and Apply provision simply confirms that once CMS has set a “maximum fair price” for a Qualifying Drug, the agency must apply that price across all of the drug’s dosage forms and strengths—*i.e.*, across all of those approved via the original NDA and any supplements. The Use of Data provision is thus designed to “remove doubt” about that scenario. *Marx*, 568 U.S. at 385. And regardless, any resulting surplusage would be just as acute under CMS’s approach, under which a Qualifying Drug already includes multiple products that share the same “active moiety.”

3. Applications and Approvals: 42 U.S.C. § 1320f-3(e)(1)(D)

Precisely the same arguments apply to the Applications and Approvals provision, which states:

For purposes of negotiating the maximum fair price of a selected drug under this part with the manufacturer of the drug, the Secretary shall consider ... [d]ata on ... ***applications and approvals under section 355(c) ... for the drug.***

42 U.S.C. § 1320f-3(e)(1)(D) (emphases added). Since this provision expressly applies “[f]or purposes of negotiating the maximum fair price of a selected drug,” it similarly comes into play when setting a price *after* a drug has been identified as a Qualifying Drug. Indeed, it applies only after a Qualifying Drug has been determined to be negotiation-eligible and has been selected for negotiation.

According to CMS, the provision’s reference to applications and approvals “in the plural, for the ‘drug,’ in the singular,” means that an individual Qualifying Drug can have multiple NDAs. *Guidance* at 13. Relying on *Teva*, the district court reached the same conclusion, reasoning that “[s]eparate NDAs are applications under § 355(c).” JA168; *see Teva*, 187 F.4th at 608 (“The terms ‘applications’ and ‘approvals’ are plural; and the term ‘the drug’ is singular.”). That reasoning is unpersuasive.

Like the Use of Data and Compute and Apply provisions, the Applications and Approvals provision is perfectly consistent with each Qualifying Drug having a single NDA. That is because the cross-referenced provision, Section 355(c), describes *both* the process for obtaining approval of an NDA *and* the process for supplemental applications for an existing NDA. *See* 21 U.S.C. § 355(c)(1) (approval of an original application); *id.* § 355(c)(5) (approval of “a supplemental application”). A single drug with a single NDA thus can have multiple “applications and approvals” under Section 355(c)—one approval for the original NDA, and any number of additional approvals for supplemental applications related to the original NDA. *See* 21 C.F.R. § 314.3(b) (NDA includes “all . . . supplements”).

The Applications and Approvals provision thus tells CMS to consider all applications and approvals *for each Qualifying Drug*: The agency must consider data submitted in connection with its original NDA, as well as data submitted in connection with any supplemental approvals. Nothing in that instruction is inconsistent with a reading under which each Qualifying Drug has its own NDA.

C. CMS’s “Active Moiety” Definition Contravenes the IRA’s Text and Purposes

Even if the three ancillary provisions that CMS invokes could somehow support defining Qualifying Drug to encompass multiple drugs with different NDAs, those provisions *still* would not justify CMS’s “active moiety” approach. At most, those provisions could justify grouping together separate products that vary only in terms of their “dosage forms and strengths.” 42 U.S.C. §§ 1320f-1(d)(3)(B), 1320f-5(a)(2). But “active moiety” is a different, and far broader, concept than dosage form or strength. For example, separate drugs can share an active moiety even when they have different *active ingredients*. So even if aggregating data “across dosage forms and strengths” required grouping some drugs that have different NDAs—though it does not—that *still* would not justify CMS’s decision to group drugs according to whether they share an “active moiety.”

In other words, even accepting CMS’s interpretation of the Use of Data, Compute and Apply, and Applications and Approvals provisions, the agency’s Guidance is still flatly inconsistent with the IRA. The Guidance simply adds an alternative definition that appears nowhere in the statute. That atextual maneuver provides an independent ground for reversal.

1. “It is a fundamental principle of statutory interpretation that absent provisions cannot be supplied by the courts.” *Rotkiske v. Klemm*, 589 U.S. 8, 14 (2019) (cleaned up). Yet while the term “active moiety” is the linchpin of CMS’s interpretation, it does not appear anywhere in the IRA’s 270 pages.

That is no accident. An “active moiety” is not itself a “drug,” but is the “molecule or ion . . . responsible for the physiological or pharmacological action of the drug substance.” 21 C.F.R. § 314.3(b). Although a new brand-name “drug” requires a new NDA (literally, a “*New Drug Application*”), *see id.* (emphasis added), it does not require a new active moiety. And while the IRA expressly ties each Qualifying Drug to its NDA—*i.e.*, to the Section 355(c) “approval” “pursuant to” which the Qualifying Drug is “marketed”—the law says nothing about “active moiety.” CMS offers no reason to “believe that Congress omitted the term . . . simply because it wanted to save ink or assumed that regulators and interested parties would understand that the omission of the term was inconsequential.” *San Francisco v. EPA*, 604 U.S. 334, 344 (2025).

Congress *could have* done things differently. Congress is familiar with the term “active moiety,” which appears in other sections of the U.S. Code. *See* 21 U.S.C. §§ 355, 360b, 360n, 360ff, 360bbb-4a. When Congress intends to

distinguish between products based on active moieties, it does so expressly. Congress's decision in the IRA to link each Qualifying Drug to its NDA, rather than to its "active moiety," reflects a legislative choice that CMS is not free to override. To the contrary: "Courts are required to give effect to Congress' express inclusions and exclusions, not disregard them." *Nat'l Ass'n of Mfrs. v. Dep't of Def.*, 583 U.S. 109, 126 (2018).

The district court nevertheless reasoned that because "Congress did not use the term 'active moiety' at all in the IRA[,] . . . its omission from the QSSD definition in Subsection (e)(1)(D) is of no interpretive consequence or significance." JA170. But that is backwards. CMS has staked out a position that the Qualifying Drug definition turns on "active moiety," so CMS needs to point to statutory language *supporting* that interpretation; AstraZeneca need not point to language *negating* the implicit incorporation of that concept. Congress's decision to omit the term altogether, despite using it in other statutes, undermines CMS's reading. Indeed, had Congress meant for "active moiety" to be the key feature of the Drug Pricing Program, it would have at least mentioned the term. At minimum, Congress would not have "sought to accomplish in a 'surpassingly strange manner' what it could have accomplished

in a much more straightforward way.” *Azar v. Allina Health Servs.*, 587 U.S. 566, 577 (2019) (citations omitted).

The district court also relied on the D.C. Circuit’s *Teva* decision to conclude that “the term ‘active moiety’ [comports] with the ordinary meaning of the word ‘drug.’” JA169. But that was not how CMS sought to justify the “active moiety” definition in its Guidance—and for good reason. To start, eligibility for the Program does not turn on whether a product meets the “ordinary meaning” of the word “drug.” Rather, the question is whether the product meets the reticulated statutory criteria that Congress has used to define a “qualifying single source drug,” which is a statutory term of art. *See Kirtz*, 601 U.S. at 59 (“[A] court must respect [statutory] definitions as virtually conclusive.”) (cleaned up).

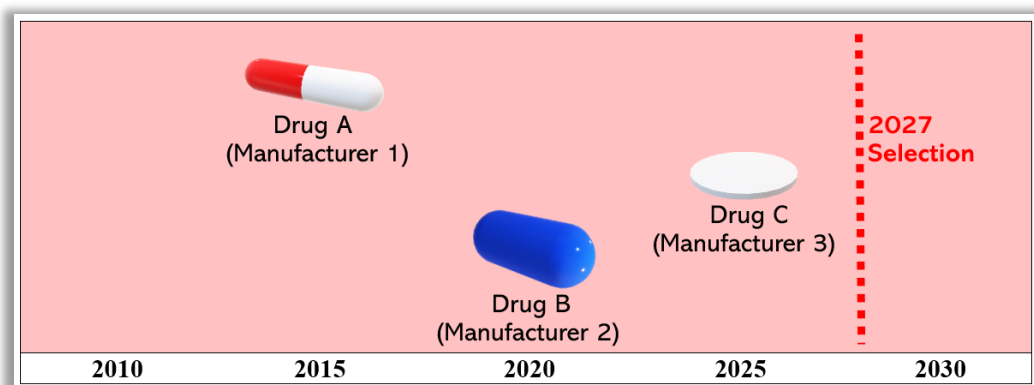
The district court’s ordinary-meaning argument also fails on its own terms, because “active moiety” *does not* “comport with the ordinary meaning of the word ‘drug.’” No fluent English speaker, when asked to define the word “drug,” would give an answer that turns on active moiety. Nor does any dictionary define the word that way. The D.C. Circuit pointed to two dictionary definitions, *Teva*, 187 F.4th at 609, but neither uses the term “active moiety.” *See Drug*, Black’s Law Dictionary (12th ed. 2024) (“A substance intended for

use in diagnosis, cure, treatment, or prevention of disease.”); Drug, Merriam-Webster’s Collegiate Dictionary (12th ed. 2025) (“[A] substance used as a medication or in the preparation of medication”). Again, for good reason: A drug’s “active moiety” is the “molecule or ion ... responsible for the physiological or pharmacological action of the drug substance.” 21 C.F.R. § 314.3(b). In other words, it is a *feature of* a drug, not a drug itself. An NDA, by contrast, is a plain-meaning way to distinguish between different drugs; it is literally an application for approval of a “new drug.” *See* 21 U.S.C. § 355. And regardless, “[t]his Court will not deviate from an express statutory definition merely because it varies from the term’s ordinary meaning.” *Kirtz*, 601 U.S. at 59 (cleaned up).

The district court further observed that “active moiety has long played a key role in determining when a drug is new.” JA169 (citing *Teva*). But that observation cuts *against* CMS’s reading. Active moiety may sometimes play a “role” in identifying new drugs, but the NDA is *the* defining feature of a “new drug.” *See* 21 U.S.C. § 355. Novel drugs that treat distinct conditions in new patient populations regularly share an active moiety with existing drugs, yet may be required under FDA’s guidance to be “included in separate original applications.” *Separate Marketing Applications Guidance* at 4. In that

circumstance, the new drug also receives separate patent protection and exclusivity. *See, e.g.*, 21 C.F.R. § 314.108(b)(4) (providing exclusivity for certain drugs “that contain[] an active moiety that *has been previously approved* in another NDA”) (emphasis added). Congress thus *could have* tied the definition of Qualifying Drug to the well-understood concept of active moiety, but instead deliberately chose to insulate *all* “new drugs” from IRA pricing.

2. CMS’s attempt to replace the NDA framework with an “active moiety” test is also at war with the IRA’s broader structure, because separate manufacturers can (and do) develop and market substantially different drugs that share an active moiety. Recall again the example in which separately approved Drugs A, B, and C share an active moiety:



Those drugs might have been developed and marketed by three separate manufacturers to treat three distinct conditions, based on health and safety data for three distinct patient populations. Yet, under an “active moiety” test,

all three of those manufacturers' distinct drugs would be treated as *one* Qualifying Drug.

This is not merely an abstract concern. Consider Prograf and Protopic, two distinct drugs that share an active moiety. Prograf was developed by Astellas Pharma U.S., Inc. and approved in 1994 to prevent organ rejection in patients receiving liver transplants. Protopic, by contrast, was developed by LEO Pharma A/S and approved in 2000 as an ointment to treat eczema. Under the IRA's plain text, Prograf and Protopic are each distinct "drugs." Yet applying an "active moiety" test would mean treating them both as *the same* drug—theoretically eligible for a *single* "maximum fair price."

The IRA's text and structure foreclose the possibility of multiple manufacturers negotiating over distinct products approved through different NDAs. Once a Qualifying Drug has been "selected" for the Program, CMS must sign an agreement to "negotiate" with "*the* manufacturer" of that selected drug. 42 U.S.C. § 1320f-2(a), (d) (emphasis added). CMS must obtain information from "*the* manufacturer," must "negotiate" a price with "*the* manufacturer," and must ensure that "*the* manufacturer" provides access to the price. *Id.* (emphases added). Those instructions are simple enough under

a one-drug, one-NDA approach: CMS will negotiate with the manufacturer who holds the NDA on which the product's status as a Qualifying Drug turns.

But if a single Qualifying Drug could encompass multiple drugs “with the same active moiety,” notwithstanding their “different NDAs,” *Guidance* at 167, then multiple manufacturers would need to “agree” to a uniform price for their significantly different products. That would render the IRA's negotiation provisions incoherent—and impossible to implement.

CMS understands that Congress intended nothing of the sort. But instead of abandoning its implausible position, CMS attempts a workaround by adding yet *another* requirement that is not in the statute: According to the Guidance, CMS will combine drugs “with the same active moiety *and the same holder of a New Drug Application.*” *Id.* (emphasis added). That is, CMS will count two drugs with the same active moiety as a single Qualifying Drug if the products share an NDA-“holder,” but *not* if different companies hold their distinct NDAs.

The Government acknowledged this problem in the district court. At argument, counsel stated that CMS *currently* would treat Prograf and Protopic as different drugs because they have different manufacturers—Astellas Pharma for Prograf and LEO Pharma for Protopic. But counsel

acknowledged that CMS would treat Prograf and Protopic as “the same drug” if (for instance) the two companies merged, or one company bought the other. JA142. That makes no sense. Nothing in the Qualifying Drug definition (or the rest of the IRA) indicates that products can come in and out of Qualifying Drug status based on fluctuations in corporate ownership.

The district court attempted to rationalize CMS’s same-NDA-holder requirement on the ground that it “accords with the IRA’s repeated direction that CMS negotiate with the manufacturer of a selected drug.” JA171. But that argument is circular. The IRA’s direction to negotiate with “the manufacturer” is not *part of* the Qualifying Drug definition and does not affect the *meaning of* Qualifying Drug; rather, it *presupposes* a Qualifying Drug definition that coheres with the IRA’s negotiation instructions.

AstraZeneca’s one-drug, one-NDA interpretation, by contrast, naturally permits “negotiation” with a single manufacturer, because a Qualifying Drug with a single NDA is a product for which a single price logically *can be* negotiated. Only CMS’s “active moiety” test requires interpolating into the text a same-NDA-holder limitation. So while it is easy to understand *why* CMS needed to add a same-NDA-holder rule, the very need to solve such practical problems by adding terms to the statute is yet another sign of how far the

agency's approach deviates from the "best" reading of the IRA's plain language. *Loper Bright*, 603 U.S. at 400.

Indeed, CMS's same-NDA-holder requirement does not even solve all of the practical problems created by its approach. Why should a pill to prevent organ rejection after transplants (Prograf) be subject to the same price cap as an eczema ointment (Protopic), even if both drugs are owned by the same company? Nothing in the IRA suggests that Congress intended such a bizarre result.

CONCLUSION

This Court should reverse the district court's order and set aside the Guidance.

Dated: October 5, 2026

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STATEMENT REGARDING ORAL ARGUMENT

Appellants request oral argument. Given the complexity and importance of the issues presented, Appellants believe that oral argument would assist the Court in its decisional process. *See* Loc. R. 34(a).

CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7) because it contains 12,244 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(f).

2. This brief complies with the typeface and type-style requirements of Federal Rules of Appellate Procedure 32(a)(5) because it has been prepared in a proportionally spaced typeface using Microsoft Word for Office 365 and is set in 14-point Century Expanded BT font.

Dated: October 5, 2026

/s/ Allon Kedem

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ADDENDUM

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42 U.S.C. § 1320f. Establishment of program

(a) In general

The Secretary shall establish a Drug Price Negotiation Program (in this part referred to as the “program”). Under the program, with respect to each price applicability period, the Secretary shall—

- (1) publish a list of selected drugs in accordance with section 1320f-1 of this title;
- (2) enter into agreements with manufacturers of selected drugs with respect to such period, in accordance with section 1320f-2 of this title;
- (3) negotiate and, if applicable, renegotiate maximum fair prices for such selected drugs, in accordance with section 1320f-3 of this title;
- (4) carry out the publication and administrative duties and compliance monitoring in accordance with sections 1320f-4 and 1320f-5 of this title.

....

42 U.S.C. § 1320f-1. Selection of negotiation-eligible drugs as selected drugs

(a) In general

Not later than the selected drug publication date with respect to an initial price applicability year, in accordance with subsection (b), the Secretary shall select and publish a list of—

- (1) with respect to the initial price applicability year 2026, 10 negotiation-eligible drugs described in subparagraph (A) of subsection (d)(1), but not subparagraph (B) of such subsection, with respect to such year (or, all (if such number is less than 10) such negotiation-eligible drugs with respect to such year);
- (2) with respect to the initial price applicability year 2027, 15 negotiation-eligible drugs described in subparagraph (A) of subsection (d)(1), but not subparagraph (B) of such subsection, with respect to such year (or, all (if such number is less than 15) such negotiation-eligible drugs with respect to such year);
- (3) with respect to the initial price applicability year 2028, 15 negotiation-eligible drugs described in subparagraph (A) or (B) of subsection (d)(1) with respect to such year (or, all (if such number is less than 15) such negotiation-eligible drugs with respect to such year); and
- (4) with respect to the initial price applicability year 2029 or a subsequent year, 20 negotiation-eligible drugs described in subparagraph (A) or (B) of subsection (d)(1), with respect to such year (or, all (if such number is less than 20) such negotiation-eligible drugs with respect to such year).

Subject to subsection (c)(2) and section 1320f-3(f)(5) of this title, each drug published on the list pursuant to the previous sentence and subsection (b)(3) shall be subject to the negotiation process under section 1320f-3 of this title for the negotiation period with respect to such initial price applicability year (and the renegotiation process under such section as applicable for any subsequent year during the applicable price applicability period).

(b) Selection of drugs**(1) In general**

In carrying out subsection (a), subject to paragraph (2), the Secretary shall, with respect to an initial price applicability year, do the following:

(A) Rank negotiation-eligible drugs described in subsection (d)(1) according to the total expenditures for such drugs under parts B and D of subchapter XVIII, as determined by the Secretary, during the most recent period of 12 months prior to the selected drug publication date (but ending not later than October 31 of the year prior to the year of such drug publication date), with respect to such year, for which data are available, with the negotiation-eligible drugs with the highest total expenditures being ranked the highest.

(B) Select from such ranked drugs with respect to such year the negotiation-eligible drugs with the highest such rankings.

....

(c) Selected drug**(1) In general**

For purposes of this part, in accordance with subsection (e)(2) and subject to paragraph (2), each negotiation-eligible drug included on the list published under subsection (a) with respect to an initial price applicability year shall be referred to as a “selected drug” with respect to such year and each subsequent year beginning before the first year that begins at least 9 months after the date on which the Secretary determines at least one drug or biological product—

(A) is approved or licensed (as applicable)—

(i) under section 355(j) of Title 21 using such drug as the listed drug; or

(ii) under section 262(k) of this title using such drug as the reference product; and

(B) is marketed pursuant to such approval or licensure.

(2) Clarification

A negotiation-eligible drug—

(A) that is included on the list published under subsection (a) with respect to an initial price applicability year; and

(B) for which the Secretary makes a determination described in paragraph (1) before or during the negotiation period with respect to such initial price applicability year;

shall not be subject to the negotiation process under section 1320f-3 of this title with respect to such negotiation period and shall continue to be considered a selected drug under this part with respect to the number of negotiation-eligible drugs published on the list under subsection (a) with respect to such initial price applicability year.

(d) Negotiation-eligible drug

(1) In general

For purposes of this part, subject to paragraph (2), the term “negotiation-eligible drug” means, with respect to the selected drug publication date with respect to an initial price applicability year, a qualifying single source drug, as defined in subsection (e), that is described in either of the following subparagraphs (or, with respect to the initial price applicability year 2026 or 2027, that is described in subparagraph (A)):

(A) Part D high spend drugs

The qualifying single source drug is, determined in accordance with subsection (e)(2), among the 50 qualifying single source drugs with the highest total expenditures under part D of subchapter XVIII, as determined by the Secretary in accordance with paragraph (3), during the most recent 12-month period for which data are available prior to such selected drug publication date (but ending no later than October 31 of the year prior to the year of such drug publication date).

(B) Part B high spend drugs

The qualifying single source drug is, determined in accordance with subsection (e)(2), among the 50 qualifying single source drugs

with the highest total expenditures under part B of subchapter XVIII, as determined by the Secretary in accordance with paragraph (3), during such most recent 12-month period, as described in subparagraph (A).

....

(3) Clarifications and determinations

....

(B) Use of data

In determining whether a qualifying single source drug satisfies any of the criteria described in paragraph (1) or (2), the Secretary shall use data that is aggregated across dosage forms and strengths of the drug, including new formulations of the drug, such as an extended release formulation, and not based on the specific formulation or package size or package type of the drug.

(e) Qualifying single source drug

(1) In general

For purposes of this part, the term “qualifying single source drug” means, with respect to an initial price applicability year, subject to paragraphs (2) and (3), a covered part D drug (as defined in section 1395w-102(e) of this title) that is described in any of the following or a drug or biological product for which payment may be made under part B of subchapter XVIII that is described in any of the following:

(A) Drug products

A drug—

- (i) that is approved under section 355(c) of Title 21 and is marketed pursuant to such approval;
- (ii) for which, as of the selected drug publication date with respect to such initial price applicability year, at least 7 years will have elapsed since the date of such approval; and
- (iii) that is not the listed drug for any drug that is approved and marketed under section 355(j) of such title.

....

42 U.S.C. § 1320f-2. Manufacturer agreements

(a) In general

For purposes of section 1320f(a)(2) of this title, the Secretary shall enter into agreements with manufacturers of selected drugs with respect to a price applicability period, by not later than February 28 following the selected drug publication date with respect to such selected drug, under which—

(1) during the negotiation period for the initial price applicability year for the selected drug, the Secretary and the manufacturer, in accordance with section 1320f-3 of this title, negotiate to determine (and, by not later than the last date of such period, agree to) a maximum fair price for such selected drug of the manufacturer in order for the manufacturer to provide access to such price—

(A) to maximum fair price eligible individuals who with respect to such drug are described in subparagraph (A) of section 1320f(c)(2) of this title and are dispensed such drug (and to pharmacies, mail order services, and other dispensers, with respect to such maximum fair price eligible individuals who are dispensed such drugs) during, subject to paragraph (2), the price applicability period; and

(B) to hospitals, physicians, and other providers of services and suppliers with respect to maximum fair price eligible individuals who with respect to such drug are described in subparagraph (B) of such section and are furnished or administered such drug during, subject to paragraph (2), the price applicability period;

....

(3) subject to subsection (d), access to the maximum fair price (including as renegotiated pursuant to paragraph (2)), with respect to such a selected drug, shall be provided by the manufacturer to—

(A) maximum fair price eligible individuals, who with respect to such drug are described in subparagraph (A) of section 1320f(c)(2) of this title, at the pharmacy, mail order service, or other dispenser at the point-of-sale of such drug (and shall be provided by the manufacturer to the pharmacy, mail order service, or other dispenser, with respect to such maximum fair price eligible

individuals who are dispensed such drugs), as described in paragraph (1)(A) or (2)(A), as applicable; and

(B) hospitals, physicians, and other providers of services and suppliers with respect to maximum fair price eligible individuals who with respect to such drug are described in subparagraph (B) of such section and are furnished or administered such drug, as described in paragraph (1)(B) or (2)(B), as applicable;

....

(b) Agreement in effect until drug is no longer a selected drug

An agreement entered into under this section shall be effective, with respect to a selected drug, until such drug is no longer considered a selected drug under section 1320f-1(c) of this title.

....

42 U.S.C. § 1320f-3. Negotiation and renegotiation process**(a) In general**

For purposes of this part, under an agreement under section 1320f-2 of this title between the Secretary and a manufacturer of a selected drug (or selected drugs), with respect to the period for which such agreement is in effect and in accordance with subsections (b), (c), and (d), the Secretary and the manufacturer—

- (1) shall during the negotiation period with respect to such drug, in accordance with this section, negotiate a maximum fair price for such drug for the purpose described in section 1320f-2(a)(1) of this title; and
- (2) renegotiate, in accordance with the process specified pursuant to subsection (f), such maximum fair price for such drug for the purpose described in section 1320f-2(a)(2) of this title if such drug is a renegotiation-eligible drug under such subsection.

(b) Negotiation process requirements**(1) Methodology and process**

The Secretary shall develop and use a consistent methodology and process, in accordance with paragraph (2), for negotiations under subsection (a) that aims to achieve the lowest maximum fair price for each selected drug.

(2) Specific elements of negotiation process

As part of the negotiation process under this section, with respect to a selected drug and the negotiation period with respect to the initial price applicability year with respect to such drug, the following shall apply:

....

(F) Limitations on offer amount

In negotiating the maximum fair price of a selected drug, with respect to the initial price applicability year for the selected drug, and, as applicable, in renegotiating the maximum fair price for such drug, with respect to a subsequent year during the price applicability period for such drug, the Secretary shall not offer (or agree to a counteroffer for) a maximum fair price for the selected drug that—

(i) exceeds the ceiling determined under subsection (c) for the selected drug and year; or

(ii) as applicable, is less than the floor determined under subsection (d) for the selected drug and year.

(c) Ceiling for maximum fair price

(1) General ceiling

(A) In general

The maximum fair price negotiated under this section for a selected drug, with respect to the first initial price applicability year of the price applicability period with respect to such drug, shall not exceed the lower of the amount under subparagraph (B) or the amount under subparagraph (C).

....

(e) Factors

For purposes of negotiating the maximum fair price of a selected drug under this part with the manufacturer of the drug, the Secretary shall consider the following factors, as applicable to the drug, as the basis for determining the offers and counteroffers under subsection (b) for the drug:

(1) Manufacturer-specific data

The following data, with respect to such selected drug, as submitted by the manufacturer:

(A) Research and development costs of the manufacturer for the drug and the extent to which the manufacturer has recouped research and development costs.

(B) Current unit costs of production and distribution of the drug.

(C) Prior Federal financial support for novel therapeutic discovery and development with respect to the drug.

(D) Data on pending and approved patent applications, exclusivities recognized by the Food and Drug Administration, and applications and approvals under section 355(c) of Title 21 or section 262(a) of this title for the drug.

(E) Market data and revenue and sales volume data for the drug in the United States.

....

42 U.S.C. § 1320f-4. Publication of maximum fair prices

(a) In general

With respect to an initial price applicability year and a selected drug with respect to such year—

(1) not later than November 30 of the year that is 2 years prior to such initial price applicability year, the Secretary shall publish the maximum fair price for such drug negotiated with the manufacturer of such drug under this part; and

(2) not later than March 1 of the year prior to such initial price applicability year, the Secretary shall publish, subject to section 1320f-2(c) of this title, the explanation for the maximum fair price with respect to the factors as applied under section 1320f-3(e) of this title for such drug described in paragraph (1).

....

42 U.S.C. § 1320f-5. Administrative duties and compliance monitoring

(a) Administrative duties

For purposes of section 1320f(a)(4) of this title, the administrative duties described in this section are the following:

....

(2) The establishment of procedures to compute and apply the maximum fair price across different strengths and dosage forms of a selected drug and not based on the specific formulation or package size or package type of such drug.

....

42 U.S.C. § 1320f-6. Civil monetary penalties

(a) Violations relating to offering of maximum fair price

Any manufacturer of a selected drug that has entered into an agreement under section 1320f-2 of this title, with respect to a year during the price applicability period with respect to such drug, that does not provide access to a price that is equal to or less than the maximum fair price for such drug for such year—

....

shall be subject to a civil monetary penalty equal to ten times the amount equal to the product of the number of units of such drug so furnished, dispensed, or administered during such year and the difference between the price for such drug made available for such year by such manufacturer with respect to such individual or hospital, physician, provider of services, or supplier and the maximum fair price for such drug for such year.

42 U.S.C. § 1320f-7. Limitation on administrative and judicial review

There shall be no administrative or judicial review of any of the following:

- (1) The determination of a unit, with respect to a drug or biological product, pursuant to section 1320f(c)(6) of this title.
- (2) The selection of drugs under section 1320f-1(b) of this title, the determination of negotiation-eligible drugs under section 1320f-1(d) of this title, and the determination of qualifying single source drugs under section 1320f-1(e) of this title the application of section 1320f-1(f) of this title,.
- (3) The determination of a maximum fair price under subsection (b) or (f) of section 1320f-3 of this title.
- (4) The determination of renegotiation-eligible drugs under section 1320f-3(f)(2) of this title and the selection of renegotiation-eligible drugs under section 1320f-3(f)(3) of this title.

21 U.S.C. § 355. New Drugs

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug.

(b) Filing application; contents

(1)(A) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as part of the application—

(i) full reports of investigations which have been made to show whether such drug is safe for use and whether such drug is effective in use;

(ii) a full list of the articles used as components of such drug;

(iii) a full statement of the composition of such drug;

(iv) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;

(v) such samples of such drug and of the articles used as components thereof as the Secretary may require;

(vi) specimens of the labeling proposed to be used for such drug;

(vii) any assessments required under section 355c of this title; and

(viii) the patent number and expiration date of each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug, and that—

(I) claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent; or

(II) claims a method of using such drug for which approval is sought or has been granted in the application.

....

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

(1) Within one hundred and eighty days after the filing of an application under subsection (b), or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(A) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

(B) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

....

(3) The approval of an application filed under subsection (b) which contains a certification required by paragraph (2) of such subsection shall be made effective on the last applicable date determined by applying the following to each certification made under subsection (b)(2)(A):

....

(E)

....

(ii) If an application submitted under subsection (b) for a drug, no active moiety (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any

successor regulations)) of which has been approved in any other application under subsection (b), is approved after September 24, 1984, no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in subsection (b)(1)(A)(i) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) before the expiration of five years from the date of the approval of the application under subsection (b), except that such an application may be submitted under subsection (b) after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A). The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) for a drug, which includes an active moiety (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any successor regulations)) that has been approved in another application approved under subsection (b), is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) for the conditions of approval of such drug in the approved

subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) if the investigations described in subsection (b)(1)(A)(i) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(iv) If a supplement to an application approved under subsection (b) is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) if the investigations described in subsection (b)(1)(A)(i) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(v) If an application (or supplement to an application) submitted under subsection (b) for a drug, which includes an active moiety (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any successor regulations)) that has been approved in another application under subsection (b), was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection and for which the investigations described in subsection (b)(1)(A)(i) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were

conducted and which refers to the drug for which the subsection (b) application was submitted effective before the expiration of two years from September 24, 1984.

....

(5)(A) The Secretary may rely upon qualified data summaries to support the approval of a supplemental application, with respect to a qualified indication for a drug, submitted under subsection (b), if such supplemental application complies with subparagraph (B).

(B) A supplemental application is eligible for review as described in subparagraph (A) only if—

(i) there is existing data available and acceptable to the Secretary demonstrating the safety of the drug; and

(ii) all data used to develop the qualified data summaries are submitted to the Secretary as part of the supplemental application.

....

(d) Grounds for refusing application; approval of application; “substantial evidence” defined

....

The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for marketing approval of a drug.

....

(j) Abbreviated new drug applications

(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

(2)(A) An abbreviated application for a new drug shall contain—

(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed

under paragraph (7) (hereinafter in this subsection referred to as a “listed drug”);

(ii)(I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;

(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of section 321(p) of this title, and such other information respecting the different active ingredient with respect to which the petition was filed as the Secretary may require;

(iii) information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug referred to in clause (i) or, if the route of administration, the dosage form, or the strength of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), such information respecting the route of administration, dosage form, or strength with respect to which the petition was filed as the Secretary may require;

(iv) information to show that the new drug is bioequivalent to the listed drug referred to in clause (i), except that if the application is filed pursuant to the approval of a petition filed

under subparagraph (C), information to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in clause (i) and the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in clause (i);

(v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers;

(vi) the items specified in clauses (ii) through (vi) of subsection (b)(1)(A);

(vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c)—

(I) that such patent information has not been filed,

(II) that such patent has expired,

(III) of the date on which such patent will expire, or

(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

....

(7)(A)(i) Within sixty days of September 24, 1984, the Secretary shall publish and make available to the public—

(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) before September 24, 1984;

(II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and

(III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published.

....

(iv) For each drug included on the list, the Secretary shall specify any exclusivity period that is applicable, for which the Secretary has determined the expiration date, and for which such period has not yet expired, under—

(I) clause (ii), (iii), or (iv) of subsection (c)(3)(E);

(II) clause (iv) or (v) of paragraph (5)(B);

(III) clause (ii), (iii), or (iv) of paragraph (5)(F);

(IV) section 355a of this title;

(V) section 355f of this title;

(VI) section 360cc(a) of this title; or

(VII) subsection (u).

....

(t) Database for authorized generic drugs

(1) In general

(A) Publication

The Commissioner shall—

(i) not later than 9 months after September 27, 2007, publish a complete list on the Internet Web site of the Food and Drug Administration of all authorized generic drugs (including drug trade name, brand company manufacturer, and the date the authorized generic drug entered the market); and

(ii) update the list quarterly to include each authorized generic drug included in an annual report submitted to the Secretary by the sponsor of a listed drug during the preceding 3-month period.

(B) Notification

The Commissioner shall notify relevant Federal agencies, including the Centers for Medicare & Medicaid Services and the Federal Trade Commission, when the Commissioner first publishes the information described in subparagraph (A) that the information has been published and that the information will be updated quarterly.

(2) Inclusion

The Commissioner shall include in the list described in paragraph (1) each authorized generic drug included in an annual report submitted to the Secretary by the sponsor of a listed drug after January 1, 1999.

(3) Authorized generic drug

In this section, the term “authorized generic drug” means a listed drug (as that term is used in subsection (j)) that—

(A) has been approved under subsection (c); and

(B) is marketed, sold, or distributed directly or indirectly to retail class of trade under a different labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trade mark than the listed drug.

....

21 C.F.R. § 314.3. Definitions

....

(b) The following definitions of terms apply to this part and part 320 of this chapter:

....

Active ingredient is any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

Active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

....

Application, new drug application, or NDA is the application described under § 314.50, including all amendments and supplements to the application. An NDA refers to “stand-alone” applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and to 505(b)(2) applications.

....

Dosage form is the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product. This includes such factors as:

- (1) The physical appearance of the drug product;
- (2) The physical form of the drug product prior to dispensing to the patient;
- (3) The way the product is administered; and
- (4) The design features that affect frequency of dosing.

....

Listed drug is a new drug product that has been approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act for safety and effectiveness or under section 505(j) of the Federal Food, Drug, and Cosmetic Act, which has not been withdrawn or suspended under section 505(e)(1) through (5) or section 505(j)(6) of the Federal Food, Drug, and Cosmetic Act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification in the current edition of FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (the list) as an approved drug. A drug product is deemed to be a listed drug on the date of approval for the NDA or ANDA for that drug product.

CENTER FOR MEDICARE

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
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DATE: October 2, 2024

TO: Interested Parties

FROM: Meena Seshamani, M.D., Ph.D., CMS Deputy Administrator and Director of the Center for Medicare

SUBJECT: Medicare Drug Price Negotiation Program: Final Guidance, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2027 and Manufacturer Effectuation of the Maximum Fair Price in 2026 and 2027

This memorandum provides interested parties with the final Medicare Drug Price Negotiation Program (the “Negotiation Program”) guidance for initial price applicability year 2027 and manufacturer effectuation of the maximum fair price (MFP) in 2026 and 2027. It includes four sections:

- A. An [introduction](#), which begins on page 1.
- B. A [summary of changes and clarifications to the draft guidance](#) released on May 3, 2024, which begins on page 3.
- C. A [summary of the public comments](#) received in response to the draft guidance and the Centers for Medicare & Medicaid Services’ (CMS’) responses, which begins on page 9.
- D. [Final guidance](#) that establishes policies on the topics discussed for initial price applicability year 2027 and manufacturer effectuation of the MFP in 2026 and 2027, which begins on page 160 and for which a table of contents appears on page 162.

CMS may supplement this guidance with further program instruction to explain how these policies will be implemented for initial price applicability year 2027 and during 2026 and 2027. Additionally, as discussed in this memorandum, CMS intends to engage in rulemaking to propose certain policies under Medicare Part D that relate to or have implications for the Negotiation Program but involve exercising authorities under the Social Security Act (hereinafter “the Act”) that are not subject to the IRA’s program instruction requirement.

A. Introduction

Sections 11001(c) and 11002(c) of the Inflation Reduction Act of 2022 (IRA) direct the Secretary of the Department of Health and Human Services (hereinafter “the Secretary”) to implement the Negotiation Program provisions in sections 11001 and 11002 of the IRA, including amendments made by such sections, for 2026, 2027, and 2028 by program instruction or other forms of program guidance. In accordance with the law, on May 3, 2024, CMS issued draft guidance for implementation of the Negotiation Program for initial price applicability year

Identification of Qualifying Single Source Drugs for Initial Price Applicability Year 2027
(Section 30.1)

Comment: One commenter suggested a specific drug be selected for initial price applicability year 2027.

Response: CMS notes that it will select drugs for negotiation in accordance with sections 11001 and 11002 of the IRA.

Comment: CMS received many comments on its reading of the statute to aggregate all dosage forms and strengths of a drug with the same active moiety and the same holder of a New Drug Application (NDA) or of a biological product with the same active ingredient and the same holder of a Biologics License Application (BLA), for the purposes of identifying potential qualifying single source drugs. Many commenters disagreed with CMS' definition of a qualifying single source drug and asserted that CMS guidance contradicts the statute. Many of these commenters claimed that the statute defines a qualifying single source drug in reference to a distinct NDA or BLA, and a few of these commenters stated that it would be reasonable and appropriate that such a definition would align with the FDA's approval and licensure processes under section 505(c) of the Federal Food Drug and Cosmetic Act ("FD&C Act") or section 351(a) of Public Health Services Act ("PHS Act"). One commenter claimed that the statute defines a qualifying single source drug by reference to the definition of a "covered Part D drug" at section 1860D-2(e) of the Act, which in turn cross-references the definition of "covered outpatient drug" at section 1927(k)(2) of the Act. The commenter asserted that, under section 1927(k)(2) of the Act, whether a single source drug is a distinct "covered outpatient drug" is based on whether the product is approved pursuant to a distinct NDA or BLA, and the only exception to this rule is for line extensions.⁹ A few other commenters appreciated CMS' consistent approach to the qualifying single source drug definition and supported the current definition. These commenters stated that this policy is critical in preventing manufacturers from gaming the drug selection process and finding inappropriate ways to exclude from the Negotiation Program drug products that might otherwise be eligible and underscored that it is consistent with section 1192(d)(3)(B) of the Act. One of these commenters specified that this policy will reduce incentives for "product hopping," wherein a manufacturer would obtain a new NDA or BLA based solely on modifications that are modest or minor—and which often do not result in increased efficacy or improved outcomes—in order to effectively reset the 7- or 11-year periods that must pass before a product is eligible as a qualifying single source drug.

Response: As discussed in CMS' response on pages 11 and 12 of the revised guidance for initial price applicability year 2026, section 1192(d)(3)(B) of the Act directs CMS to "use data that is aggregated across dosage forms and strengths of the drug, including new formulations of the drug, such as an extended release formulation, and not based on the specific formulation or package size or package type of the drug" for purposes of determining whether a qualifying single source drug is a negotiation-eligible drug. Similarly, section 1196(a)(2) of the Act directs

⁹ Section 1927(c)(2)(C) of the Act defines a "line extension" as, "with respect to a drug, a new formulation of the drug, such as an extended release formulation, but does not include an abuse-deterrent formulation of the drug (as determined by the Secretary), regardless of whether such abuse-deterrent formulation is an extended release formulation."

CMS to establish procedures “to compute and apply the maximum fair price across different strengths and dosage forms of a selected drug and not based on the specific formulation or package size or package type of such drug.” In addition, section 1194(e)(1)(D) of the Act instructs CMS, for purposes of the negotiation process discussed in further detail in section 60 of this final guidance, to consider, among other information, “applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic Act or section 351(a) of the Public Health Service Act,” in the plural, for the “drug,” in the singular. The aggregation rules under sections 1192(d)(3)(B), 1194(e)(1)(D), and 1196(a)(2) of the Act are clear and are designed to ensure that the Negotiation Program delivers benefits to the Medicare program and its beneficiaries as intended by the law. Because different dosage forms and strengths, as well as different formulations, containing the same active moiety / active ingredient may be approved or licensed under multiple NDAs or BLAs, the suggestion from commenters to define a qualifying single source drug in reference to a distinct NDA or BLA is inconsistent with sections 1192(d)(3)(B) and 1196(a)(2) of the Act. Contrary to the views of some commenters, such section 1192(d)(3)(B) refers to the aggregation of data “across dosage forms and strengths of the drug, including new formulations of the drug,” thereby necessarily establishing that the statutory negotiation procedures apply more broadly than to a distinct NDA or BLA. Unlike the views offered by some commenters, CMS’ understanding of the statutory language gives full effect to all relevant provisions of the statute, including sections 1192(d)(3)(B), 1192(e), 1194(e)(1)(D), and 1196(a)(2) of the Act; CMS is applying an interpretation of the statute that follows the statutory criteria for the identification of a qualifying single source drug under section 1192(e) of the Act and, consistent with sections 1192(d)(3)(B), 1194(e)(1)(D), and 1196(a)(2) of the Act, gives effect to the statutory policy that a drug that may be selected for negotiation includes multiple dosage forms and strengths and formulations of that drug.

CMS agrees with commenters that complying with the statutory requirement to identify a qualifying single source drug using data that is aggregated across different dosage forms and strengths, as described in the draft guidance, will decrease incentives for pharmaceutical manufacturers to engage in “product hopping.” This statutory requirement ensures that products by the same sponsor with the same active moiety / active ingredient are subject to the same processes under the Negotiation Program, and that a manufacturer is therefore limited in its ability to inappropriately exclude from the Negotiation Program drug products that might otherwise be eligible based on modest or minor modifications. Reducing “product hopping” is consistent with the purpose of the statute, which is to ensure that the Negotiation Program delivers benefits to the Medicare program and its beneficiaries. For the above reasons, in this final guidance, CMS maintains the approach described in the draft guidance for identifying potential qualifying single source drugs.

Comment: Many commenters stated that CMS’ definition of a qualifying single source drug is overly broad and expressed concerns that it will be detrimental to future innovation and patient access to medications and limit manufacturers from researching new formulations or routes of administration, post-approval research, follow-on indications for selected drugs, new products that address unmet medical needs, and orphan drug development. One commenter asked CMS to explore with the wider patient community the degree to which the definition of qualifying single source drug may constitute a deterrent for investment and research into novel indications. One commenter raised concern that identifying a potential qualifying single source drug using data

aggregated across dosage forms and strengths of the drug, including new formulations, and recommended that the MFP should align to each distinct dosage form of the drug because manufacturing costs vary based on product form. One commenter recommended that CMS use a case-by-case analysis when deciding whether to aggregate products, stating that minor changes like formulation or labeling updates should be aggregated under the same qualifying single source drug and that meaningful product approval data, when available, should be considered when deciding if a product should be aggregated into a qualifying single source drug or be considered as its own standalone qualifying single source drug.

Response: CMS thanks these commenters for their input. As discussed in CMS' response on page 12 of the revised guidance for initial price applicability year 2026, CMS is committed to recognizing the clinical benefit of products, including products with different dosage forms and strengths, formulations or routes of administration from other products that are aggregated as part of the same qualifying single source drug, and directs readers to section 60.3.3 of this final guidance, which details CMS' approach to adjusting the starting point for an initial offer based on section 1194(e)(2) factors, which includes factors related to clinical benefit as compared to therapeutic alternatives. As further illustrated by section 60.3.3, the negotiation process aims to reward manufacturers' innovation and improved benefits across patient populations.

CMS appreciates the commenters' suggestions for alternate aggregation approaches but will continue to use the process outlined in section 30.1 of this final guidance. As stated in section 60.1 of this final guidance, CMS will identify a single price for use at each step in the negotiation process described in section 60, meaning each offer and counteroffer, described in section 60.4 of this final guidance, will include a single price, even for a selected drug with multiple dosage forms and strengths. Section 60.5 of this final guidance details how the MFP will be applied across dosage forms and strengths.

Comment: A couple of commenters expressed support for the draft guidance policy on fixed combination drugs with two or more active moieties / active ingredients, which treats the distinct combination of active moieties / active ingredients as one active moiety / active ingredient for the purpose of identifying potential qualifying single source drugs. A couple of commenters raised a concern that this policy creates a gaming opportunity and a way for manufacturers to evade negotiation and frustrate competition by allowing strategic development by manufacturers of combination products that would not differ significantly from the original single product, not contribute directly to the drug's therapeutic effect, and provide minimal additional patient benefit. One commenter recommended that CMS use a case-by-case methodology for aggregating fixed combination drugs into qualifying single source drugs, and they requested that CMS treat each formulation of a vaccine as a distinct fixed combination biologic product, precluding aggregation with earlier versions of the vaccine and resetting the 11-year post licensure eligibility timeframe.

Response: As discussed in CMS' response on pages 13 and 14 of the revised guidance for initial price applicability year 2026, CMS appreciates commenters' support for its interpretation of the statutory language and acknowledges the concern outlined by commenters. CMS will treat a fixed combination drug as distinct in its composition from the individual active moieties / active ingredients and in this final guidance maintains its approach on fixed combination drugs, which

treats the distinct combination of active moieties / active ingredients as one active moiety / active ingredient for the purpose of identifying qualifying single source drugs. Section 30.1 of this final guidance details how CMS intends to treat fixed combination drugs and gives an example to illustrate the application. The policies described in section 30.1 of this final guidance apply no differently to vaccines than to other products.

Comment: A few commenters asserted that the distinct time periods for when a drug and a biological product will be eligible for negotiation are arbitrary and that CMS should implement the Negotiation Program so that, for any drug or biological product to qualify as a qualifying single source drug, the same number of years must have elapsed since the drug or biological product was approved or licensed, respectively. One commenter stated their support for statutory changes that would require CMS to treat all genetically targeted therapies as biologics that could be negotiated after 13 years since approval or licensure by the FDA.

Response: CMS thanks these commenters for their feedback and suggestions. As discussed in CMS' response on page 13 of the revised guidance for initial price applicability year 2026, section 1192(e)(1)(A)(ii) of the Act states that for a drug product to be considered a qualifying single source drug, at least 7 years must have elapsed since the drug product was approved by the FDA.¹⁰ Section 1192(e)(1)(B)(ii) of the Act states that for a biological product to be considered a qualifying single source drug, at least 11 years must have elapsed since the biological product was licensed by the FDA.¹¹ CMS is implementing the Negotiation Program in accordance with these statutory requirements.

Comment: One commenter expressed concern regarding CMS' statement in section 30.1 of the draft guidance that, if there are multiple NDAs or BLAs with the same active moiety or active ingredient with non-identical names reported for the NDA or BLA holder, CMS will investigate whether such NDAs or BLAs are held by the same entity for the purposes of identifying a potential qualifying single source drug. This commenter asserted that CMS does not explain the scope of the investigation, nor the factors CMS will consider in making its determination, and asked CMS to clarify what it intends by this statement. This commenter also asked for clarity regarding whether CMS intends to aggregate across NDAs and BLAs to include NDA and BLA holders that are different entities.

Response: In the course of CMS' review of potential qualifying single source drugs, CMS has found, in rare circumstances, NDAs and BLAs with the same active moiety or active ingredient that appeared to be held by the same entity had non-identical names reported for the NDA holder or BLA holder due to inconsistencies in manufacturer reporting to FDA, such as typos or unstandardized use of abbreviations in the NDA or BLA holder name, and situations where it appears the NDA or BLA holder name has not yet been updated. In such circumstances, CMS

¹⁰ For drug products, to determine the date of approval for a potential qualifying single source drug with more than one FDA application number, section 30.1 of this final guidance specifies that CMS will use the earliest date of approval of the initial FDA application number assigned to an NDA for the active moiety for which the manufacturer is the holder of the NDA.

¹¹ For biological products, to determine the date of approval for a potential qualifying single source drug with more than one FDA application number, section 30.1 of this final guidance specifies that CMS will use the earliest date of licensure of the initial FDA application number assigned to a BLA for the active ingredient for which the manufacturer is the holder of the BLA.

may further investigate whether such NDA(s) and BLA(s) are held by the same entity for the purposes of identifying a potential qualifying single source drug using FDA sources that are publicly available and other relevant publicly available sources as CMS deems appropriate (as described in section 30.1 of this final guidance). For example, CMS may consider manufacturer names included on FDA labels or correspondence between FDA and manufacturers, the complete applicant name in the Orange Book, and other public sources to determine whether the holders of the NDAs or BLAs are the same entity. This investigation will not be used to aggregate across NDA or BLA holder names that do not represent the same entity.

Comment: One commenter stated that CMS statements are “inconsistent and ill-defined” regarding how CMS will identify a drug’s active moiety or active ingredient, and that this identification is pivotal to determining the “drug bundle.” The commenter referenced an October 2023 FAQ document available on the CMS website at <https://www.cms.gov/files/document/medicare-drug-price-negotiation-program-faqs-ipay-2026.pdf> for initial price applicability year 2026 that stated CMS used the National Library of Medicine’s RxNorm database to identify active ingredient(s) for biological products, and a combination of RxNorm and FDA’s Active Ingredient-Active Moiety Relationship / Basis of Strength file to identify active moiety(ies) for small molecule drugs. The commenter stated that, in the Proposed MFP File Layout and Definitions Document,¹² CMS changed how it identifies “active moiety” for small molecule drugs and updated its position by identifying a specific field, the “Ingredient” / IN field within RxNorm to identify active ingredient for biologics. The commenter also argued that CMS’ approach could lead to inaccurate results that are contrary to determinations made by FDA. The commenter recommended that CMS refer to a drug’s nonproprietary name appearing in its FDA labeling and approval documents (typically the United States Adopted Name (USAN) as identified by FDA) to identify the active moiety for small molecule drugs and active ingredients for biologics instead of relying on RxNorm and reconciling multiple, potentially conflicting, fields within that database.

Response: CMS thanks this commenter for the feedback but disagrees with the statement that CMS has been inconsistent in its approach to identifying active moiety for small molecule drugs and active ingredient for biologics; both the October 2023 FAQ document and the Proposed MFP File Layout and Definitions Document accurately state that CMS used RxNorm to identify active ingredients for biologics. As a result of operational refinements, CMS has described in section 30.1 of this final guidance that it may use additional sources beyond those specific fields in RxNorm and FDA’s Active Ingredient-Active Moiety Relationship / Basis of Strength file to identify the active moiety or active ingredient of the drug, such as OpenFDA and FDALabel, for drug selection for initial price applicability year 2027. CMS may also consult with FDA as needed, for example, to clarify whether a suffix or prefix in an active moiety or active ingredient name represents a genuine difference in active moiety or active ingredient. CMS’ experience to date is that the “Ingredient” / IN field within RxNorm and the “active moiety” field within FDA’s Active Ingredient-Active Moiety Relationship / Basis of Strength file may not be standardized because they are derived from multiple non-standardized data sources. Therefore, the use of additional sources may on occasion be helpful to properly identify the active moiety or active ingredient consistent with the statute.

¹² Proposed Maximum Fair Price File Layout and Definitions Document. Released May 3, 2024.
<https://www.cms.gov/files/zip/proposed-maximum-fair-price-file-layout-and-definitions-document.zip>.

payment between pharmaceutical supply chain entities. Given the timing overlap between the development of the final guidance for initial price applicability year 2027 and the negotiation period for initial price applicability year 2026, CMS has made certain additional adjustments in the final guidance based on the agency's experience, including experience from the first cycle of negotiations.

In accordance with sections 11001 and 11002 of the IRA, which created Part E under Title XI of the Act (sections 1191 through 1198), the Secretary is required to establish the Negotiation Program to negotiate MFPs for certain high expenditure, single source drugs covered by Medicare. With respect to each initial price applicability year, CMS shall: (1) publish a list of selected drugs in accordance with section 1192 of the Act; (2) enter into agreements with manufacturers of selected drugs in accordance with section 1193 of the Act; (3) negotiate and, if applicable, renegotiate MFPs for such selected drugs, in accordance with section 1194 of the Act; (4) publish MFPs for selected drugs in accordance with section 1195 of the Act; (5) carry out administrative duties and compliance monitoring in accordance with section 1196 of the Act; and (6) impose civil monetary penalties (CMPs) in accordance with section 1197 of the Act. Section 1198 of the Act establishes certain limitations on administrative and judicial review relevant to the Negotiation Program.

To allow for public input, CMS voluntarily solicited comments on all sections of the draft guidance, except for section 90.3 (which states that the Department of the Treasury is in the process of rulemaking to establish regulations that govern the administration of the excise tax).

Topics that are not relevant to Negotiation Program implementation for initial price applicability year 2027 or for MFP effectuation in 2026 and 2027 are not addressed in this guidance. CMS intends to provide additional information in the future related to implementation for initial price applicability year 2028 and beyond.

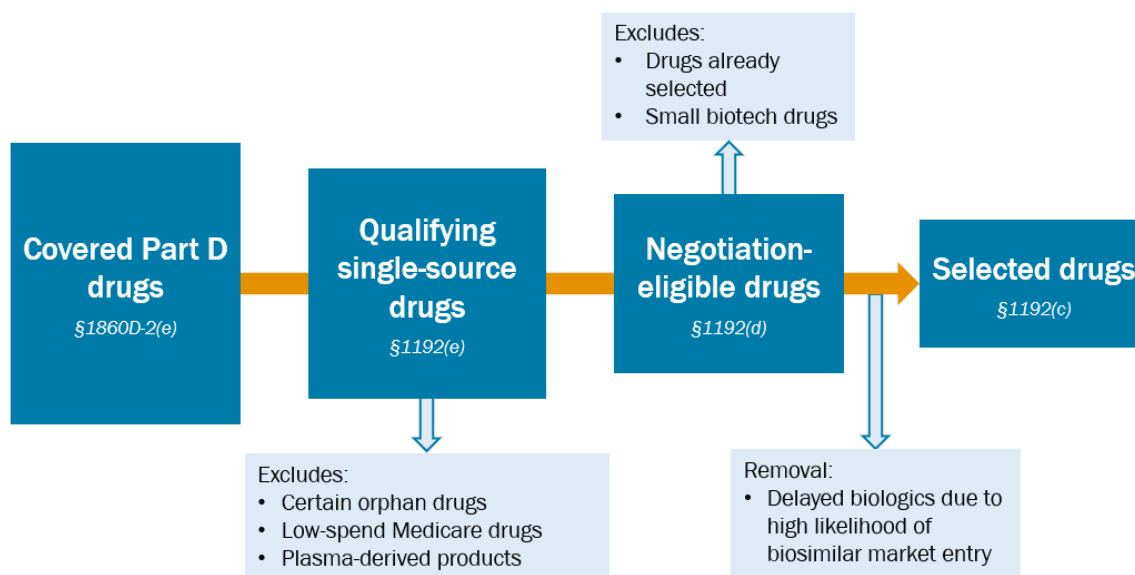
30. Identification of Selected Drugs for Initial Price Applicability Year 2027

Section 1192 of the Act establishes the requirements governing the identification of qualifying single source drugs, the identification of negotiation-eligible drugs, the ranking of negotiation-eligible drugs and identification of selected drugs, and the publication of the list of selected drugs for an initial price applicability year. First, CMS will identify qualifying single source drugs in accordance with section 1192(e) of the Act, as described in section 30.1 of this final guidance. CMS will exclude certain drugs in accordance with section 1192(e)(3) of the Act. Next, in accordance with section 1192(d) of the Act, using Total Expenditures⁵⁴ under Part D of Title XVIII of the Act for these qualifying single source drugs calculated using Part D prescription drug event (PDE) data for dates of service between November 1, 2023, and October 31, 2024, and other information described below, CMS will identify negotiation-eligible drugs for initial price applicability year 2027 as described in section 30.2 of this final guidance (in this step, CMS will also exclude certain drugs in accordance with sections 1192(d)(2) and (3) of the Act).

⁵⁴ For the purposes of the Negotiation Program, Total Expenditures under Part D of Title XVIII are defined in section 1191(c)(5) of the Act as total gross covered prescription drug costs (as defined in section 1860D-15(b)(3)). The term "gross covered prescription drug costs" is also defined in the Part D regulations at 42 C.F.R. § 423.308.

In accordance with section 1192(d)(1) of the Act, CMS will rank negotiation-eligible drugs for initial price applicability year 2027 according to the Total Expenditures for such drugs under Part D of Title XVIII for the 12-month period (defined above), as described in section 30.3 of this final guidance. In accordance with section 1192(a) of the Act and subject to the Special Rule to delay the selection and negotiation of biologics for biosimilar market entry described in section 1192(f) of the Act, CMS will select up to 15 negotiation-eligible drugs with the highest Total Expenditures under Part D of Title XVIII of the Act for negotiation for initial price applicability year 2027 (described in section 30.3 of this final guidance) and publish a list of up to 15 selected drugs not later than February 1, 2025 (described in section 30.4 of this final guidance). Figure 1 provides a visual depiction of this process. Detailed guidance pertaining to this process for initial price applicability year 2027 is included further below.

Figure 1: Diagram of Process for Selecting Drugs for Negotiation for Initial Price Applicability Year 2027



30.1 Identification of Qualifying Single Source Drugs for Initial Price Applicability Year 2027

For initial price applicability year 2027, in accordance with section 1192(e)(1) of the Act, CMS will define a qualifying single source drug as a covered Part D drug (as defined in section 1860D-2(e) of the Act) that meets the following criteria:

- For drug products, a qualifying single source drug is a drug: (1) that is approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act (“FD&C Act”) and marketed pursuant to such approval; (2) for which, as of the selected drug publication date with respect to a given initial price applicability year, at least 7 years have elapsed since the date of such approval; and (3) that is not the listed drug for any drug approved and marketed under an Abbreviated New Drug Application (ANDA) under section 505(j) of the FD&C Act.

- For biological products, a qualifying single source drug is a biological product: (1) that is licensed under section 351(a) of the Public Health Service Act (“PHS Act”) and marketed pursuant to such licensure; (2) for which, as of the selected drug publication date with respect to a given initial price applicability year, at least 11 years have elapsed since the date of such licensure; and (3) that is not the reference product for any biological product that is licensed and marketed under section 351(k) of the PHS Act.

Section 1192(d)(3)(B) of the Act states that CMS shall use data that are aggregated across dosage forms and strengths of the drug, including new formulations of the drug, such as an extended release formulation, and not based on the specific formulation, package size, or package type of the drug for purposes of determining whether a qualifying single source drug is a negotiation-eligible drug under section 1192(d)(1) of the Act and applying the exception for small biotech drugs under section 1192(d)(2) of the Act. Similarly, section 1196(a)(2) of the Act directs CMS to establish procedures “to compute and apply the maximum fair price across different strengths and dosage forms of a selected drug and not based on the specific formulation or package size or package type of such drug.” In addition, section 1194(e)(1)(D) of the Act instructs CMS, for purposes of the negotiation process discussed in further detail in section 60 of this final guidance, to consider, among other information, “applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic Act or section 351(a) of the Public Health Service Act,” in the plural, for the “drug,” in the singular.

Identifying potential qualifying single source drugs:

In accordance with the statutory language cited above, for purposes of the Negotiation Program, CMS will identify a potential qualifying single source drug⁵⁵ using:

- For drug products, all dosage forms and strengths of the drug with the same active moiety and the same holder of a New Drug Application (NDA),⁵⁶ inclusive of products that are marketed pursuant to different NDAs. If there are multiple NDAs with the same active moiety that include non-identical names reported for the NDA holder, including situations where it appears the NDA holder name has not yet been updated, CMS may further investigate whether such NDA(s) are held by the same entity for the purposes of identifying a potential qualifying single source drug using U.S. Food and Drug Administration (FDA) sources that are publicly available and other relevant publicly available sources as CMS deems appropriate. The potential qualifying single source drug will also include all dosage forms and strengths of the drug with the same active moiety and marketed pursuant to the same NDA(s) described in the prior sentences that are: (1) repackaged and relabeled products⁵⁷ that are marketed pursuant to such NDA(s); (2) authorized generic drugs that are marketed pursuant to such NDA(s); or (3) multi-market

⁵⁵ Throughout this final guidance, a qualifying single source drug means the specific constituent dosage forms and strengths (at the NDC-9 or NDC-11 level) that are identified as aggregated under the New Drug Application (NDA(s)) / Biologics License Application (BLA(s)) for the active moiety / active ingredient as outlined in section 30.1 of this final guidance.

⁵⁶ As described in section 505(c) of the FD&C Act.

⁵⁷ For purposes of the Negotiation Program, the terms “repackage” and “relabel” have the meaning specified in 21 C.F.R. § 207.1.

approval (MMA)⁵⁸ products imported under section 801(d)(1)(B) of the FD&C Act that are marketed pursuant to such NDA(s);⁵⁹

- For biological products, all dosage forms and strengths of the biological product with the same active ingredient and the same holder of a Biologics License Application (BLA),⁶⁰ inclusive of products that are marketed pursuant to different BLAs. If there are multiple BLAs with the same active ingredient that include non-identical names reported for the BLA holder, including situations where it appears the BLA holder name has not yet been updated, CMS may further investigate whether such BLA(s) are held by the same entity for the purposes of identifying a potential qualifying single source drug using FDA sources that are publicly available and other relevant publicly available sources as CMS deems appropriate. The potential qualifying single source drug will also include all dosage forms and strengths of the biological product with the same active ingredient and marketed pursuant to the same BLA(s) described in the prior sentences that are: (1) repackaged and relabeled products that are marketed pursuant to such BLA(s); (2) authorized biological products that are marketed pursuant to such BLA(s); or (3) MMA products imported under section 801(d)(1)(B) of the FD&C Act that are marketed pursuant to such BLA(s).⁶¹

CMS will identify the active moiety or active ingredient of the drug using public sources such as RxNorm, OpenFDA, FDALabel, and FDA's Active Ingredient-Active Moiety Relationship/Basis of Strength file. CMS may also consult with FDA as appropriate to, for example, clarify whether a suffix or prefix in an ingredient name represents a genuine difference in active ingredient.

As an example, illustrated in Table 1 below, Entity A holds three NDAs for drug products with the same active moiety approved in NDA-1, NDA-2, and NDA-3. Entity A manufactures and markets three different strengths as an immediate release tablet pursuant to NDA-1, three different strengths as an extended-release tablet pursuant to NDA-2, and three different strengths as an oral solution pursuant to NDA-3. Additionally, under an agreement with Entity A, Entity B repackages three strengths of the immediate release tablets manufactured by Entity A and markets them pursuant to NDA-1. In this scenario, all 12 of these drug products, including the repackaged products, will be aggregated as a single potential qualifying single source drug for purposes of identifying negotiation-eligible drugs.

Table 1: Example Application of NDAs Containing the Same Active Moiety to Identification of a Potential Qualifying Single Source Drug

⁵⁸ See: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/importation-certain-fda-approved-human-prescription-drugs-including-biological-products-and>.

⁵⁹ Any dosage forms and strengths of the drug with the same active moiety that are distributed by a private label distributor and marketed pursuant to such NDAs will also be aggregated in the potential qualifying single source drug of that holder of the NDA.

⁶⁰ As described in section 351(a) of the PHS Act.

⁶¹ Any dosage forms and strengths of the biological product with the same active ingredient that are distributed by a private label distributor and marketed pursuant to such BLAs will also be aggregated in the potential qualifying single source drug of that holder of the BLA.

NDA's containing the same active moiety	NDCs marketed by Entity A (holder of NDA-1, NDA-2, and NDA-3)	NDCs repackaged and marketed by Entity B
NDA-1	NDC #1, NDC #2, NDC #3	NDC #10, NDC #11, NDC #12
NDA-2	NDC #4, NDC #5, NDC #6	
NDA-3	NDC #7, NDC #8, NDC #9	
12 Total NDCs included in this single potential qualifying single source drug		

This approach to identifying a potential qualifying single source drug aligns with the requirement in section 1192(d)(3)(B) of the Act to use data aggregated across dosage forms and strengths of the drug, including new formulations of the drug. Consistent with this statutory instruction, this approach is also appropriate because CMS is aware that existing NDA / BLA holders have obtained approval for new dosage forms or different routes of administration of the same active moiety / active ingredient under different NDAs or BLAs.

Section 1192(e)(2)(A) of the Act states that an authorized generic drug and the qualifying single source drug that is the listed drug or reference product of that authorized generic drug shall be treated as the same qualifying single source drug. An authorized generic drug is defined in section 1192(e)(2)(B) of the Act as: (1) in the case of a drug product, an authorized generic drug (as such term is defined in section 505(t)(3) of the FD&C Act); and (2) in the case of a biological product, a product that has been licensed under section 351(a) of the PHS Act⁶² and is marketed, sold, or distributed directly or indirectly to the retail class of trade under a different labeling, packaging (other than repackaging as the reference product in blister packs, unit doses, or similar packaging for institutions), product code, labeler code, trade name, or trademark than the reference product.

If a drug is a fixed combination drug⁶³ with two or more active moieties / active ingredients, the distinct combination of active moieties / active ingredients will be considered as one active moiety / active ingredient for the purpose of identifying potential qualifying single source drugs. Therefore, all formulations of this distinct combination offered by the same NDA / BLA holder will be aggregated across all dosage forms and strengths of the fixed combination drug. A product containing only one (but not both) of the active moieties / active ingredients that is offered by the same NDA / BLA holder will not be aggregated with the formulations of the fixed combination drug and will be considered a separate potential qualifying single source drug. For example, a corticosteroid inhaler would not be aggregated with a fixed combination inhaler from the same NDA / BLA holder that contains the same corticosteroid combined with a long-acting beta agonist. In this example, the corticosteroid inhaler would be considered as a separate potential qualifying single source drug from the fixed combination inhaler.

Applying statutory criteria for qualifying single source drugs:

⁶² CMS is interpreting the reference to “licensed under section 351(a) of such Act” to mean licensed under section 351(a) of the PHS Act. Section 351(a) of the PHS Act addresses the licensure of a biological product.

⁶³ For purposes of the Negotiation Program, the term “fixed combination drug” has the meaning specified in 21 C.F.R. § 300.50.

In accordance with section 1192(e)(1) of the Act, to be considered a qualifying single source drug, at least 7 years (for drug products) or 11 years (for biological products) must have elapsed between the FDA date of approval or licensure, as applicable, and the selected drug publication date. To determine the date of approval or licensure for a potential qualifying single source drug with more than one FDA application number, CMS will use the earliest date of approval or licensure of the initial FDA application number assigned to the NDA / BLA holder for the active moiety / active ingredient, or in the case of fixed combination drugs, for the distinct combination of active moieties / active ingredients. The selected drug publication date for initial price applicability year 2027 is February 1, 2025, as specified in section 1191(b)(3) of the Act. As such, for initial price applicability year 2027, the initial approval for a drug product to be considered a qualifying single source drug must have been on or before February 1, 2018, and the date of initial licensure for a biological product to be considered a qualifying single source drug must have been on or before February 1, 2014.

For example, if 12 years had elapsed between the original approval for NDA-1 cited in the previous example above and February 1, 2025, then the potential qualifying single source drug defined above would meet this statutory criterion for qualifying single source drugs (even if less than seven years had elapsed between the approval dates for NDA-2 or NDA-3 and February 1, 2025), consistent with the statutory directive in section 1192(d)(3)(B) of the Act to aggregate data across dosage forms and strengths of the drug, including new formulations of the drug.

In accordance with section 1192(e)(1) of the Act, to be considered a qualifying single source drug, a product cannot be the listed drug for any drug approved and marketed under an ANDA under section 505(j) of the FD&C Act, and a biological product cannot be the reference product for any biological product that is licensed and marketed under section 351(k) of the PHS Act. CMS will use FDA reference sources, including the Orange Book⁶⁴ and Purple Book,⁶⁵ to determine whether a generic drug or biosimilar biological product⁶⁶ has been approved or licensed for any of the strengths or dosage forms of the potential qualifying single source drugs for initial price applicability year 2027.

CMS will consider a generic drug or biosimilar to be marketed when the totality of the circumstances, including the data specified below, reveals that the manufacturer of that approved generic drug or licensed biosimilar is engaging in bona fide marketing of that drug or biosimilar. In accordance with sections 1192(c) and (e) of the Act for the purpose of identifying qualifying single source drugs for initial price applicability year 2027, CMS will review PDE data for the 12-month period beginning January 16, 2024 and ending January 15, 2025, using PDE data

⁶⁴ See: <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm>.

⁶⁵ See: <https://purplebooksearch.fda.gov/>.

⁶⁶ The terms “biosimilar biological product” and “biosimilar” mean the same thing for purposes of sections 11001 and 11002 of the IRA. Specifically, section 1192(f)(5) of the Act, as added by section 11002 of the IRA, uses the meaning given to “biosimilar biological product” from section 1847A(c)(6) of the Act. This guidance will use the term “biosimilar” hereinafter unless otherwise noted, such as related to the discussion of the Biosimilar Delay under section 11002 of the IRA in section 30.3.1 of this final guidance. For references to biological products licensed pursuant to an application submitted under section 351(a) of the PHS Act, the term “biological product” is used.

available on January 16, 2025, as well as Average Manufacturer Price (AMP)⁶⁷ data for the 12-month period beginning December 1, 2023 and ending November 30, 2024, using the AMP data reported to CMS by December 31, 2024, for a given generic drug or biosimilar for which a potential qualifying single source drug is the listed drug or reference product. CMS has chosen these time periods to enable CMS to use the most recent possible data to make this determination while still allowing for sufficient time for such data to inform the selected drug list published no later than February 1, 2025, in accordance with section 1192(a) of the Act.

The determination whether a generic drug or biosimilar is marketed on a bona fide basis will be a holistic inquiry, but these sources of data over the specified intervals will be informative for that determination. The determination whether an approved generic drug or licensed biosimilar is being marketed on a bona fide basis is a totality of the circumstances inquiry that will not necessarily turn on any one source of data. Additional relevant factors may include whether the generic drug or biosimilar is regularly and consistently available for purchase through the pharmaceutical supply chain and whether any licenses or other agreements between a Primary Manufacturer (as defined in section 40 of this final guidance) and a generic drug or biosimilar manufacturer limit the availability or distribution of the selected drug, as articulated further in sections 70 and 90.4 of this final guidance.

If any strength or dosage form of a potential qualifying single source drug is the listed drug or reference product, as applicable, for one or more generic or biosimilar products that CMS determines are approved or licensed, as applicable, and marketed based on the process described in this final guidance, the potential qualifying single source drug will not be considered a qualifying single source drug for initial price applicability year 2027. If CMS determines that the potential qualifying single source drug will not be considered a qualifying single source drug for initial price applicability year 2027 because a manufacturer of such generic drug or biosimilar product has engaged in bona fide marketing of the generic drug or biosimilar, CMS will monitor to ensure continued bona fide marketing of the generic drug or biosimilar based on the approach described in section 90.4 of this final guidance.

30.1.1 Orphan Drug Exclusion from Qualifying Single Source Drugs

In accordance with section 1192(e)(3)(A) of the Act, CMS will exclude certain orphan drugs when identifying qualifying single source drugs as described in section 30.1 of this final guidance (“the Orphan Drug Exclusion”). Specifically, CMS will exclude a drug or biological product that is designated as a drug for only one rare disease or condition under section 526 of the FD&C Act and for which the only approved indication (or indications)⁶⁸ is for such disease or condition. To be considered for the Orphan Drug Exclusion, the drug or biological product must: (1) be designated as a drug for only one rare disease or condition under section 526 of the FD&C Act; and (2) be approved by the FDA only for one or more indications within such designated rare disease or condition. A drug that has orphan designations for more than one rare

⁶⁷ “Average Manufacturer Price” means, with respect to a covered outpatient drug of a manufacturer for a rebate period (calendar quarter), the average price paid to the manufacturer for the drug in the United States by: (i) wholesalers for drugs distributed to retail community pharmacies; and (ii) retail community pharmacies that purchase drugs directly from the manufacturer, subject to certain exclusions. See section 1927(k)(1) of the Act.

⁶⁸ For purposes of applying the Orphan Drug Exclusion, CMS understands “approved indication,” as that term is used in section 1192(e)(3)(A) of the Act, to refer to the FDA-approved indication that is described in information included in drug labeling per 21 C.F.R. § 201.57(c)(2) or other applicable FDA regulation(s).

disease or condition will not qualify for the Orphan Drug Exclusion, even if the drug has not been approved for any indications for the additional rare disease(s) or condition(s). CMS will consider only active designations and active approvals when evaluating a drug for the Orphan Drug Exclusion; that is, CMS will not consider withdrawn orphan designations or withdrawn approvals as disqualifying a drug from the Orphan Drug Exclusion.

To qualify for the Orphan Drug Exclusion, all dosage forms and strengths of the qualifying single source drug described in section 30.1 of this final guidance must meet the criteria for exclusion. CMS will use the FDA Orphan Drug Product designation database⁶⁹ and information on FDA-approved indications from other publicly available databases and documents (such as FDALabel, FDA Online Label Repository, Drugs@FDA, and NLM Daily Med⁷⁰) to determine whether a drug meets the requirements in section 1192(e)(3)(A) of the Act to qualify for the Orphan Drug Exclusion. CMS will also consult with FDA, as appropriate, including to determine whether a drug is designated for, or approved for indications for, one or more rare disease(s) or condition(s). In the event that a drug or biological product loses Orphan Drug Exclusion status, pursuant to sections 1192(e)(1)(A)(ii) and (B)(ii) of the Act, CMS will use the date of the earliest approval of the drug or licensure of the biological product (as described above in section 30.1) to determine whether the product is a qualifying single source drug that may be selected for negotiation if it meets all other Negotiation Program eligibility criteria, regardless of whether the drug or biological product previously qualified for an exclusion under section 1192(e)(3)(A) of the Act.

CMS continues to evaluate whether there are additional actions CMS can take in its implementation of the Negotiation Program to best support orphan drug development.

30.1.2 Low-Spend Medicare Drug Exclusion from Qualifying Single Source Drugs

In accordance with section 1192(e)(3)(B) of the Act, CMS will exclude low-spend Medicare drugs or biological products with less than \$200 million, increased by the percentage increase in the consumer price index for all urban consumers (CPI-U)⁷¹ for the period beginning on June 1, 2023 and ending on September 30, 2024,⁷² in combined expenditures under Medicare Part B and Part D when identifying qualifying single source drugs (“the Low-Spend Medicare Drug Exclusion”). For initial price applicability year 2027, CMS will identify low-spend Medicare drugs as follows:

- CMS will identify PDE data combined with Part B claims data for each potential qualifying single source drug for dates of service during the 12-month period beginning November 1, 2023 and ending October 31, 2024. To allow a reasonable amount of time for Part D plan sponsors to submit PDE data, CMS will use PDE data for the dates of

⁶⁹ See: <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/>.

⁷⁰ FDALabel: <https://nctr-crs.fda.gov/fdalabel/ui/search>; FDA Online Label Repository: <https://labels.fda.gov/>; Drugs@FDA: <https://www.accessdata.fda.gov/scripts/cder/daf/>; NLM Daily Med: <https://dailymed.nlm.nih.gov/dailymed/>.

⁷¹ The “CPI-U” means the consumer price index for all urban consumers (United States city average) as published by the Bureau of Labor Statistics (<https://www.bls.gov/>).

⁷² Section 1192(e)(3)(B)(ii) of the Act specifies that, for initial price applicability year 2027, CMS increase the \$200 million amount by “the annual percentage increase” in the CPI-U “for the period beginning on June 1, 2023, and ending on September 30, 2024.” CMS interprets this language to mean that, for initial price applicability year 2027, the \$200 million amount is increased by the percentage increase in the CPI-U from June 2023 to September 2024.

service described above that have been submitted no later than 30 days⁷³ after October 31, 2024, i.e., by November 30, 2024. CMS will exclude any PDE data with a compound code indicating the PDE record is for a compounded drug.⁷⁴ To allow a reasonable amount of time for providers and suppliers to submit Part B claims, CMS will use Part B claims data for the dates of service described above that have been submitted no later than 30 days after October 31, 2024, i.e., by November 30, 2024.

- For each potential qualifying single source drug as described in section 30.1 of this final guidance, CMS will use PDE data to calculate the Total Expenditures under Part D and Part B claims data to calculate the total allowed charges under Part B, inclusive of beneficiary cost sharing, for purposes of determining Total Expenditures under Part B.⁷⁵ Payment for drugs and biological products covered under Part B is made on the basis of claims for units of a drug or biological product's Healthcare Common Procedure Code System (HCPCS) code. Typically, single source drugs and biologicals are assigned to unique HCPCS codes; however, there may be cases where a potential qualifying single source drug is assigned to a HCPCS code with other products. In such cases, CMS will use Average Sales Price (ASP) sales volume data to apportion Part B expenditures based on the ratio of reported sales volume of the potential qualifying single source drug compared to reported sales volume of all products assigned to the HCPCS code to calculate the Total Expenditures under Part B for the purposes of implementing the Low-Spend Medicare Drug Exclusion. Expenditures for a drug or biological product that are bundled or packaged into the payment for another service will be excluded from the calculation of total allowed charges under Part B.
- CMS will exclude from the final list of qualifying single source drugs for initial price applicability year 2027 any drugs for which the sum of Total Expenditures under Part D and Part B is less than \$200 million, increased by the percentage increase in the CPI-U for the period beginning on June 1, 2023, and ending on September 30, 2024.

30.1.3 Plasma-Derived Product Exclusion from Qualifying Single Source Drugs

In accordance with section 1192(e)(3)(C) of the Act, CMS will exclude plasma-derived products when identifying qualifying single source drugs as described in section 30.1 of this final guidance (“the Plasma-Derived Product Exclusion”). For purposes of this exclusion, a plasma-derived product is a licensed biological product that is derived from human whole blood or plasma, as indicated on the approved product labeling. CMS will refer to product information available on the FDA Approved Blood Products website, including the list of fractionated plasma

⁷³ For purposes of this final guidance, CMS defines all days as calendar days unless otherwise specified in statute, guidance, or regulation.

⁷⁴ In response to comments on page 51 and as described in section 40.4.2.1 of this final guidance, CMS provides that, for operational reasons at this time for 2026 and 2027, MFP refunds will not be required for PDE records for selected drugs that were billed as compounds. For alignment, CMS provides in sections 30.1.2, 30.2, 60.2.1, 60.3.2, and 60.5 of this final guidance that, for initial price applicability year 2027, PDE records with a compound code indicating the PDE record is for a compounded drug will be excluded from the PDE data used to calculate the low-spend Medicare drug exclusion (section 30.1.2), the rankings of negotiation-eligible drugs (section 30.2), the ceiling for the MFP (section 60.2.1), the Net Part D Plan Payment and Beneficiary Liability of a therapeutic alternative(s) (section 60.3.2), and the application of the MFP across dosage forms and strengths (section 60.5).

⁷⁵ For the purposes of this final guidance, Total Expenditures under Part B are calculated as the sum of the total allowed amounts from Part B professional claims and the total paid amounts from Part B facility claims.

products,⁷⁶ and will refer to databases such as FDALabel and the FDA Online Label Repository⁷⁷ to verify if the product is derived from human whole blood or plasma. CMS will also consult with FDA, as appropriate.

30.2 Identification of Negotiation-Eligible Drugs for Initial Price Applicability Year 2027

In accordance with sections 1192(a) and 1192(d)(1) of the Act, a negotiation-eligible drug for initial price applicability year 2027 is a qualifying single source drug that is among the 50 qualifying single source drugs with the highest Total Expenditures under Part D. CMS will identify the negotiation-eligible drugs for initial price applicability year 2027 as follows:

- CMS will identify all qualifying single source drugs for initial price applicability year 2027 using the process described in section 30.1 of this final guidance. CMS will exclude any drugs that qualify for the exclusions listed in sections 30.1.1 through 30.1.3 of this final guidance.
- CMS will identify PDE data for each 11-digit National Drug Code (NDC-11)⁷⁸ of a qualifying single source drug for dates of service during the 12-month period beginning November 1, 2023 and ending October 31, 2024. To allow a reasonable time for Part D plan sponsors to submit PDE data, CMS will use PDE data for the dates of service described above that have been accepted no later than 30 days after October 31, 2024, i.e., by November 30, 2024. CMS will exclude any PDE data with a compound code indicating the PDE record is for a compounded drug.
- CMS will use this PDE data to calculate the Total Expenditures under Part D for each qualifying single source drug during the 12-month applicable period.
- CMS will: (1) remove drugs that are already selected drugs in accordance with section 1192(d)(3)(A)(i) of the Act; (2) remove drugs that are subject to the exception for small biotech drugs, described in section 30.2.1 of this final guidance; (3) rank the remaining qualifying single source drugs by Total Expenditures under Part D during the applicable 12-month period; and (4) identify the 50 qualifying single source drugs that have the highest Total Expenditures under Part D during the applicable 12-month period.
- These 50 drugs will be considered negotiation-eligible drugs for initial price applicability year 2027.

When two or more qualifying single source drugs have the same Total Expenditures to the dollar under Part D, and such Total Expenditures are the 50th highest among qualifying single source drugs, CMS will rank the qualifying single source drugs based on which drug has the earlier approval or licensure date, as applicable, for the initial FDA application number with its active moiety / active ingredient, until CMS has identified 50 negotiation-eligible drugs.

30.2.1 Exception for Small Biotech Drugs

In accordance with section 1192(d)(2) of the Act, the term “negotiation-eligible drug” excludes, with respect to initial price applicability years 2026, 2027, and 2028, a qualifying single source drug that meets the requirements for the exception for small biotech drugs (the “Small Biotech

⁷⁶ See: <https://www.fda.gov/vaccines-blood-biologics/blood-blood-products/approved-blood-products>.

⁷⁷ FDA Label: <https://nctr-crs.fda.gov/fdalabel/ui/search>; FDA Online Label Repository: <https://labels.fda.gov/>.

⁷⁸ NDC-9 and NDC-11 numbers are identical except for two numbers in NDC-11s that indicate package size. Because of this, NDC-11 is more granular than NDC-9, and multiple NDC-11 numbers can aggregate under a single NDC-9 number.

CERTIFICATE OF SERVICE

I hereby certify that on October 5, 2026, I electronically filed the foregoing document and accompanying materials with the United States Court of Appeals for the Fourth Circuit by using the appellate CM/ECF system. I certify that all participants in the case are registered CM/ECF users and that service will be accomplished by the appellate CM/ECF system.

/s/ Allon Kedem

Allon Kedem

Counsel for Plaintiffs-Appellants