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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

NOVARTIS PHARMACEUTICALS CORPORATION,

Plaintiff,

v.

XAVIER BECERRA, in his official capacity as Secretary of Health and Human Services et al.,

Defendants.

Case No. 3:23-CV-14221-ZNQ-DEA

PLAINTIFF'S MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF MOTION FOR SUMMARY JUDGMENT

ORAL ARGUMENT REQUESTED

Motion Day: March 18, 2024

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INTRODUCTION

This case challenges an unprecedented and unconstitutional attempt to compel the nation's drug manufacturers to hand over their products at any price the government demands. Instead of using the government's market power or granting CMS traditional price-setting authority to help lower drug prices in a lawful manner, Congress instead created a regime that compels manufacturers to transfer ownership of their most valuable drugs upon penalty of ruinous fines. It simultaneously compels the participants to publicly—and falsely—declare that they are engaged in a "negotiation" to establish the "maximum fair price." Despite its numerous intricacies, the crux of the "Drug Price Negotiation Program" (the "Program") is very simple: it requisitions property by threatening an enterprise-destroying fine, and then forces the affected parties to misrepresent the scope of the government's intrusion.

The Program is thus unconstitutional in three distinct ways. *First*, it effects a physical taking of private property for public use without just compensation, in violation of the Fifth Amendment. The Program does not merely set the price for the drug; rather, by virtue of its access requirement, it *compels a transfer* by requiring that manufacturers provide their drug to Medicare beneficiaries at prices the government dictates. And these compelled sales do not give manufacturers like Novartis Pharmaceuticals Corporation ("Novartis") the just compensation the Fifth

Amendment demands. To the contrary, the Program expressly *forbids* the government from paying the market value of patented drugs like Novartis's ENTRESTO®, instead mandating prices that *at most* are far below the market value—and can be as little as one penny, if the government so chooses. That forced transfer of property violates the Fifth Amendment.

Second, the Program forces manufacturers to espouse views with which they fundamentally disagree. Manufacturers must say that they are involved in a "negotiation"; that the price set by CMS is "fair"; and that it is actually the "maximum fair price" (and thus, implicitly, that the market-based prices the manufacturer currently charges are unfair)—all of which are viewpoints on matters of heightened public concern with which Novartis vehemently disagrees. This is not regulation of speech incidental to conduct—Congress can (and does) regulate similar conduct without compelling any such statements. Rather, these speech regulations exist solely to force manufacturers, including Novartis, to parrot the government's preferred narrative regarding the Program, despite Novartis's profound disagreement. The First Amendment prohibits private speech being compelled for that purpose.

Third, the Program imposes massive penalties on any manufacturer that refuses to comply with its demands. Those penalties take the form of a so-called "excise tax" running up to nineteen times the manufacturer's nationwide revenues

from the sale of the drug. This purported "tax" is so plainly punitive that the government itself does not anticipate deriving any revenue from it—because no manufacturer would or could ever pay it. In reality, this "excise tax" is a civil fine for refusal to participate in the government's scheme, and is so wildly disproportionate that it violates the Eighth Amendment's Excessive Fines Clause.

All of this amounts to a forced sales regime that is unique in American history. Never before has the government compelled private companies to hand over their products at a price and quantity of the government's demand. And, while the government hides behind the contention that this Program is "voluntary," the Supreme Court has squarely rejected the notion that physical takings can be justified simply because a participant has the supposed "freedom" to withdraw from the relevant market. Tellingly, all the out-of-circuit cases on which the government has relied in other litigation involved *regulatory*, not physical, takings. The Program is thus as unprecedented as it is misguided. It recklessly gambles with public health and violates core tenets of our constitutional order, for no purpose other than to advance the government's preferred narrative and then shield the government from any resulting political accountability for its decisions. It must be struck down.

BACKGROUND

A. Market-Based Pricing For Pharmaceutical Drugs Is Critical To Pharmaceutical Innovation

Novartis is one of the world's leading pharmaceutical companies. It deploys cutting-edge research to address some of society's most challenging healthcare problems and has developed a number of groundbreaking pharmaceutical drugs. One such drug is ENTRESTO®, a medication that treats heart failure by helping to improve the heart's ability to pump blood to the body. ENTRESTO® represents a significant advance in the treatment of heart failure, and provides a 20% relative risk reduction of cardiovascular death compared to patients receiving other heart failure medications. Vineis Decl. ¶¶ 6, 7 ("Decl."). To date, ENTRESTO® has helped approximately 2 million United States heart failure patients, including almost 600,000 Medicare beneficiaries in just the past twelve months. *Id.*

Developing a lifesaving drug such as ENTRESTO® entails enormous investments in time and expenses—on average, it takes nearly $3 billion, and ten to fifteen years, to develop just one new medicine. *See* Meron Decl. Ex. A, Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20, 25-26 (2016).[1] And given the nature of pharmaceutical research and the complexity of the regulatory process, manufacturers like Novartis

[1] All exhibits referenced herein are attached to the concurrently filed Declaration of Daniel Meron.

make these investments with no guarantee of a return. The vast majority of drugs never even secure Food and Drug Administration ("FDA") approval. *See* Ex. B, Sandra Kraljevic et al., *Accelerating Drug Discovery*, 5 EMBO Reports 837, 837 (2004); *Catalyst Pharms., Inc. v. Becerra*, 14 F.4th 1299, 1302-03 (11th Cir. 2021). Even where a manufacturer like Novartis does secure approval, few drugs provide an economic return significant enough to allow for continued innovation. *See* Ex. C, John A. Vernon & Joseph H. Golec, Pharmaceutical Price Regulation: Public Perceptions, Economic Realities, and Empirical Evidence 7 (2008).

The Medicare program includes two parts relevant here. Medicare Part B insures Medicare beneficiaries with respect to a wide variety of outpatient healthcare services, including coverage for drugs administered by physicians. *See* 42 U.S.C. § 1395k(a)(1); *id.* § 1395x(s)(2)(A). Medicare Part D permits beneficiaries to choose from a variety of insurance plans offered by private insurers under contracts with the government, which provide coverage for self-administered drugs. Together, Medicare Parts B and D "dominate" the United States prescription drug market, accounting "for almost half the annual nationwide spending on prescription drugs." *Sanofi Aventis U.S. LLC v. HHS*, 58 F.4th 696, 699 (3d Cir. 2023).

Until Congress's passage of the Inflation Reduction Act ("IRA"), both parts of the Medicare program guaranteed manufacturers market-based pricing. Medicare Part B reimbursement is based on a drug's average sales price, which ensures that

reimbursement tracks market prices. *See* 42 U.S.C. § 1395w-3a. And Medicare Part D expressly prohibits the Department of Health and Human Services ("HHS") from "[i]nterfer[ing] with the negotiations between drug manufacturers[,] pharmacies[,] and [private health plans]" regarding the price of Part D drugs in order to ensure that market forces drive pricing. *Id.* § 1395w-111(i). Historically, plan sponsors "can and do negotiate prices with prescription drug manufacturers," and have market incentives to secure lower pharmaceutical prices. Ex. D, Ryan Knox, *More Prices, More Problems*, 18 Yale J. Health Pol'y L. & Ethics 191, 206-07 (2020).

B. The Inflation Reduction Act Mandates The Transfer Of Drugs At Prices Set By CMS

The Program upends that market-driven approach by compelling manufacturers such as Novartis to agree to the government's unilaterally set price, while also forcing them to endorse those prices as "maximum fair prices" arrived at via "negotiations." The Program functions in the following way:

CMS first identifies the drugs that account for the highest Medicare Part D expenditures and selects a subset of those drugs for negotiation. 42 U.S.C. § 1320f-1(b)(1)(A). Each year, starting in 2023, at least ten drugs will be selected, with the number of selected drugs rising to twenty in 2027. *Id.* §§ 1320f-1(a)(1), (a)(4).

After a drug is chosen, the manufacturer has only 30 days to enter into an initial "agreement" with CMS to participate in the Program's "negotiation" process. 42 U.S.C. § 1320f(d)(2)(A); *id.* § 1320f-2(a). That initial "agreement," which the

manufacturer must sign on pain of ruinous fines, commits the manufacturer to "agreeing" that the price CMS eventually chooses—no matter how low—is the "maximum fair price" for the drug. *See* Ex. E, "Agreement" Between CMS and Novartis; Ex. F, Memorandum from M. Seshamani, CMS Deputy Admin., to Interested Parties on Medicare Drug Price Negotiation Program: Revised Guidance 118 (June 30, 2023) ("Revised Guidance"). If a manufacturer refuses to sign the initial agreement by the statutory deadline, the statute imposes a swiftly increasing penalty based on all United States sales of the listed drug (not merely Medicare sales), which the Program terms an "excise tax." 26 U.S.C. § 5000D(b).

The penalty is designed to force a manufacturer to enter into the "agreement." The penalty is based on a formula for an "applicable percentage," which begins at 65% of the drug's total price and increases by 10% for each quarter the manufacturer is out of compliance until it reaches 95% of the total price. *Id.* § 5000D(d). Under the statutory formula, the penalty is "an amount such that the applicable percentage is equal to the ratio of (1) such tax, divided by (2) the sum of such tax and the price for which so sold." *Id.* § 5000D(a). Applying that statutory formula, for a drug sold for $100 and subject to the 65% applicable percentage, the penalty would be $186 (or 186% of the "pre-tax" price) per sale. Once that percentage goes up to 95%, the penalty would be $1,900 per sale—1,900% of the drug's daily revenue. *See* Ex. G, Cong. Rsch. Serv., R47202, Tax Provisions in the Inflation Reduction Act of 2022

(H.R. 5376) 4 tbl. 2 (2022).[2] In order to escape the Program and its gargantuan penalties, a manufacturer would need to exit Medicare and Medicaid entirely—not merely for the selected drug, but for *all* of its drugs. *See* 26 U.S.C. § 5000D(c). That is not a step Novartis could rationally take. Decl. ¶ 30.

Once a manufacturer has entered into the initial "agreement" in the face of ruinous monetary penalties, the manufacturer then has little say in the "negotiation" that follows. Manufacturers are forced to provide all "information that [CMS] requires to carry out the negotiation." § 1320f-2(a)(4)(B). And although the manufacturer can provide a "counteroffer"—based only on categories of evidence CMS specifies and not on those the manufacturer might believe is relevant—this does nothing to salvage the process, as CMS is under no obligation to consider that counteroffer. *See* 42 U.S.C. §§ 1320f-3(b)(2)(C)(ii), 1320f-3(e).

At the end of this process, CMS has the unfettered discretion, unchecked by any processes of administrative or judicial review, to unilaterally set a "maximum fair price." 42 U.S.C. § 1320f-7. The Program provides no floor below which CMS

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[2] On October 2, 2023, the Internal Revenue Service ("IRS") issued a nonbinding notice announcing its intent, at some unspecified point in the future, to promulgate regulations implementing the "excise tax." Ex. H, IRS, Notice 2023-52 (Aug. 4, 2023) ("Notice"). As described *infra,* this notice purports to limit application of the "excise tax" to Medicare sales and apply a lower penalty rate. But in addition to being nonbinding, these aspects of the notice are at odds with the language of the statute, and an intention to issue future regulations obviously can have no impact on the Court's construction of the statute today. *See infra* at 38-40.

may not set the price (with one limited exception not relevant here). 42 U.S.C. §§ 1320f-3(c), (b)(2)(F)(ii). While CMS is required to provide an explanation for this price, *see, e.g.*, Ex. F, Revised Guidance, at 69, there is no mechanism by which manufacturers can request the information that manufacturers believe is relevant be considered by CMS or included in that explanation.

The law does impose a ceiling on how *high* a price CMS can set. Under the Program, CMS is directed to use as the ceiling price the lowest number produced by two specified statutory methods. §§ 1320f-3(c)(1)(A), (b)(2)(F). These methods are expressly designed to yield prices that are well below market value. *See* Compl. ¶¶ 44-45; Ex. F, Revised Guidance, at 138-42.

The Program next imposes a date by which manufacturers must "agree" that CMS's demand is the "maximum fair price" for their drugs. For drugs subject to price caps in 2026, that date is August 1, 2024. §§ 1320f(d)(5), 1320f-3(b)(2)(E). While CMS claims that manufacturers are bound to respond to CMS's "final offer" by "either accepting or rejecting [it]," Ex. F, Revised Guidance, at 158, manufacturers cannot in reality "reject" CMS's offer and walk away as in a normal negotiation. Decl. ¶¶ 16-17. If a manufacturer rejects CMS's final "maximum fair price" demand, it is subjected to the previously discussed, enterprise-destroying excise "tax" that starts at over 180% and runs up to 1900% (nineteen times) of the total revenue derived from sales of that drug in the United States. § 1320f-2(a)(1);

§ 5000D; *see* Ex. G, Cong. Rsch. Serv., R47202, at 29 tbl. A-2. No rational manufacturer could ever pay that penalty. Decl. ¶ 33. Congress was well aware of this reality; in fact, the Congressional Budget Office ("CBO") projected that this "tax" would raise exactly zero dollars. *See* Ex. I, Cong. Budget Off., Estimated Budgetary Effects of Public Law 117-169, to Provide for Reconciliation Pursuant to Title II of S. Con. Res. 14 4-5 (Sept. 7, 2022).

The Program then requires manufacturers to provide "access" to their drugs at the "maximum fair price" to a wide array of individuals and entities: all eligible individuals dispensed drugs under Medicare Parts B and D; all "pharmacies, mail order services, and other dispensers" dispensing drugs to Medicare beneficiaries; and all "hospitals, physicians, and other providers of services and suppliers" dispensing or administering drugs to Medicare beneficiaries. § 1320f-2(a)(1)(A)-(B); § 1320f(c)(2). If a manufacturer does not do so, it is subject to civil monetary penalties at the extraordinary rate of ten times the alleged overcharge. § 1320f-2(a)(1); 42 U.S.C. § 1320f-6(a)-(b). The Program thus compels manufacturers to provide "access" to the selected drugs at whatever price the government selects, and at whatever quantities Medicare beneficiaries may be prescribed.

C. ENTRESTO® Has Been Selected For Negotiation

On August 29, 2023, CMS selected Novartis's ENTRESTO® for "negotiation." In 2022, ENTRESTO®'s gross sales in the United States totaled $4.9

billion, which means that the penalty for not reaching an agreement would quickly rise to an annual rate of $93.1 billion—almost double Novartis's total global annual net revenue. Decl. ¶¶ 8-11. Thus, under threat of this catastrophic penalty, Novartis was forced to sign the "agreement" with the Secretary on September 28, 2023, and enter into the so-called "negotiation" process established by the statute. *Id.* ¶ 10. Novartis will continue engaging in the "negotiation" process only because the excise tax would be devastating. *Id.* ¶ 11.

LEGAL STANDARD

"The court shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). Courts regularly resolve pre-enforcement constitutional challenges to federal statutes through summary judgment. *See, e.g.*, *Gen. Elec. Co. v. EPA*, 360 F.3d 188, 189 (D.C. Cir. 2004).

ARGUMENT

I. THE PROGRAM TAKES NOVARTIS'S PROPERTY WITHOUT JUST COMPENSATION

The Program violates Novartis's Fifth Amendment property rights by forcing Novartis to transfer ENTRESTO® to third parties on the government's terms, and capping Novartis's compensation at below-market prices. The Program thus goes far beyond merely regulating drug prices and constitutes a *per se* taking of Novartis's protected personal property.

A. The Program Effects A Taking Of Novartis's Property Without Just Compensation

The Fifth Amendment's Takings Clause prevents the government from taking "private property … for public use, without just compensation." U.S. Const. amend. V. A physical appropriation of property is the "clearest sort of taking." *Cedar Point Nursery v. Hassid*, 141 S. Ct. 2063, 2071 (2021). When it "appropriate[s] personal property" in this way, the government "has a categorical duty to pay just compensation." *Horne v. Dep't of Agric.*, 576 U.S. 350, 358-59 (2015). "[J]ust compensation" means "the market value of the property at the time of the taking." *Id.* at 368-69. Only that remedy can put the owner "in the same position monetarily as he would have occupied if his property had not been taken." *United States v. Reynolds*, 397 U.S. 14, 16 (1970).

The Supreme Court's decision in *Horne* illustrates these principles. In *Horne*, a statute directed farmers to "turn over a percentage of their raisin crop" under pain of penalties, subject to the right to recover some proceeds if the government resold the raisins. 576 U.S. at 361-62. The Court held that the statute effectuated a physical taking because the farmers were required to transfer title to their property, losing the "right to control their [raisins'] disposition." *Id.* at 358, 364.

The Program appropriates Novartis's medicines in much the same way. It deprives manufacturers of their right to control their personal property and compels sales on terms of the government's choosing. It is a classic, *per se* taking.

1. The Program's Compelled Sales Regime Is A *Per Se* Taking Of Protected Property

As a threshold matter, Novartis's drugs are undoubtedly "private property" protected by the Takings Clause. The drugs themselves are—until they are sold—the manufacturers' personal property, and are therefore protected from uncompensated takings. *See, e.g.*, *id.* at 358-59. And Novartis's patented pharmaceutical drugs, including ENTRESTO®, are also protected as a matter of intellectual property. A patent confers on the patentee "an exclusive property in the patented invention which cannot be appropriated or used by the government itself, without just compensation." *Id.* at 359 (citation omitted).

Under the Program, Novartis *must* transfer its products to third parties at the dictated price; it cannot refuse to sell to them on those terms. *See* 42 U.S.C. § 1320f(c)(2)(A); *id.* § 1320f-2(a)(3). The Program expressly requires that Novartis "provid[e]" "access" to its drugs at the maximum fair price to Medicare beneficiaries and those who buy drugs on their behalf. § 1320f(c)(2)(A); § 1320f-2(a)(3); *see also* Ex. H, Notice, at 2 (recognizing that the Program requires manufacturers "to provide access to selected drugs" to eligible buyers).

In its briefing in other cases, the government has suggested that manufacturers can avoid the demands of the Program simply by not selling the selected drugs to Medicare beneficiaries. *See, e.g.*, Opp'n to Pl.'s Mot. for Summ. J. & Cross-Mot. at 23, 29, *Bristol Myers Squibb Co. v. Becerra*, No. 23-3335 (D.N.J. Oct. 16, 2023),

ECF No. 38-1. But it is not feasible for Novartis to avoid sales of ENTRESTO® to Medicare beneficiaries, as the Medicare Part D statute now requires that each selected drug be included in every Medicare Part D insurance plan formulary. *See* 42 U.S.C. § 1395w-104(b)(3)(I). Due to this statutory requirement and the nature of how the United States pharmaceutical supply chain operates, Novartis cannot avoid selling ENTRESTO® to Medicare beneficiaries. Manufacturers like Novartis sell their drugs directly to wholesalers, who in turn distribute those drugs to pharmacies. Decl. ¶¶ 24-25. The pharmacies are the ones who then decide whether to sell certain drugs to Medicare beneficiaries based on whether those drugs are covered by Part D plans—and here, ENTRESTO® always will be covered. And once a Medicare beneficiary seeks to fill his or her prescription for ENTRESTO®, the IRA requires Novartis to provide that drug to the pharmacy for dispensing to the beneficiary at the "maximum fair price." 42 U.S.C. §§ 1320f(c)(2)(A), 1320f-2(a)(3).

In short, every time a Medicare beneficiary requests the listed drug, it will be transferred to that beneficiary at the (below-market) "maximum fair price." This mechanism strips Novartis of its right to "control" the "use and dispos[ition]" of its property. *Horne*, 576 U.S. at 361-62.[3] Novartis must provide access to its drugs,

[3] Given the reality of how pharmaceutical sales occur, the only way a manufacturer could avoid having its own selected drug dispensed to Medicare beneficiaries would be to divest its interests in the drug to another, unrelated

and it will necessarily have a large share of those drugs transferred to Medicare beneficiaries at the government-prescribed price.

As in *Horne*, the Program uses the threat of penalties as a means of ensuring that manufacturers comply with the forced transfer of their property at below-market terms. *See id.* at 356. Failing to provide access to ENTRESTO® at CMS's chosen "maximum fair price" would trigger approximately *$93.1 billion* in annual penalties, almost double Novartis's total global annual net revenue. Decl. ¶ 11. That Novartis could hypothetically avoid giving up its property rights by incurring these crippling penalties does not change the fact that a taking has occurred. *See, e.g.*, *id.* (finding a physical taking even though the scheme alternatively provided for a civil penalty); *see also Valancourt Books, LLC v. Garland*, 82 F.4th 1222, 1234-35 (D.C. Cir. 2023) (that owners could pay a $250 fine instead of handing over their property did not "affect" the takings analysis because "[a] statute can effect a taking even if the property owner never actually forfeits property and is instead subject to a fine"). Were the law otherwise, "the government could avoid the strictures of the Takings Clause by purporting to 'simply give the owner a choice of either surrendering

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manufacturer. *See* Ex. F, Revised Guidance, at 131-32. But the fact that Novartis could theoretically *abandon* its property—at a price that would be discounted to reflect the cost of the unlawful takings yet to come—does not change the takings analysis. Either way, Novartis is forced to transfer "title" and "lose[s] any right to control" its property. *Horne*, 576 U.S. at 364.

[property] or making a payment equal to the [property's] value.'" *Id.* at 9 (quoting *Koontz v. St. Johns River Water Mgmt. Dist.*, 570 U.S. 595, 612 (2013)).

This forced-sale aspect distinguishes the Program from a genuine rate-setting regime. When the government engages in true rate setting, the result is a regulatory cap on what the seller may charge—but that does not mean the seller has to sell at that price. *Yee v. City of Escondido*, 503 U.S. 519, 527-28 (1992). Thus, a challenge to that cap would properly be evaluated as a potential regulatory taking. Here, however, the Program goes much further because it does not just set a price, but it compels manufacturers to *provide* "*access*" to their drugs at that government-set price. § 1320f-2(a)(3) (emphasis added); § 1320f(c)(2)(A). In other words, the Program forces manufacturers to hand over their property. That is a quintessential taking.

2. The Program's Government-Dictated Compensation Is Constitutionally Inadequate

Because the Program appropriates manufacturers' patented personal property for public use, the government must pay "just compensation" equivalent to the "market value of the property at the time of the taking." *Reynolds*, 397 U.S. at 16; *United States v. 564.54 Acres of Land*, 441 U.S. 506, 511 (1979). But the Program actually ensures that the government does *not* pay just compensation. The statutory ceiling, which is the lowest number yielded by alternative calculations, ensures a price well below the going market rate. Under one calculation, CMS must extract at

least a 25% discount (and almost certainly far steeper discounts) off of the average price paid by pharmaceutical drug buyers other than the federal government. *See* 42 U.S.C. § 1320f-3(c)(1)(C). In other words, CMS would force Novartis to turn over to the government a supply of ENTRESTO® at a minimum of 25% *less* than its current market price. That is, by definition, not just compensation. *See, e.g.*, *Reynolds*, 397 U.S. at 16; *see also Horne*, 576 U.S. at 362-63.

The same is true for the other "ceiling" arrived at by the alternative calculation. That method uses the average Part D net price from the latest year with complete data—which, for the first year of the Program, is 2022—as the highest price CMS can offer. § 1320f-3(c)(2)(A); Ex. F, Revised Guidance, at 138-39. But this number does not take into account inflation from the years between selection and implementation—which means Novartis would be forced to sell ENTRESTO® in 2026 based on the unadjusted *2022* Part D net price. This alone guarantees that the price set by CMS will be below the going market price. And, of course, CMS is free to—and almost certainly will—go far below whichever ceiling applies, given Congress's directive that CMS "achieve the lowest" possible price for each selected drug, § 1320f-3(b)(1), with no floor and no prospect of judicial review, 42 U.S.C. § 1320f-7. Indeed, there is nothing in the statute that would prevent CMS from unilaterally determining that the "maximum fair price" for a drug is one penny.

II. THE PROGRAM CANNOT BE UPHELD AS PART OF A VOLUNTARY EXCHANGE

The government cannot defend its physical taking of Novartis's property by arguing that Novartis "voluntarily" accepts forced below-market requisitioning of its products by electing to participate in the Medicare and Medicaid markets. *First*, the Program cannot be justified on the ground that manufacturers could theoretically avoid the taking by withdrawing from Medicare. The Supreme Court has time and again rejected the premise that the government can justify a *physical* taking on the ground that a party could withdraw from the relevant market. *Second*, the Program likewise cannot be justified as a "condition" on Medicare participation, because it is not applied to all participants nor actually tied to the receipt of a government benefit. Rather, it is selectively imposed on certain companies, who receive no additional benefit for handing over their drugs. And, in any event, even if the taking could be viewed as a "condition" of Medicare participation, it would plainly run afoul of the unconstitutional conditions doctrine, because it is unduly coercive.

A. Voluntariness Arguments Do Not Apply To *Per Se* Takings Claims

Any potential defense by the government that Novartis could avoid the Program's forced-sales requirements by leaving the Medicare and Medicaid markets would fail here because such voluntariness arguments are "insufficient to defeat a physical taking claim." *Yee*, 503 U.S. at 531 (citing *Loretto v. Teleprompter*

Manhattan CATV Corp., 458 U.S. 419, 439 n.17 (1982)) (a landlord's ability to control his property "may not be conditioned on his forfeiting the right to compensation for a physical occupation").

In *Horne*, the government tried this exact argument—attempting to recast its physical appropriation of raisins as voluntary because growers could, in theory, avoid it by forfeiting the right "to participate in the raisin market." 576 U.S. at 356-57, 365. The Supreme Court rejected the government's reformulation, explaining that "property rights cannot be so easily manipulated" and the ability to participate in a particular market cannot be held "hostage, to be ransomed by the waiver of constitutional protection." *Id.* at 365-67. This Court should do the same here. Congress can no more require manufacturers to abandon a vast swath of the United States prescription drug market to avoid a physical taking of their property than it can tell farmers to stop selling raisins in order to avoid having to turn over a portion of their crop to the government. Either way, the government is unlawfully holding access to a market "hostage" to compel a party to physically hand over its property.

Indeed, treating these forced sales as avoidable based on the theoretical ability to abandon the sale of drugs to Medicare and Medicaid beneficiaries would render the *per se* takings framework a nullity. Consider *Loretto*, the seminal physical-takings case. *See* 458 U.S. at 435-38. There, the Supreme Court had little trouble concluding that the attachment of a cable box to Loretto's apartment building was a

per se, unlawful taking—even though the imposition could have just as easily been cast as "avoidable" due to Loretto's "choice" to enter the rental property market.

That the Program effectuates a physical taking of Novartis's property distinguishes this case from those where courts outside of the Third Circuit have found that participation in a particular market excused a *regulatory* taking or a particular rate-setting regime. *See, e.g.*, *Garelick v. Sullivan*, 987 F.2d 913, 916 (2d Cir. 1993); *Minnesota Ass'n of Health Care Facilities, Inc. v. Minnesota Dep't of Pub. Welfare*, 742 F.2d 442, 446 (8th Cir. 1984). In each case, the law at issue simply set the price a provider could charge for a particular service, and so was properly evaluated as a regulatory taking. None of those cases involved a forced sale provision like 42 U.S.C. § 1320f(c)(2)(A). And, in any event, each of those cases predate *Horne*—which made clear that, when it comes to physical takings, a property owner's ability to exit a particular market before a taking occurs *cannot* render an appropriation of its property voluntary as a matter of law.

Here, the antecedent "option" of Novartis being forced to leave the Medicare and Medicaid markets entirely—for all its products, not just ENTRESTO®—in order to avoid the taking would be just as harmful as forcing the grape producers in *Horne* to reorient their business away from raisins. Medicare and Medicaid "dominate[]" the United States prescription drug market and for some drugs account for an overwhelming majority of sales. *Sanofi Aventis U.S. LLC v. HHS*, 58 F.4th

696, 699 (3d Cir. 2023); *see also* Decl. ¶ 30. Abandoning these markets is not a step Novartis can rationally take, and doing so would upend deeply settled expectations in its property. *See, e.g.*, *Union Pac. R. R. Co. v. Pub. Serv. Comm'n*, 248 U.S. 67, 70 (1918) (economic "duress" negates a purported "choice" where it is "practically impossible *not* to comply with the terms of the law" (emphasis added)); *Tenoco Oil Co. v. Dep't of Consumer Affs.*, 876 F.2d 1013, 1027 (1st Cir. 1989) (holding that the supposed freedom to temporarily leave the gasoline market was illusory due to fixed costs, overhead, and salaries). It also would leave millions of patients without access to their medications—a devastating result that neither the government nor Novartis actually wants to happen here.

Indeed, the government's argument ultimately boils down to the absurd contention that *any* taking by the government is voluntary so long as the property owner had some prior opportunity to avoid it—no matter how onerous that option is. Under the government's logic, instead of the price-setting scheme it created, Congress in the IRA could have directed the Secretary to seize without just compensation the manufacturing plants and raw materials of the 10 highest spend drugs and then produce those drugs itself—and the nationalization of those factories would not even implicate the Takings Clause because it would be a "condition" of the manufacturers' participation in Medicare and Medicaid. Under that view, there would be no limit to what the government could expropriate, so long as it frames the

taking of property as a condition of selling something—no matter how unrelated—in a market regulated by the government. That is preposterous. Physical takings must be accompanied by just compensation—no matter how they "come[] garbed." *Cedar Point*, 141 S. Ct. at 2072.

B. There Is No Voluntary Exchange Here

The government also cannot defend its requisitioning of Novartis's property as a valid "condition" for participation in Medicare or Medicaid. *See, e.g.*, *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1007 (1984). While the government can impose conditions that "place[] a direct *restriction*," *Gruver v. Louisiana Board of Supervisors*, 959 F.3d 178, 183 (5th Cir. 2020) (emphasis added), on the receipt of government benefits, such as conditions attached to "a license to sell dangerous chemicals," *Horne*, 576 U.S. at 366-67, that principle has no application here. The Program does not operate like a condition because its obligations are not a general prerequisite for participation in Medicare. Rather, they are a unique burden placed on a small subset of Medicare participants, and they are enforced not by "direct[ly] restrict[ing]" Medicare participation, *Gruver*, 959 F.3d at 183, but by a separate fine.

That there is no exchange—voluntary or otherwise—is fatal to any possible "conditions" argument by the government. There is no possible lawful "condition" when, as here, the property owner does not receive any "special government benefit" in "*exchange*" for handing over its property. *Horne*, 576 U.S. at 365-66 (emphasis

added); *see also Cedar Point*, 141 S. Ct. at 2079-80 (rejecting argument that government could "require property owners to cede a right of access as a condition of receiving certain benefits" because access rule was not "germane to any benefit provided to [the property owners] or any risk posed to the public").

The D.C. Circuit's post-*Horne* decision in *Valancourt Books v. Garland*, 82 F.4th 1222 (D.C. Cir. 2023) (Srinivasan, J.), is instructive. There, the Court held that the Copyright Act's requirement that copyright holders deposit copies of their works with the government on pain of fines was an unconstitutional taking. *Id.* at 1231. In doing so, it rejected the government's argument that taking the books could be excused as part of a "voluntary exchange" for copyright protection, because the owners did not need to deposit their works to secure or retain the benefits of copyright. *Id.* at 1232-33. Copyright protection would apply regardless. The government accordingly could not point to a "single *incremental* benefit" owners received from handing over their works—which meant this deposit requirement could not "represent a voluntary exchange for a benefit." *Id.* at 1233 (emphasis added). Instead, there was "no benefit at all" and thus no "*quid pro quo*." *Id.*

The same is true here: Novartis receives no incremental benefit from giving the government its drugs pursuant to the Program. As in *Valancourt*, the requirement that Novartis turn over its property is enforced by separate penalties; failure to comply with the Program's new obligations does not cause a manufacturer

to lose coverage under Medicare or Medicaid, *even for the selected product*. Thus, the Program's demands are not a "condition" of participation in the Medicare or Medicaid markets—they are merely requirements backed by a penalty.

In addition, the fact that the Program revises the terms of Novartis's Medicare and Medicaid agreements *after* such agreements already have been signed confirms that the Program's demands are not part of a "voluntary exchange" for Novartis's participation in those markets. Manufacturers like Novartis "could hardly [have] anticipate[d]" the Program's bait-and-switch when they joined Medicare and Medicaid years ago or, more critically, when they spent billions of dollars to develop their products—long before the IRA was enacted—under the expectation that they would be able to determine the prices at which they would offer the few products that made it to the market. *Nat'l Fed'n of Indep. Bus. v. Sebelius*, 567 U.S. 519, 579-80, 583-85 (2012) ("*NFIB*") (holding that threats to withhold "existing Medicaid funds" and "terminate other significant independent grants" if States would not accept "new conditions" was unlawful). Having used promises of market pricing to attract manufacturers to federal healthcare programs and then gain control of the prescription drug market, the government cannot now leverage that control to revise the terms of the original bargain and, in doing so, coerce Novartis to give up its right to "control" the "disposition" of its property. *Horne*, 576 U.S. at 361-62.

C. Regardless, The Purported Conditions Are Unlawful

Finally, even if complying with the Program could be viewed as a "condition" on receiving Medicare and Medicaid benefits, that still would not save the Program. That is because the "unconstitutional conditions doctrine" forbids the government from using its market power to "coerc[e] people into giving [] up" their constitutional rights, including "the Fifth Amendment right to just compensation." *Koontz*, 570 U.S. at 604; *see also Koslow v. Pennsylvania*, 302 F.3d 161, 174 (3d Cir. 2002) ("The 'unconstitutional conditions' doctrine is based on the proposition that government incentives may be inherently coercive."). In the Takings Clause context, the government can condition receipt of certain government benefits on the forfeiture of a property right only when there is an "essential nexus" and "rough proportionality" between the taken property and the social costs of the owner receiving that government benefit. *Dolan v. City of Tigard*, 512 U.S. 374, 375, 386 (1994); *Nollan v. Cal. Coastal Comm'n*, 483 U.S. 825, 837 (1987) (same); *see also Cedar Point*, 141 S. Ct. at 2079-80. Even if one were to view the relinquishment of property as a "condition" of participation in the Medicare and Medicaid programs, that purported "condition" would flunk both prongs of the *Nollan* and *Dolan* test.

First, the supposed condition lacks the requisite nexus to the allegedly impacted benefits, because it leverages not just the drug at issue, but the entirety of a manufacturer's participation in Medicare. And, even worse, it also leverages the

manufacturer's participation in *Medicaid*—and the provision of lifesaving drugs to over 87 million of the lowest-income and most vulnerable Americans. The Program provides no explanation (nor has CMS offered one) as to how forcing Novartis to hand over discounted ENTRESTO® bears any "nexus" to retaining Medicare coverage for Novartis's *other* distinct products. Nor has it offered any explanation for why Medicaid is implicated at all. There simply is no "reasonable relationship" between the supposedly voluntary condition of handing over ENTRESTRO® and the participation rights afforded by Novartis's existing Medicare and Medicaid agreements. *Dolan*, 512 U.S. at 395. As the Supreme Court has explained, threatening to withhold an *unrelated* benefit to compel surrender of property is not a condition, but "extortion." *Id.* at 387; *see also Harris v. McRae*, 448 U.S. 297, 317 n.19 (1980) (recognizing that a "substantial constitutional question would arise if Congress had attempted to withhold all Medicaid benefits from an otherwise eligible candidate" based on exercise of constitutional right).

Second, the required "condition" of terminating Medicare and Medicaid coverage for all of a manufacturer's products to avoid the demands of the Program is grossly disproportionate to the government's interests in reducing the prices of specific prescription drugs offered under Medicare plans. *See, e.g.*, *FCC v. League of Women Voters*, 468 U.S. 364, 400 (1984) (invalidating condition that required radio station receiving "only 1% of its overall income" from government grants to

abstain from "all editorializing"). The Program involves only one Novartis drug—ENTRESTO®—and only because of that drug's use in one Medicare program—Medicare Part D. *See* 42 U.S.C. §§ 1320f-1(b)(2), (d)(1)(A). Yet the Program purportedly conditions Novartis's ability to offer all its other products in every part of Medicare and Medicaid. 26 U.S.C. § 5000D. That is not remotely proportional.

Accordingly, treating the Program as a mere condition on federal funds or participation in a marketplace would not save it—that construction would merely render it unlawful "coercion" to pressure manufacturers to "giv[e] … up" their constitutional rights. *Koontz*, 570 U.S. at 604. However framed, the Program is simply a way for the government to take the manufacturers' private property without paying just compensation.

III. THE PROGRAM UNCONSTITUTIONALLY COMPELS SPEECH

In addition to unconstitutionally taking Novartis's property, the Program also forces the company to sign a compelled "agreement," wrongly declare that it is engaging in a "negotiation," and ultimately endorse and espouse the contention that the price it is forced to accept is the "maximum fair price" for its drug—and thus that the price it has been charging up to that point is unfair. Those speech-related aspects to the Program are wholly unnecessary. They serve solely to force the manufacturers to promote the government's preferred narrative while disguising, and misleading the public about, the true nature of the Program.

The First Amendment protects both the right to speak and the right to refrain from speaking. *See Wooley v. Maynard*, 430 U.S. 705, 714 (1977); *see also Janus v. Am. Fed'n of State, City & Mun. Emps.*, 138 S. Ct. 2448, 2463-64 (2018). And laws compelling private speech, like the Program does here, are subject to strict scrutiny. *Wooley*, 430 U.S. at 714-15. "[S]uch laws 'are presumptively unconstitutional and may be justified only if the government proves that they are narrowly tailored to serve compelling state interests.'" *Nat'l Inst. of Fam. & Life Advocs. v. Becerra*, 138 S. Ct. 2361, 2371 (2018).

A. The Program Forces Novartis To Deliver Messages With Which It Disagrees

Compelled speech lies at the heart of the Program. Congress adopted this convoluted process, rather than straightforward price-setting, to give the false impression that a "negotiation" has taken place and to force the manufacturers to state that they agree that the prices the government will pay reflect the "maximum fair prices" for their drugs. The purpose of this structure is to force manufacturers to endorse the government's claim that they are simply "negotiating" with manufacturers rather than dictating the price at which they must sell, and thus shift responsibility for any of the potential negative consequences of that dictate from the government to manufacturers.

From top to bottom, the Program is designed to compel manufacturers to engage in forced messaging, namely that this process constitutes a "negotiation,"

reflects Novartis's "agreement" and results in the "maximum fair price" for the product. *First*, Congress forced manufacturers like Novartis to represent that they voluntarily engaged in a "negotiation" when, in reality, the government unilaterally sets the price. 42 U.S.C. § 1320f-2(a); § 5000D. Congress expressly provided that manufacturers must enter into agreements imposing the obligation to "*negotiate* to determine … a maximum fair price" for a drug. § 1320f-2(a)(1) (emphasis added). And Novartis has been forced to convey this exact idea in the agreement it was compelled to sign. Ex. E, Agreement, at 2; *see also id.* at 1 (claiming Program "sets forth a framework under which manufacturers and CMS *may negotiate* to determine a price" (emphasis added)). Congress has also obligated manufacturers to actively participate in this "negotiation" process by signing the agreement, providing information purportedly used in that process, 42 U.S.C. § 1320f-3(b)(2)(A), and either being forced to publicly accept the government's first offer or being forced to counteroffer, § 1320f-3(b)(2)(C). Those actions are purely performative, completely unnecessary in light of the government's unfettered power to unilaterally set the price, and imposed solely to force Novartis to convey a message with which it profoundly disagrees.

Second, Congress compelled manufacturers to state that they "agree" to the price CMS ultimately sets, even though there can be no genuine "agreement" in the face of the Program's massive penalties. The IRA purports in various of its phases

to provide that manufacturers will "agree" to a "maximum fair price." § 1320f-(a)(1). Novartis's initial "agreement" with CMS thus compelled Novartis to state that it was entering an "agreement" with the aim of ultimately "agree[ing] to" a maximum fair price. Ex. E, Agreement, at 2; *see also id.* at 1 (titled "Medicare Drug Price Negotiation Program Agreement"). And after the "negotiation" process ends, Novartis will be forced to represent again that it agrees to a price. *Id.* at 2; § 1320f-2(a)(1). But these "agreements" are being entered into only under the threat of billions of dollars of penalties. § 5000D. Novartis is in no way voluntarily agreeing to negotiate, or to the price set by CMS.

Third, Congress required manufacturers to sign an "agreement" that purported to accept a "maximum fair price." 42 U.S.C. § 1320f(c)(3); *id.* § 1320f-2(a)(1). In choosing that language, Congress not only requires manufacturers to agree that CMS's set price is reflective of the drug's value—a contention that Novartis disputes—it actually forces manufacturers to convey that the current market prices charged by manufacturers, including those agreed to in genuine negotiations with private insurers, are *unfair*. 42 U.S.C. § 1320f(c)(3). Indeed, the agreement Novartis was forced to sign refers to the "maximum fair price" nearly two dozen times. *See generally* Ex. E, Agreement.

This type of performative, forced messaging is not a run-of-the-mill conduct regulation that only incidentally affects speech. A comparison with the 340B Drug

Pricing Program demonstrates that the government's regulation of speech is not "incidental," but rather the *goal* of these provisions. Under the 340B Program, HHS enters into agreements with manufacturers that specifies they must offer their drugs for sale to certain entities at a price below the statutorily defined "ceiling price." 42 U.S.C. § 256b(a)(1). But the statute and the agreement do not force manufacturers to say they "negotiated" for the relevant price, or otherwise portray that "ceiling price" as the product of "negotiation."[4] Rather, the agreement simply memorializes in writing that the manufacturer is obligated to charge a *government-set* price. The 340B statute straightforwardly acknowledges that the ceiling price is set by the government and that it is "the maximum price that covered entities may permissibly be *required to pay*." § 256b(a)(1) (emphasis added). Congress has elsewhere similarly used neutral terms like "average sales price," 42 U.S.C. § 1395w-3a(c)(1); "wholesale acquisition cost," § 1395w-3a(c)(6)(B); and "widely available market price," § 1395w-3a(d)(5)(A). The Program, by contrast, sweeps well beyond that type of neutral language. Congress's deviation from that standard practice reinforces that its goal here was forced messaging, not merely conduct regulation.

The government's attempt to conceal its imposition of governmental price controls by portraying CMS's unilaterally imposed price as the subject of a joint

[4] Ex. J, Health Res. & Serv. Admin., Healthcare Sys. Bureau OMB NO. 0915-0327.

"agreement" between manufacturers and regulators cannot withstand constitutional scrutiny. It is fundamental that "the government may not compel a person to speak its own preferred messages." *303 Creative LLC v. Elenis*, 600 U.S. 570, 586 (2023) (collecting cases). Indeed, when the government "requires the utterance of a particular message favored by the government," it "seeks not to advance a legitimate regulatory goal, but to … manipulate the public debate through coercion." *Turner Broad. Sys., Inc. v. FCC*, 512 U.S. 622, 641 (1994).

The Program's compulsion of speech cannot survive strict scrutiny (or indeed any level of scrutiny), because those speech compulsions serve *no* valid purpose, let alone a compelling one.[5] The government may have an interest in minimizing what it pays for prescription drugs. But requiring manufacturers to express "agreement" with the prices CMS sets, and to pretend that this is an actual negotiation process, is unnecessary to achieving *that* goal. Setting aside its other fatal constitutional

[5] The Program should be subject to strict scrutiny, *see supra* at 28, but the requirement that manufacturers state falsely that they "agree" with prices unilaterally set by CMS cannot be upheld under any level of constitutional scrutiny. As to intermediate scrutiny, the forced messaging at issue here does not serve an important government objective, and it is not substantially related to the only government objective that could legitimately be claimed: the amount of payment for drugs. The forced messaging also fails even rational basis review—regardless of what interest the government claims it seeks to advance, it has "no legitimate reason to force" businesses to convey "false information." *Video Software Dealers Ass'n v. Schwarzenegger*, 556 F.3d 950, 967 (9th Cir. 2009), *aff'd sub nom. Brown v. Ent. Merch. Ass'n*, 564 U.S. 786 (2011).

infirmities, the Program would work exactly as intended without these compelled speech provisions. The only interest served by these provisions is to promote the fiction that the Program establishes a market-based negotiation process rather than a potentially unpopular price control. That is not a legitimate governmental interest, let alone a compelling or substantial one.

Nor are the compelled speech provisions of the "negotiation" process narrowly tailored to any compelling government interest. After all, as explained above, Congress could have enacted the same basic Program, along the lines of 340B, without requiring manufacturers to engage in any forced messaging at all. *See R.A.V. v. City of St. Paul*, 505 U.S. 377, 395 (1992) (narrow tailoring requires that a statute be "*necessary* to serve the asserted compelling interest").

B. CMS's Inconsistent Disclaimer Reinforces Rather Than Resolves The Compulsion

Even the government seems to recognize that the statute, as written, violates the Constitution. In an attempt to save the statute, CMS added a disingenuous disclaimer to the Agreement, stating that it does not reflect an "endorsement of CMS['s] views" and that signing it should not be taken as agreement that "fair" means "fair" in the "colloquial" sense. Ex. E, Agreement, at 4. It goes on to state that terms should be "given the meaning specified in the statute." *Id.* But the statute uses those terms to convey their ordinary meanings, and the "definition" provided in the statute simply says that a price set under the statute should be understood as

the "maximum fair price." § 1320f(c)(3). The statute plainly requires manufacturers to purport to "agree" to a price that is set solely by the government and then endorse the government's claim that this is the "maximum fair price."

The disclaimer also raises the obvious question of why Congress would use—and force the manufacturers to parrot—the words "fair" "agreement" and "negotiation" if that is not in fact what Congress meant. The question answers itself. Those words were carefully chosen by Congress to deliver the message intended by their ordinary meaning. Nothing the agency can do or has done can alter that reality.

Not only does the disclaimer run headlong into the statute, it is also inconsistent with how the Program is described in the rest of the agreement. *See supra* at 29-30 (discussing the terms of the agreement and its references to "negotiation" and "maximum fair price"). The purported disclaimer does nothing to resolve the compelled speech requirement imposed by the statute and made clear in the remaining text of the agreement. In any event, adding a "disclaimer" cannot cure a compelled speech problem, because the government cannot "require speakers to affirm in one breath that which they deny in the next." *Pac. Gas & Elec. Co. v. Pub. Utils. Comm'n of Cal.*, 475 U.S. 1, 15 n.11 & 16 (1986) (plurality op.).

Nor is it any answer, as the government may contend, that Novartis could potentially announce its disagreement through speech in other places. *Reno v. ACLU*, 521 U.S. 844, 880 (1997) ("[O]ne is not to have the exercise of his liberty of

expression in appropriate places abridged on the plea that it may be exercised in some other place." (citation omitted)); *Pac. Gas.*, 475 U.S. at 16; *Miami Herald Publ'g Co. v. Tornillo*, 418 U.S. 241, 257-58 (1974). And, from a practical standpoint, speech by an individual entity like Novartis is unlikely to reach the same audience as the repeated statements by the government regarding Novartis's purported "voluntary" agreement to the government's unilaterally set price.

Finally, to the extent that the government advances a voluntariness argument, it disregards that Congress cannot use funding conditions to "requir[e] recipients to profess a specific belief" or "the Government's view on an issue of public concern." *Agency for Int'l Dev. v. All. for Open Soc'y Int'l, Inc.*, 570 U.S. 205, 218 (2013); *see supra* at 25 (discussing the unconstitutional conditions doctrine). Because the Program compels manufacturers to speak the government's own preferred messages, it violates the First Amendment.

IV. THE PROGRAM IMPOSES EXCESSIVE FINES

Finally, the Program is unconstitutional in a third respect. It uses a draconian fine—an "excise tax" in name only—to coerce manufacturers into "agreements" to "negotiate" and, ultimately, to give into its pricing scheme for drugs. That escalating "excise tax" begins at 186% and, after 271 days, reaches 1900% (19 times) of a drug's total national sales revenues. 26 U.S.C. § 5000D(b)(1)-(4). For Novartis, the excise tax would quickly reach $93.1 billion each year. Decl. ¶ 11. This penalty is

financially catastrophic given Novartis's total Fiscal Year 2022 net sales of $50.5 billion and net income of $6.9 billion. *Id.* That punishment violates the Constitution because it is grossly disproportionate to the "offenses" triggering the fine.

A. The Program Imposes Grossly Disproportional Fines

The Eighth Amendment bars "fines" that are "grossly disproportional to the gravity of [the] offense." *United States v. Bajakajian*, 524 U.S. 321, 334 (1998); *see* U.S. Const. amend. VIII. A monetary sanction is a "fin[e]" within the meaning of the Eighth Amendment if it "serv[es] in part to punish," *Austin v. United States*, 509 U.S. 602, 610 (1993), for example by "deter[ring]" conduct with more than a merely "remedial purpose," *Bajakajian*, 524 U.S. at 329. Because "'sanctions frequently serve more than one purpose,' … the Excessive Fines Clause applies" if "the law 'cannot fairly be said *solely* to serve a remedial purpose.'" *Tyler v. Hennepin Cnty.*, 598 U.S. 631, 648 (2023) (Gorsuch, J., concurring) (emphasis added) (quoting *Austin*, 509 U.S. at 610).

The Program's so-called "excise tax" is a fine within the meaning of the Excessive Fines Clause because it is punitive and intended to punish and coerce. In similar contexts, courts have considered the size and purpose of a fine in determining whether it has a punitive character and found taxes of five- and eight-times the value of the taxed product to be punitive. *See Dep't of Revenue of Mon. v. Kurth Ranch*, 511 U.S. 767, 780 (1994) (tax of eight-times value); *Dye v. Frank*, 355 F.3d 1102,

1105 (7th Cir. 2004) (tax of five-times value). The penalty here is far more severe—it quickly escalates to fully *nineteen times* the manufacturer's nationwide revenues from the drug's sales if the manufacturer fails to accede to CMS. 26 U.S.C. § 5000D(d); *see also* Ex. G, Cong. Rsch. Serv., R47202, at 4 tbl. 2 ("The excise tax rate would range from 185.71% to 1,900% of the selected drug's price depending on the duration of noncompliance."). A "tax" of that scale is unquestionably punitive for purposes of the Excessive Fines Clause. *See Bajakajian*, 524 U.S. at 329 (deterrence has "traditionally been viewed as a goal of punishment").

The penalty is so substantial that incurring it would be financially ruinous for Novartis, which could not possibly pay the full weight of the excise tax for long without declaring bankruptcy. Accordingly, the "so-called tax" is sufficiently coercive and divorced from the raising of revenue that it has "lost its character as such and becomes a mere penalty." *Kurth Ranch*, 511 U.S. at 779-80 ("Whereas fines, penalties, and forfeitures are readily characterized as sanctions, taxes are typically different because they are usually motivated by revenue-raising, rather than punitive, purposes."); *NFIB*, 567 U.S. at 565 (looking to a provision's "practical characteristics" to determine whether it imposed a penalty or a tax).

It is also disproportionate to the gravity of the offense that it is designed to punish. "The touchstone of the constitutional inquiry under the Excessive Fines Clause is the principle of proportionality," so the "amount of the [fine] must bear

some relationship to the gravity of the offense that it is designed to punish." *Bajakajian*, 524 U.S. at 334. In evaluating proportionality, courts consider "(1) the degree of the defendant's reprehensibility or culpability; (2) the relationship between the penalty and the harm to the victim caused by the defendant's actions; and (3) the sanctions imposed in other cases for comparable misconduct." *Cooper Indus., Inc. v. Leatherman Tool Grp., Inc.*, 532 U.S. 424, 425 (2001).

The "excise tax" fails this test because it imposes draconian punishments for totally innocent conduct—failing to agree on contractual terms with the government. *See* 26 U.S.C. § 5000D(b)(1)-(4). It goes without saying that the most severe monetary penalty that the federal government has ever imposed is grossly disproportionate to that alleged "wrong-doing." *See Bajakajian*, 524 U.S. at 337.

B. The IRS's Nonbinding Notice Does Not Render The Excise Tax Constitutional

As with CMS's attempt to cure the statute's defects under the First Amendment, the IRS has now attempted to fix the unconstitutional "excise tax." The IRS recently issued a non-binding Notice announcing its intention to propose a rulemaking to limit the scope of the penalty. *See* Ex. H, Notice. That non-binding Notice offers no present basis for defending the Program. And even if the rulemaking were someday adopted, its proposed provisions lack any grounding in the statutory text. An agency may not "rewrite clear statutory terms to suit its own sense of how the statute should operate." *Util. Air Regul. Grp. v. EPA*, 573 U.S.

302, 328 (2014). The government's attempt to administratively create a more defensible statute fails.

First, the Notice asserts that the excise tax would be imposed only on "sales of designated drugs dispensed, furnished, or administered to individuals under the terms of Medicare." Ex. H, Notice § 3.01. The statute contains no such limitation. It "impose[s]" the penalty "on the sale by the manufacturer, producer, or importer of any designated drug during [a noncompliance period]." § 5000D(a). Moreover, CMS itself has acknowledged that the Program leverages participation in Medicaid to ensure compliance with the mandate. *See* Ex. F, Revised Guidance, at 120-121. Yet under the interpretation in the IRS Notice, a manufacturer that exited Medicare but not Medicaid would owe zero tax whatsoever. That is not consistent with the understanding of Congress or CMS, which both made clear that a manufacturer has to exit *both* Medicare and Medicaid to avoid the penalty. § 5000D(c); Ex. F, Revised Guidance, at 120-121.

Second, the Notice presumes that the amount charged for a drug subject to the excise tax includes both the "price" of the drug and the excise tax itself, such that a drug initially priced at $100 would be understood to actually cost only $5 with a massive $95 tax tacked onto it. Ex. H, Notice §3.02. There is no basis for that bizarre presumption. The price of ENTRESTO® was established before the Program—and obviously did not include any tax. And Novartis is, in fact, statutorily

barred from increasing its price to incorporate any tax payments. *See* 42 U.S.C. § 1395w-114b(b)(1)(A). Yet, under the government's reading, once a tax has been levied, the price of the drug inexplicably declines by the taxed amount. That is utter sophistry—and only underscores that even the government cannot defend the magnitude of the tax on its own terms.

In any event, even under the rules articulated in the Notice, the fine is grossly excessive. The government pretends as if taking 95% of a drug's value is not an excessive fine. But that formula applied to Novartis would still result in a fine of over *$2 billion.* That is excessive by any measure.

Ultimately, this case illustrates why the bar on excessive fines is "fundamental to our scheme of ordered liberty." *Timbs v. Indiana*, 139 S. Ct. 682, 689 (2019). "Exorbitant tolls" are not only wrongful, they also threaten to "undermine other constitutional liberties." *Id.* The "excise tax" here was enacted for just such a purpose—to coerce manufacturers into complying with the government's forced taking and compelled speech regime. The result is a reticulated vice of constitutional violations. This Court's intervention is urgently needed.

CONCLUSION

For the foregoing reasons, the Court should declare the Program unconstitutional and enjoin Defendants from enforcing it against Novartis.

Dated: November 22, 2023

Respectfully submitted,

s/ *Gregory Mortenson*

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

NOVARTIS PHARMACEUTICALS CORPORATION, *Plaintiff*, v. XAVIER BECERRA, in his official capacity as Secretary of Health and Human Services, et al., *Defendants*.	Case No. 3:23-CV-14221-ZNQ-DEA **DECLARATION OF MARK VINEIS**

I, Mark Vineis, declare as follows pursuant to 28 U.S.C. § 1746:

1. I am the Chief Market Access Officer for Innovative Medicines US at Novartis Pharmaceuticals Corporation ("Novartis"). I am submitting this declaration on behalf of Novartis in support of Novartis's Motion for Summary Judgment. This Declaration is based on information within my personal knowledge as well as information within the knowledge of authorized Novartis employees, upon whom I have relied. The facts contained in the Declaration are true and correct to the best of my knowledge, information, and belief.

2. I have been employed by Novartis for approximately seven years. In my current position at Novartis, I am responsible for, among other things, Novartis's operations concerning the "negotiations" with the Centers for Medicare & Medicaid Services ("CMS") relating to ENTRESTO®'s selection for the initial year of the Inflation Reduction Act's ("IRA") "Medicare Drug Price Negotiation Program" (the "Program").

DRUG DEVELOPMENT AND ENTRESTO®

3. Novartis is one of the world's leading pharmaceutical companies. It engages in cutting-edge research to address some of society's most challenging healthcare problems. Novartis's mission is to develop new, high-value medicines that transform the treatment of diseases across many therapeutic areas with high unmet patient needs.

4. Novartis makes significant investments to support its research and development focus. In 2022, Novartis invested $10 billion in research and development. In 2021, Novartis invested $9.5 billion in research and development. As of 2022, approximately 21,000 Novartis employees work in research and development—around one fifth of its total workforce—and over 5,000 of these research and development employees are located in the United States.

5. Because of the uncertainty inherent in pharmaceutical research and the complexity of the regulatory process, the development of new drugs such as ENTRESTO® requires Novartis to invest very large sums of money into research and development, with no guarantee of a return on that investment. Most drugs never secure FDA approval.

6. ENTRESTO® is one of the lifesaving drugs developed by Novartis. It is a medicine for heart failure that helps improve the heart's ability to pump blood to the body. ENTRESTO® contains two active ingredients that work in different ways. The first, valsartan, has been used for years to treat heart failure. But the second, sacubitril, works unlike any existing heart failure treatment to relax blood vessels and decrease sodium and fluid in the body. Sacubitril is not found in any other medication. The combination of these two ingredients represents a significant innovation and advance in the treatment of heart failure. ENTRESTO® has transformed the standard of care for patients with heart failure.

7. On July 7, 2015, the United States Food and Drug Administration ("FDA") first approved ENTRESTO® as a treatment for heart failure. ENTRESTO® is recommended as a first-line therapy for patients with heart failure with reduced ejection fraction. It provides a 20% relative risk reduction of cardiovascular death compared to patients receiving other heart failure medications. ENTRESTO® has helped over 2 million United States heart failure patients, including close to 600,000 Medicare beneficiaries in just the past twelve months.

8. In 2022, ENTRESTO®'s gross sales in the United States totaled $4.9 billion, including Medicare sales of $2.3 billion and Medicaid sales of $450 million. In that same year, ENTRESTO® registered global net sales of $4.6 billion.

9. On August 29, 2023, Novartis's ENTRESTO® was selected by CMS for negotiation under the Program.

10. Under threat of penalties, Novartis was forced to sign the "Negotiation Program Agreement" with the Secretary on September 28, 2023, and engage in the so-called "negotiation" process dictated by the Program.

11. Novartis will continue engaging in the "negotiation" process only because incurring the excise tax would be devastating. Novartis understands that the penalty for not reaching an agreement would quickly rise to an annual rate of $93.1 billion—greater than Novartis's annual net sales of $50.5 billion and far

exceeding Novartis's annual earnings of approximately $6.9 billion. This is not a penalty that Novartis could possibly incur.

12. Similarly, abandoning Medicare and Medicaid entirely is not a step Novartis can rationally take. Together, Medicare Parts B and D dominate the U.S. prescription drug market, accounting for almost half the annual nationwide spending on prescription drugs. Abandoning these two markets also would have the devastating consequence of leaving millions of patients without access to their medications.

THE PROGRAM HAS COMPELLED NOVARTIS TO ARTICULATE VIEWS THAT IT REJECTS, AND WILL CONTINUE TO DO SO

13. The publicly available "Negotiation Program Agreement" Novartis was coerced into signing purports to convey Novartis's "agreement" to participate in the Program's "negotiations." It further indicates that Novartis will "agree" to CMS's dictated price, which the Agreement and the IRA itself characterize as the "maximum fair price." Novartis will then have to sell its drugs at that price or risk daily penalties of up to 1,900% of the revenues of the covered drug. *See* 26 U.S.C. § 5000D. CMS will effectuate this requirement through an addendum to the Agreement, setting forth the requirements for providing ENTRESTO® at the "maximum fair price."

14. By coercing Novartis to sign the Agreement, the government has forced Novartis to publicly represent that it is voluntarily entering into bona fide

negotiations with CMS and, at the end of that process, that those negotiations culminated in an agreed-upon price that Novartis considers "fair."

15. Novartis rejects the misleading characterization of the Program set forth in the Agreement and the messages it compels Novartis to communicate.

16. First, Novartis disagrees that the Program will entail price "negotiations." To the contrary, the government is unilaterally dictating the price. CMS holds complete control over this process, and the Program sets a price ceiling well below the drug's market value. While the Program allows Novartis to submit a "counteroffer," CMS is free to ignore that counteroffer and impose a price completely of its choosing, subject only to the ceiling price. At both the beginning and the end, CMS's price-setting discretion is unconstrained. The Program therefore does not resemble anything like the "negotiations" Novartis undertakes in the ordinary course of business.

17. Second, Novartis disagrees that it will ultimately "agree" to the price set by CMS. The IRA states that manufacturers will "agree" to "a maximum fair price." 42 U.S.C. § 1320f-(a)(1). And Novartis was compelled to state that it was entering the "Agreement" to ultimately "agree to" a maximum fair price. Of course, failure to reach agreement on CMS's terms triggers a severe tax penalty. So Novartis cannot fairly be characterized as "agreeing" to anything.

18. Third, Novartis rejects the message manifested in the Agreement that the government-mandated price at the end of the "negotiation" process is the "maximum fair price." Novartis does not wish to convey that viewpoint, which is contrary to its own understanding of what price for ENTRESTO® is "fair." Novartis objects to forcing manufacturers to convey that the current market prices charged by manufacturers, including those agreed to in genuine negotiations with private insurers, are *unfair*. Novartis believes that its products should be priced to support the necessary expenses associated with researching, developing, and obtaining regulatory approval for groundbreaking treatments such as ENTRESTO®, and to reflect the value these products provide to the healthcare market and to patients. The Program's characterization of CMS's preferred price as the maximum "fair" price is fundamentally incompatible with Novartis's beliefs, and taking ENTRESTO® at below-market prices is not "fair."

19. Because Novartis has been forced to sign the Agreement, it will have to engage in a so-called "negotiation" process. CMS will start with an "initial offer" subject only to the Program's requirement that the "offer" represent a discount of at least 25% off ENTRESTO's nonfederal average manufacturer price ("non-FAMP"), with potentially even greater discounts determined in CMS's sole discretion. 42 U.S.C. § 1320f–3(C). Novartis may submit a "counteroffer," but CMS nevertheless remains free to impose the price contained in its "initial offer."

20. The Program's first round of this process "shall end" by July 31, 2024. At that time, Novartis must respond to CMS's final offer.

21. The Program requires Novartis to "accept" that offer by "agree[ing] to" CMS's final "maximum fair price." 42 U.S.C. § 1320f–2(a)(1). If Novartis does not accept the final offer and in doing so convey that it is "fair" and the result of a "negotiation," Novartis will incur the same tens of billions of dollars in annual penalties it would by failing to enter the original "manufacturer agreement." 26 U.S.C. § 5000D.

22. Again, Novartis rejects each premise behind this final "agreement" to sell at the government's "fair price" and every message it compels Novartis to communicate.

THE PROGRAM WILL FORCE NOVARTIS TO TRANSFER ITS PROPERTY

23. After Novartis has been compelled to "agree" to sell its drugs at a price far below market, it then must provide eligible individuals and entities participating in Medicare "access to such price." 42 U.S.C. § 1320f–2(a)(1). Novartis thus must provide third-parties access to its physical drugs at CMS's dictated-terms. *See, e.g.*, IRS, Notice 2023-52, at 2 (Aug. 4, 2023) (recognizing that the Program requires manufacturers "to provide access to selected drugs" to eligible buyers).

24. In its briefing in other cases, the government has suggested that manufacturers can avoid the demands of the Program simply by not selling their

selected drugs to Medicare beneficiaries. But it is not feasible for Novartis to avoid sales of ENTRESTO® to Medicare beneficiaries, as the Medicare Part D statute now requires that each selected drug be included in every Medicare Part D insurance plan formulary. *See* 42 U.S.C. § 1395w-104(b)(3)(I). A "formulary" is a particular plan's list of covered drugs.

25. Due to this statutory requirement and the nature of how the U.S. pharmaceutical supply chain operates, Novartis cannot avoid selling ENTRESTO® to Medicare beneficiaries. Novartis sells its drugs directly to distributors, which then sell and deliver those drugs to end-customers, such as pharmacies. The pharmacies then decide whether to sell (*i.e.*, dispense) particular drugs to Medicare beneficiaries based on whether those drugs are covered by Part D plans—and here, due to the Program's formulary inclusion requirement, the selected drugs always will be covered.

26. The Program enforces its "access" requirement with civil monetary penalties of ten times the difference between the price charged and the mandated price, *id.* § 1320f–6(a), plus an additional penalty for violation of the negotiated price "agreement," *id.* § 1320f–6(c). Novartis will incur such penalties if it fails to turn over ENTRESTO® products at the price dictated by CMS. Novartis thus will have no choice but to accede to such forced sales.

27. These forced sales must continue at CMS's dictated price (increased

only to account for inflation) until CMS either determines that a generic or biosimilar version of the drug has been approved and marketed, *id.* § 1320f–1(c)(1), or subjects the drug to a "renegotiation" through essentially the same process, *id.* § 1320f–3(f)(2). Accordingly, Novartis will be forced to indefinitely sell its drugs at massive discounts. Practically speaking, the Program compels Novartis to transfer its property to others at a fraction of fair market value.

NOVARTIS'S PARTICIPATION IN THE PROGRAM IS NOT VOLUNTARY

28. Novartis entered Medicare Part D based on the promise of market pricing enshrined in the Part D statute. *See* 42 U.S.C. § 1395w–111(i). Neither Congress nor CMS presented the IRA's Program to Novartis as a condition on participation in or reimbursement through Medicare or Medicaid when Novartis joined these programs. Accordingly, Novartis had no notice that anything like the Program or its penalties would be a condition on participation in Medicare Part D when it decided to offer its products through Medicare. And Novartis has relied on the expectation of market pricing in these programs when spending many billions of dollars to develop its products.

29. Moreover, participation in the Program is not a "condition" for participation in Medicare because the former is not a prerequisite for the latter. Novartis has been forced to enter the Program because of the threat of fines and will receive no benefit from any "agreement" to participate in the Program.

30. Novartis could avoid the coercive threat of the Program's penalties only by terminating all of its Medicare Part D manufacturer-discount agreements and Medicaid rebate agreements. Doing so would exclude all Novartis drugs from payments under Medicare and Medicaid. Novartis cannot rationally do this given that these programs represent nearly half of the U.S. prescription drug market, and a majority of the U.S. market for certain drugs.

31. If Novartis were to terminate all of its Medicare and Medicaid agreements, it would leave millions of current patients without access to vital medications—including, but not limited to, ENTRESTO®—and it would lose billions of dollars in revenue each year.

32. The government thus has provided no choice for Novartis at all. Novartis remains subject to the Program's demands not because of Novartis's own voluntary choice, but rather because of the Program's intended overwhelming coercion.

33. As noted above, incurring the "excise tax" associated with refusing to agree to a "maximum fair price" would result in catastrophic penalties, as would imposition of civil monetary penalties. These penalties are so massive that incurring them would be irrational for any manufacturer, and financially ruinous for Novartis.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: November 22, 2023

Mark Vineis

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

NOVARTIS PHARMACEUTICALS CORPORATION, *Plaintiff*, v. XAVIER BECERRA, in his official capacity as Secretary of Health and Human Services et al., *Defendants*.	Case No. 3:23-CV-14221-ZNQ-DEA **DECLARATION OF DANIEL MERON IN SUPPORT OF PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT**

I, Daniel Meron, declare as follows pursuant to 28 U.S.C. § 1746:

1. I am a partner of the law firm of Latham & Watkins LLP, 555 Eleventh Street, NW, Suite 1000, Washington, DC 20004-1304, counsel for Plaintiff Novartis Pharmaceuticals Corporation in the above-titled action. I am admitted to practice law in the District of Columbia, and my application to be admitted *pro hac vice* in this matter is pending. I am over the age of 18 and have personal knowledge of the facts set forth here.

2. Attached as Exhibit A is a true and correct copy of Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20 (2016).

3. Attached as Exhibit B is a true and correct copy of Sandra Kraljevic et al., *Accelerating Drug Discovery*, 5 Eur. Molecular Biology Org. Reps. 837 (2004).

4. Attached as Exhibit C is a true and correct copy of John A. Vernon & Joseph H. Golec, Pharmaceutical Price Regulation: Public Perceptions, Economic Realities, and Empirical Evidence (2008).

5. Attached as Exhibit D is a true and correct copy of Ryan Knox, *More Prices, More Problems*, 18 Yale J. Health Pol'y L. & Ethics 191 (2020).

6. Attached as Exhibit E is a true and correct copy of the "Medicare Drug Price Negotiation Program Agreement" to which Novartis and CMS are parties.

7. Attached as Exhibit F is a true and correct copy of a document issued on June 30, 2023, by CMS entitled "Medicare Drug Price Negotiation Program: Revised Guidance, Implementation of Sections 1191–1198 of the Social Security Act for Initial Price Applicability Year 2026" (last visited November 21, 2023), at https://www.cms.gov/files/document/revised-medicare-drug-price-negotiation-program-guidance-june-2023.pdf.

8. Attached as Exhibit G is a true and correct copy of the Congressional Research Service report updated on August 10, 2022 entitled "Tax Provisions in the Inflation Reduction Act of 2022 (H.R. 5376)" (last visited November 21, 2023), at https://crsreports.congress.gov/product/pdf/R/R47202.

9. Attached as Exhibit H is a true and correct copy of a document issued on August 4, 2023, by the Internal Revenue Service entitled "Notice 2023-52" (last visited November 21, 2023), at https://www.irs.gov/pub/irs-drop/n-23-52.pdf.

10. Attached as Exhibit I is a true and correct copy of the Congressional Budget Office 2022 publication entitled "Estimated Budgetary Effects of Public Law 117-169, to Provide for Reconciliation Pursuant to Title II of S. Con. Res. 14" (last visited November 21, 2023), at https://www.cbo.gov/system/files/2022-09/PL117-169_9-7-22.pdf.

11. Attached as Exhibit J is a true and correct copy of a document issued by the Health Resources and Services Administration, entitled "Healthcare Systems

Bureau OMB No. 0915-0327" (last visited November 22, 2023), at https://www.hrsa.gov/sites/default/files/hrsa/opa/pharmaceutical-pricing-agreement-example.pdf.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: November 22, 2023

Daniel Meron

Attorney for Novartis Pharmaceuticals Corporation

EXHIBIT A

Journal of Health Economics 47 (2016) 20–33

Contents lists available at ScienceDirect

Journal of Health Economics

journal homepage: www.elsevier.com/locate/econbase

Innovation in the pharmaceutical industry: New estimates of R&D costs☆

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ARTICLE INFO

Article history:
Received 15 August 2014
Received in revised form 28 January 2016
Accepted 29 January 2016
Available online 12 February 2016

JEL classification:
L65
O31

Keywords:
Innovation
R&D cost
Pharmaceutical industry
Discount rate
Technical success rates

ABSTRACT

The research and development costs of 106 randomly selected new drugs were obtained from a survey of 10 pharmaceutical firms. These data were used to estimate the average pre-tax cost of new drug and biologics development. The costs of compounds abandoned during testing were linked to the costs of compounds that obtained marketing approval. The estimated average out-of-pocket cost per approved new compound is $1395 million (2013 dollars). Capitalizing out-of-pocket costs to the point of marketing approval at a real discount rate of 10.5% yields a total pre-approval cost estimate of $2588 million (2013 dollars). When compared to the results of the previous study in this series, total capitalized costs were shown to have increased at an annual rate of 8.5% above general price inflation. Adding an estimate of post-approval R&D costs increases the cost estimate to $2870 million (2013 dollars).

1. Introduction

We provide an updated assessment of the value of the resources expended by industry to discover and develop new drugs and biologics, and the extent to which these private sector costs have changed over time. The costs required to develop these new products clearly play a role in the incentives to invest in the innovative activities that can generate medical innovation. Our prior studies also have been used by other researchers, including government agencies, to analyze various policy questions (US Congressional Budget Office, 1998, 2006).

The full social costs of discovering and developing new compounds will include these private sector costs, but will also include government-funded and non-profit expenditures on basic and clinical research that can result in leads and targets which drug developers can explore. These additional costs can be substantial.[1] However, it is difficult to identify and measure non-private expenditures that can be linked to specific new therapies. Thus, we focus here on the private sector costs.

The methodological approach used in this paper follows that used for our previous studies, although we apply additional statistical tests to the data (Hansen, 1979; DiMasi et al., 1991, 1995a,b, 2003, 2004; DiMasi and Grabowski, 2007). Because the methodologies are consistent, we can confidently make comparisons of the results in this study to the estimates we found for the earlier studies, which covered earlier periods, to examine and illustrate trends

☆ We thank the surveyed firms for providing data, and individuals in those firms who kindly gave their time when we needed some of the responses clarified. All errors and omissions are the responsibility of the authors. The Tufts Center for the Study of Drug development (CSDD) is funded in part by unrestricted grants from pharmaceutical and biotechnology firms, as well as companies that provide related services (e.g., contract research, consulting, and technology firms) to the research-based industry. Tufts CSDD's financial disclosure statement can be found here: http://csdd.tufts.edu/about/financial_disclosure. The authors and Tufts CSDD did not receive any external funding to conduct this study. The R&D cost and expenditure data for individual compounds and companies are proprietary and cannot be redistributed. Other data used were obtained from subscription databases and the Food and Drug Administration (FDA) and other websites.

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[1] For example, for fiscal year 2013, the United States National Institutes of Health (NIH) spent nearly $30 billion on the activities that it funds (http://officeofbudget.od.nih.gov/pdfs/FY15/Approp%20%20History%20by%20IC%20through%20FY%202013.pdf).

http://dx.doi.org/10.1016/j.jhealeco.2016.01.012
0167-6296/

in development costs. These studies used compound-level data on the cost and timing of development for a random sample of new drugs first investigated in humans and annual company pharmaceutical R&D expenditures obtained through surveys of a number pharmaceutical firms.

We analyze private sector R&D activities as long-term investments. The industrial R&D process is marked by substantial financial risks, with expenditures incurred for many development projects that fail to result in a marketed product. Thus, our approach explicitly links the costs of unsuccessful projects to those that are successful in obtaining marketing approval from regulatory authorities. In addition, the pharmaceutical R&D process is very lengthy, often lasting a decade or more (DiMasi et al., 2003). This makes it essential to model accurately how development expenses are spread over time.

Given our focus on resource costs and how they have changed over time, we develop estimates of the average pre-tax cost of new drug development and compare them to estimates covering prior periods. We corroborated the basic R&D cost results in this study by examining the representativeness of our sample firms and our study data, and by incorporating a number of independently derived results and data relating to the industry and the drug development process into analyses that provide rough comparators for at least components of our cost results. The details of those analyses are provided in our online supplement.

The remainder of this paper is organized as follows. We briefly discuss the literature on pharmaceutical industry R&D costs since our 2003 study in Section 2. Section 3 briefly outlines the standard paradigm for the drug development process. In Section 4 we describe the survey sample data and the population from which they were drawn, and briefly outline the methodology used to derive full R&D cost estimates from data on various elements of the drug development process. We present base case pre- and post-marketing approval R&D cost estimates in Section 5. Sensitivity analyses are presented in Section 6. We describe the representativeness of our data, various approaches to validating our results, and responses to various critiques in Section 7. Finally, we summarize our findings in Section 8.

2. Previous studies of the cost of pharmaceutical innovation

Much of the literature on the cost of pharmaceutical innovation dating back decades has already been described by the authors in their previous two studies (DiMasi et al., 1991, 2003). The interested reader can find references and discussions about the prior research in those studies. The earliest studies often involved a case study of a single drug (typically without accounting for the cost of failed projects) or they analyzed aggregate data. We will focus here on studies and reports that have emerged since DiMasi et al. (2003) that involve the use of new data for at least some parts of the R&D process. The basic elements of these analyses are shown in Table 1.

Adams and Brantner (2006, 2010) sought to assess the validity of the results in DiMasi et al. (2003) with some alternative data. Specifically, in their 2006 article, they used a commercial pipeline database to separately estimate clinical approval and phase attrition rates, as well as phase development times.[2] They found a similar overall cost estimate ($868 million versus $802 million in year 2000 dollars).[3] The authors followed that study with another study that featured clinical phase out-of-pocket cost estimates derived from regressions based on publicly available data on company R&D expenditures (Adams and Brantner, 2010). They found a somewhat higher overall cost estimate ($1.2 billion in year 2000 dollars).[4]

In a paper authored by two of the authors of this study (DiMasi and Grabowski, 2007), we provided a first look at the costs of developing biotech products (specifically, recombinant proteins and monoclonal antibodies). The methodological approach was the same as that used for our studies of traditional drug development. We used some data from DiMasi et al. (2003) combined with new data on the costs of a set of biotech compounds from a single large biopharmaceutical company. Biotech drugs were observed to have a higher average clinical success rate than small molecule drugs, but this was largely offset by other cost components. We found that the full capitalized cost per approved new compound was similar for traditional and biotech development ($1.3 billion for biotech and $1.2 billion for traditional development in year 2005 dollars), after adjustments to compare similar periods for R&D expenditures.

The other studies shown in Table 1 are discussed in detail in the online supplement. One important finding emerging from the survey of cost studies in Table 1 is that clinical success rates are substantially lower for the studies focused on more recent periods. This observed trend is consistent with other analyses of success probabilities (DiMasi et al., 2010; DiMasi et al., 2013; Hay et al., 2014; Paul et al., 2010) and our analysis below. Average R&D (inflation-adjusted) cost estimates are also higher for studies focused on more recent periods, suggesting a growth in real R&D costs. While suggestive, these studies are not strictly comparable to our earlier analyses of R&D costs given methodological differences and data omissions that are discussed in the online supplement (Appendix A).

3. The new drug development process

The new drug development process need not follow a fixed pattern, but a standard paradigm has evolved that fits the process well in general. We have described the process in some detail in previous studies, and the FDA's website contains a schematic explaining the usual set of steps along the way from test tube to new compound approval (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm053131.htm). Marketing approval applications for investigational compounds submitted to the FDA for review by manufacturers are referred to as new drug applications (NDAs) or biologic license applications (BLAs), depending on the type of product.

In basic form, the paradigm portrays new drug discovery and development as proceeding along a sequence of phases and activities (some of which often overlap). Basic and applied research initiate the process with discovery programs that result in the synthesis or isolation of compounds that are tested in assays and animal models in preclinical development. We do not have the level

[2] For mean out-of-pocket phase costs, they used the estimates in DiMasi et al. (2003).

[3] The Adams and Brantner (2006) study used records in the pipeline database that were reported to have entered some clinical testing phase from 1989 to 2002. Thus, they did not follow the same set of drugs through time. The data for the commercial pipeline databases are also thin prior to the mid-1990s. The DiMasi et al. (2003) study covered new drugs that had first entered clinical testing anywhere in the world from 1983 to 1994 and followed the same set of drugs through time.

[4] However, the authors interpreted their estimate as a marginal, as opposed to an average, drug cost. The concept, though, of marginal cost has an unclear meaning here. With high fixed costs and a development process that varies by drug, it is difficult to understand what marginal pharmaceutical R&D cost means in this context. It seems that the relevant marginal concept here is marginal profitability. The marginally profitable drug could have a very high or a very low cost. What's more, marginal profitability may only have meaning at the firm, not the industry, level. The cost of a marginally profitable drug in the pipeline of a firm may be high for one firm and low for another firm.

Table 1
Prior studies and analyses of pharmaceutical R&D costs (2003–2012).

Study	Study period	Clinical success rate	Real cost of capital	Inflation adjustment	Cost estimate
DiMasi et al. (2003)	First-in-humans, 1983–1994	21.5%	11.0%	2000 dollars	$802 million
Adams and Brantner (2006)	First-in-humans, 1989–2002	24.0%	11.0%	2000 dollars	$868 million
Adams and Brantner (2010)	Company R&D expenditures, 1985–2001	24.0%	11.0%	2000 dollars	$1.2 billion
DiMasi and Grabowski (2007)	First-in-humans, 1990–2003 (large molecule)	30.2% (large molecule)	11.5%	2005 dollars	$1.2 billion
Gilbert et al. (2003)	2000–2002 (launch)	8.0%	NA	2003 dollars	$1.7 billion
O'Hagan and Farkas (2009)	2009 (launch)	NA	NA	2009 dollars	$2.2 billion
Paul et al. (2010)	≈2007	11.7%	11.0%	2008 dollars	$1.8 billion
Mestre-Ferrandiz et al. (2012)	In clinical development, 1997–1999	10.7%	11.0%	2011 dollars	$1.5 billion

of granularity to disaggregate R&D expenditure data into discovery and preclinical development testing costs, so for the purposes of this study, as in prior studies, discovery and preclinical development costs are grouped and referred to as pre-human costs.[5]

Clinical (human) testing typically proceeds through three successive, sometimes overlapping phases. Historically, human testing has often been initiated first outside the United States (DiMasi, 2001). For any of these clinical phases, pharmaceutical companies may pursue development of their investigational compounds in multiple indications prior to and/or after the initial indication approval.

4. Data and methods

Ten multinational pharmaceutical firms of varying sizes provided data through a confidential survey of their new drug and biologics R&D costs.[6] Data were collected on clinical phase expenditures and development phase times for a randomly selected sample of the investigational drugs and biologics of the firms participating in the survey.[7] The sample was taken from a Tufts Center for the Study of Drug Development (CSDD) database of the investigational compounds of top 50 firms. Tufts CSDD gathered information on the investigational compounds in development and their development status from commercial pipeline intelligence databases (*IMS R&D Focus* and *Thomson Reuters Cortellis* database [formerly the *IDdb3* database]), published company pipelines, clinicaltrials.gov, and web searches. Cost and time data were also collected for expenditures on the kind of animal testing that often occurs concurrently with clinical trials.[8] The compounds chosen were self-originated in the following sense. Their development from synthesis up to initial regulatory marketing approval was conducted under the auspices of the surveyed firm. This inclusion criterion is broader than it might at first seem since it includes compounds of firms that were acquired or merged with the survey firm during development and drugs that originated with the survey firm and were co-developed (and for which full cost data were available).[9] Licensed-in and co-developed compounds without partner clinical cost data were excluded because non-survey firms would have conducted significant portions of the R&D.[10]

We also collected data from the cost survey participants on their aggregate annual pharmaceutical R&D expenditures for the period 1990–2010. The firms reported on total annual R&D expenditures broken down by expenditures on self-originated new drugs, biologics, diagnostics, and vaccines. Data were also provided on annual R&D expenditures for licensed-in or otherwise acquired new drugs, and on already-approved drugs. Annual expenditures on self-originated new drugs were further decomposed into expenditures during the pre-human and clinical periods.

The survey firms accounted for 35% of both top 50 firm pharmaceutical sales and pharmaceutical R&D expenditures. Of the 106 investigational compounds included in the project dataset, 87 are small molecule chemical entities (including three synthetic peptides), and 19 are large molecule biologics (10 monoclonal antibodies and nine recombinant proteins). For ease of exposition, we will refer to all compounds below as new drugs, unless otherwise indicated. Initial human testing anywhere in the world for these compounds occurred during the period 1995–2007. Development costs were obtained through 2013.

We selected a stratified random sample of investigational compounds.[11] Stratification was based on the status of testing as of the end of 2013. Reported costs were weighted to reflect the development status of compounds in the population relative to those in the cost survey sample, so that knowledge of the distribution of development status in the population from which the sample was drawn was needed. The population is composed of all investigational compounds in the Tufts CSDD investigational drug database that met study criteria: the compounds were self-originated and first tested in humans anywhere in the world from 1995 to 2007. We found 1442 investigational drugs that met these criteria. Of these compounds, 103 (7.1%) have been approved for marketing, 13 (0.9%) had NDAs or BLAs that were submitted and are still active, 11 (0.8%) had NDAs or BLAs submitted but abandoned, 576 (39.9%) were abandoned in phase I, 19 (1.3%) were still active in phase I, 492 (34.1%) were abandoned in phase II, 84 (5.8%) were still active in phase II, 78 (5.4%) were abandoned in phase III, and 66 (4.6%) were still active in phase III. For both the population and the cost survey sample, we estimated approval and discontinuation shares for the active compounds by phase so that the population and sample distributions consisted of shares of compounds that were approved or discontinued in phase I, phase II, phase III, or regulatory review. The

[5] We capture out-of-pocket discovery costs with our data, but the pre-synthesis discovery period is highly variable with no clear starting point. For our analyses we began our representative discovery and development timeline at the point of compound synthesis or isolation. Thus, our estimates of time costs are somewhat conservative.

[6] Using pharmaceutical sales in 2006 to measure firm size, 5 of the survey firms are top 10 companies, 7 are top 25 firms, and 3 are outside the top 25 (*Pharmaceutical Executive*, May 2007).

[7] A copy of the survey instrument can be found in our online supplement (Appendix G).

[8] Long-term teratogenicity and carcinogenicity testing may be conducted after the initiation of clinical trials, and is often concurrent with phase I and phase II testing.

[9] The criterion also does not preclude situations in which the firm sponsors trials that are conducted by or in collaboration with a government agency, an individual or group in academia, a non-profit institute, or another firm.

[10] Large and mid-sized pharmaceutical firms much more often license-in than license-out new drug candidates. Firms that license-in compounds for further development pay for the perceived value of the prior R&D typically through up-front fees, development and regulatory milestone payments, and royalty fees if the compound should be approved for marketing. For a breakdown of new drugs and biologics approved in the United States in the 2000s by business arrangements among firms initiated during clinical development, see DiMasi et al. (2014).

[11] To ease the burden of reporting and increase the likelihood that firms would respond, we limited the number of compounds to be reported on to a maximum of 15 for any firm (with fewer compounds for smaller firms).

cost survey sample was purposely weighted toward compounds that lasted longer in development to increase the amount of information on drugs that reached late-stage clinical testing. Weights, determined as described above, were then applied to the compounds in the cost dataset so that the results would reflect the development status distribution for the population from which the sample was drawn.

Some firms were not able to provide full phase cost data for every new drug sampled. For example, phase I cost data were available for 97 of the 106 new drugs in the dataset (92%). Of the 82 compounds in the dataset that had entered phase II, cost data were available for 78 (95%). For phase III, cost data were available for 42 of the 43 compounds that entered the phase (98%). However, we had cost data for at least one phase for each of the 106 drugs in the sample. In aggregate, we had cost data for all phases entered for 94 of the 106 compounds (89%).[12] In addition, five compounds were still active in a phase at the time that data were reported. For these drugs it is likely that there will be some additional future costs for the drug's most recent phase. Thus, for this reason our cost estimates are likely to be somewhat conservative. However, given the small number of drugs in this category and the fact that the impact would be on only one phase for each of these drugs, our overall cost estimates are not likely to be substantially affected.

The methodology that we use to estimate development costs is the same as the approach used in our earlier studies (Hansen, 1979; DiMasi et al., 1991, 2003). We refer the reader to the earlier studies and to our online supplement (Appendix A) for details. The methodology results in a full risk-adjusted cost per approved new compound that also takes into account time costs. That is, we link the cost of compound failures to the cost of the successes (investigational compounds that attain regulatory marketing approval), and we utilize a representative time profile along with an industry cost of capital to monetize the cost of the delay between when R&D expenditures are incurred and when returns to the successes can first be realized (date of marketing approval). We refer to the sum of out-of-pocket cost (actual cash outlays) and time cost per approved new compound as the capitalized cost per approved new compound. The full capitalized cost estimate is built through a number of estimates of various components of the drug development process. These individual component estimates are interesting as objects of analysis in their own right, and we provide estimates for those components.

5. Base case R&D cost estimates

5.1. Out-of-pocket clinical cost per investigational drug

To determine expected costs, we need estimates of the clinical development risk profile. We examined the dataset of 1442 self-originated compounds of top 50 pharmaceutical firms described above and estimated the phase transition probabilities shown in Fig. 1. The overall probability of clinical success (i.e., the likelihood that a drug that enters clinical testing will eventually be approved) was estimated to be 11.83%. This success rate is substantially lower than the rate of 21.50% estimated for the previous study, but consistent with several recent studies of clinical success rates.[13] Such an increase in overall risk will contribute greatly to an increase in costs per approved new drug, other things equal.

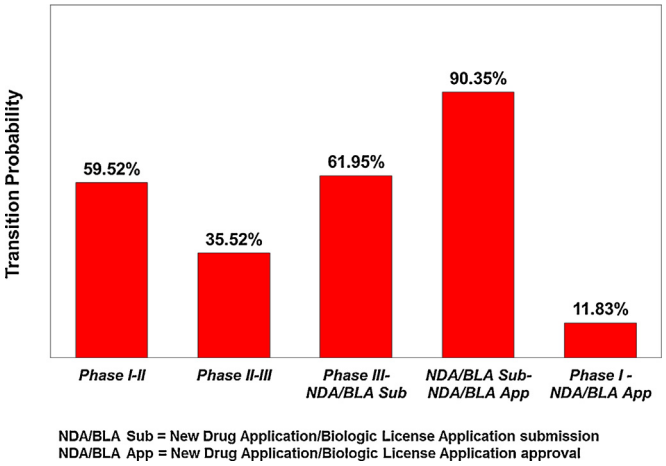


Fig. 1. Estimated phase transition probability and overall clinical approval success rates for self-originated new molecular entity (NME) and new therapeutically significant biologic entity (NBE) investigational compounds first tested in humans anywhere from 1995 to 2007.

As described above, we calculated weighted means, medians, standard deviations, and standard errors for clinical phase costs. Some of the firms could not separate out long-term animal testing costs during clinical development, and instead, included these costs in their phase cost estimates by year. To be consistent, therefore, for those compounds where animal costs were separately reported, we allocated those costs to the clinical phases according to when the animal testing costs were incurred. Thus, the clinical phase costs presented in Table 2 are inclusive of long-term animal testing costs.[14]

Weighted mean and median costs per investigational drug entering a phase[15] increase for later clinical phases, particularly for phase III (which typically includes a number of large-scale trials). In comparison to our previous study (DiMasi et al., 2003), both mean and median phase III cost are notably higher relative to the earlier phases. While the ratio of mean phase III cost to mean phase I cost was 5.7 for the previous study, it was 10.1 here. Similarly, the ratio of mean phase III to phase II cost was 3.7 for the earlier study, but was 4.4 for this study. Mean phase II cost was also higher relative to phase I cost in the current study compared to the previous one (2.3 times as high compared to 1.5 times as high).[16] Thus, while mean cost in real dollars for phase I increased 28% relative to the previous study,[17] phase I costs were notably lower relative to both phase II and phase III for the current study.

As we will see below, the differential in cost per approved new drug between the two studies will be much greater than cost per investigational drug because of the much lower overall clinical approval success rate. However, our results do show that the impact is mitigated to some degree by firms failing the drugs that they do abandon faster for the current study period. The distribution of clinical period failures for this study were 45.9% for phase I, 43.5% for phase II, and 10.6% for phase III/regulatory review. The

[12] Phase cost correlation results presented in the online supplement, together with an examination of relative phase costs for drugs that had some missing phase cost data, suggest that our phase cost averages (exclusive of missing data) are conservative.

[13] See, for example, Paul et al. (2010), DiMasi et al. (2013), and Hay et al. (2014).

[14] When animal testing costs occurred in a year during which costs were incurred for two clinical phases, the animal costs were allocated to the two phases according to their relative costs for the year.

[15] Averages for unweighted costs did not differ greatly from the weighted cost figures. On an unweighted basis, mean phase I, phase II, and phase III costs were $29.7 million, $64.7 million, and $253.5 million, respectively.

[16] The ratios for median costs for the current study are 11.6 for phase III relative to phase I, 4.5 for phase III relative to phase II, and 2.6 for phase II relative to phase I. The corresponding ratios for the previous study are 4.5, 3.6, and 1.2, respectively.

[17] In real terms, median phase I cost was actually 4% lower for the current study compared to the previous study.

Table 2
Average out-of-pocket clinical period costs for investigational compounds (in millions of 2013 dollars).[a]

Testing phase	Mean cost	Median cost	Standard deviation	Standard error	N[b]	Probability of entering phase (%)	Expected cost
Phase I	25.3	17.3	29.6	3.0	97	100.0	25.3
Phase II	58.6	44.8	50.8	6.6	78	59.5	34.9
Phase III	255.4	200.0	153.3	34.1	42	21.1	54.0
Total							114.2

[a] All costs were deflated using the GDP implicit price deflator. Weighted values were used in calculating means, medians, and standard deviations.
[b] *N* = number of compounds with cost data for the phase.

Table 3
Nominal and real cost of capital (COC) for the pharmaceutical industry, 1994–2010.

	1994	2000	2005	2010
Nominal COC (%)	14.2	14.9	13.3	11.4
Inflation rate (%)	3.1	3.1	2.5	2.0
Real COC (%)	11.1	11.8	10.8	9.4

corresponding figures for the previous study were 36.9% for phase I, 50.4% for phase II, and 12.6% for phase III/regulatory review.

5.2. Cost of capital estimates

To account for the time value of money in our previous paper (DiMasi et al., 2003), we utilized an 11% real after-tax weighted average cost of capital (WACC). In particular, we employed the capital asset pricing model (CAPM) to estimate the cost of equity capital. This was combined with the cost of debt, appropriately weighted with the cost of equity, to yield a representative, pharmaceutical industry weighted after-tax cost of capital. The resultant parameters were estimated at regular intervals from the mid-1980s to the year 2000, given the time period spanned by our sample of R&D projects.

In the present paper, we follow the same methodology to compute WACC. In the current R&D cost analysis, we have a sample of new drugs that began clinical trials in 1995 through 2007 and which have an average introduction period in the latter part of the 2000 decade. Hence, a relevant time period for our cost of capital is the mid-1990s through 2010. Our analysis yielded an after-tax weighted cost of capital of 10.5%, moderately lower than in our last paper. This reflects the fact that the cost of equity capital has declined in pharmaceuticals since 2000 (as well as for other industrial sectors). Research intensive industries, including the pharmaceutical industry, generally finance most of their investments through equity, rather than through debt. This is the case even when the cost of debt is significantly below the cost of equity (Hall, 2002; Vernon, 2004). One of the primary reasons is that servicing debt requires a stable source of cash flows, while the returns to R&D activities are skewed and highly variable (Scherer and Harhoff, 2000; Berndt et al., 2015). Given the low debt-to-equity ratios that exist for pharmaceutical firms, the cost of equity component dominates the computed WACC values in Table 3.

To obtain a real cost of capital, we first compute the nominal values and then subtract the expected rate of inflation. The nominal cost of capital in 1994 is from a CAPM study by Myers and Howe (1997). The estimates for 2000, 2005, and 2010 are based on our own analysis, utilizing a comparable approach, with a large sample of pharmaceutical firms.[18] As this table shows, the estimated nominal cost of capital for pharmaceuticals was fairly stable during the period 1994–2000 (14.2–14.9%). However, it decreased during the decade of 2000s, particularly after the global recession occurred (with a value of 11.4% observed in 2010).

As discussed in DiMasi et al. (2003), the rate of inflation was above historical values during the first part of the 1980s, but then receded back to or below historical levels throughout most of the 1990s. Hence, we utilized the long run historical value for inflation for the expected inflation level in 1994 and 2000 (3.1%), as in our prior work. For the 2000s decade, inflation was significantly below historical values. In this case, we employed a 5-year lagged moving average to compute the expected rate of inflation in 2005 and 2010 (calculated as 2.5% and 2.0%, respectively).

As shown in Table 3, our estimates for the real cost of capital varied between 9.4% and 11.8% for pharmaceutical firms over the 1994–2010 period. We elected to use the midpoint of this range, or approximately 10.5%, as the representative COC to capitalize our R&D cost estimates.

The focus of our analysis is R&D investment expenditures and privately financed resources for new drugs undertaken by the biopharmaceutical industry. Accordingly we capitalized these expenditures utilizing a cost of capital estimate based on financial data from publicly listed firms. Drug development is also sponsored and funded by government and non-profit agencies (e.g., public–private partnerships devoted to developing medicines for neglected diseases). To the extent that our cost estimates are applicable to these ventures, a social rate of discount would be appropriate to capitalize R&D outlays. We provide a sensitivity analysis in Section 6 with respect to a wide spectrum of alternative cost of capital values.

5.3. Capitalized clinical cost per investigational drug

Opportunity cost calculations for clinical period expenditures require estimates of average phase lengths and average gaps or overlaps between successive clinical phases to generate an average clinical development and regulatory review timeline. Mean phase lengths and the mean lengths of time between successive phases are shown in Table 4, along with the associated capitalized mean phase costs and capitalized expected phase costs by phase for investigational compounds. The time between the start of clinical testing and submission of an NDA or BLA with the FDA was estimated to be 80.8 months, which is 12% longer (8.7 months) than the same period estimated for the previous study. The average time from the start of clinical testing to marketing approval for our timeline was 96.8 months for the current study, 7% (6.5 months) longer than for the earlier study. The difference is accounted for by shorter FDA approval times. The period for the previous study included, in part, a period prior to the implementation of the *Prescription Drug User Fee Act of 1992* (PDUFA), and, in part, the early user fee era for which approval times were somewhat higher than for later user fee periods (Berndt et al., 2005).[19] While the approval

[18] The sample is composed of all publically traded drug firms in the *Value Line Survey* which also provides beta values and the other pharma-specific parameters used in the CAPM calculations for the relevant years. The long-term horizon equity risk premium, and the yield on long-term government bonds employed in the CAPM analysis, are from Ibbotson Valuation yearbooks for 2000, 2005, and 2010.

[19] The user fee legislation sunsets every 5 years. It has been renewed every 5 years since its original enactment. Performance goals for FDA review of marketing

Table 4
Average phase times and clinical period capitalized costs for investigational compounds (in millions of 2013 dollars).[a]

Testing phase	Mean phase length	Mean time to next phase	Capitalized mean phase cost[b,c]	Capitalized expected phase cost[b,c]
Phase I	33.1	19.8	49.6	49.6
Phase II	37.9	30.3	95.3	56.7
Phase III	45.1	30.7	314.0	66.4
Total				172.7

[a] All costs were deflated using the GDP implicit price deflator. Weighted values were used in calculating means for costs and phase times. Phase times are given in months.
[b] The NDA/BLA approval phase was estimated to be 16.0 months on average (2000–2012).
[c] Costs were capitalized at an 10.5% real discount rate.

phase averaged 18.2 months for the earlier paper's study period, that phase averaged 16.0 months for drugs covered by the current study.Other things being equal, the observed longer times from clinical testing to approval yielded higher capitalized costs relative to out-of-pocket costs. However, the discount rate that we used for the current study is also lower than for the previous study (10.5% versus 11.0%). The two effects work in offsetting ways. In addition, capitalized clinical cost per investigational compound will also depend on the gaps and overlaps between phases. On net, the ratio of mean capitalized to out-of-pocket cost per investigational compound was slightly lower for the current study compared to the previous one (1.5 versus 1.7).[20]

5.4. Clinical cost per approved new drug

Average cost estimates for investigational drugs are useful, but we are primarily interested in estimates of cost per approved new drug. As noted above, our analysis of drugs in development for the relevant period yielded a predicted overall clinical success rate of 11.83%. Applying this success rate to our estimates of out-of-pocket and capitalized costs per investigational drug results in estimates of cost per approved new drug that link the cost of drug failures to the successes.

Aggregating across phases, we found an out-of-pocket clinical period cost per approved new drug estimate of $965 million and a capitalized clinical period cost per approved new drug estimate of $1460 million. In constant dollars, these costs are 2.6 and 2.4 times higher than those we found in our previous study, respectively.

5.5. Pre-human out-of-pocket and capitalized costs per approved drug

The pre-human period, as defined here, includes discovery research as well as preclinical development. Some costs incurred during this period cannot be associated with specific compounds. To deal with this issue, we analyzed reported aggregate annual firm expenditures on self-originated new drugs by the pre-human and clinical periods. We gathered data on aggregate expenditures for these periods from survey firms for 1990–2010. Both times series tended to increase over time in real terms. Given this outcome, and the fact that the clinical expenditures in 1 year will be associated with pre-human expenditures that occurred years earlier, the ratio of total pre-human expenditures to total R&D (pre-human plus clinical) expenditures over the entire study period would yield an overestimate of the share of total cost per new drug that is accounted for by the pre-human period. To accurately estimate

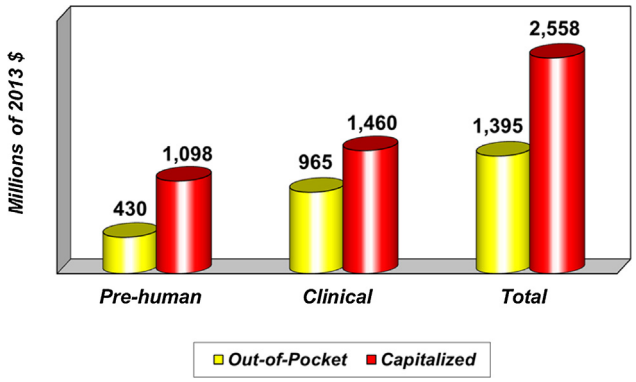


Fig. 2. Pre-human phase, clinical phase, and total out of-pocket and capitalized costs per approved new compound.

this share we built in a lag structure that associates pre-human expenditures with clinical expenditures incurred some time later.

The survey firms reported on dates of synthesis or isolation for compounds for which we sought cost data, as well as dates of first human testing. We had data for the period from synthesis to first human testing for 78 of the compounds. The average time from synthesis to initial human testing for these compounds was 31.2 months, down considerably from 52.0 months for the previous study.[21] Our analyses of clinical phase lengths and phase gaps and overlaps indicated a period of 95.2 months over which clinical period development costs are incurred. We approximated the lag between pre-human and clinical expenditures for a representative new drug as the time between the midpoints of each period. This yields a lag of 63.2 months, or approximately 5 years. Thus, we used a 5-year lag in analyzing the aggregate expenditure data, although we also examined 4-year and 6-year lags. A 5-year lag applied to the aggregate expenditure data resulted in a pre-human to total R&D expenditure ratio of 30.8%, which was only slightly different from the corresponding ratio used in our previous study (30.0%). The share was applied to our clinical cost estimates to determine associated pre-human cost estimates.

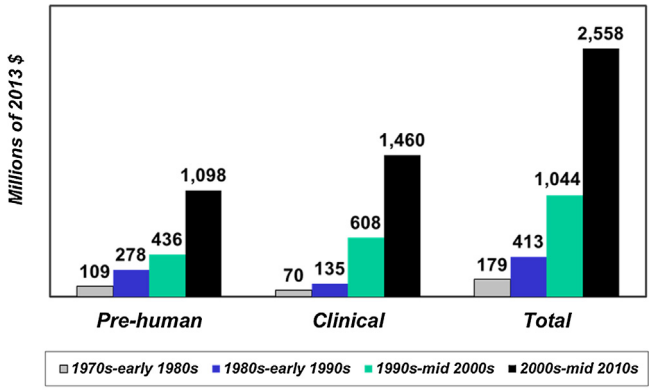
Given the estimates of out-of-pocket and capitalized clinical cost per approved new drug noted in Section 5.4 and the pre-human expenditure to total R&D expenditure ratio, we can infer pre-human out-of-pocket and capitalized costs per approved new drug of $430 million and $1098 million, respectively (Fig. 2). The results are very robust to different values for the length of the lag structure. For example, if we assume a lag of 4 years instead of 5 years, then out-of-pocket pre-human costs would be 6.8% higher. Alternatively, if we assume a 6-year lag, then out-of-pocket pre-human costs would be 8.5% lower.[22]

applications under PDUFA were tightened somewhat for some applications after the initial 5-year period.

[20] The differences in the ratios of capitalized to out-of-pocket cost for the individual phases were also small. For the current study they were 2.0, 1.6, and 1.2 for phase I, phase II, and phase III, respectively. For the earlier study, we found the ratios to be 2.0, 1.8, and 1.3 for phase I, phase II, and phase III, respectively.

[21] The results for the current study are consistent with data for a small number of compounds reported in a recently published study (Stergiopoulas and Getz, 2012). The mean time from synthesis to human testing there was 37.9 months for 17 compounds.

[22] The pre-human to total R&D expenditure ratios for four- and six-year lags were 32.2% and 28.9%, respectively.



Sources: 1970s-early 1980s, Hansen (1979); 1980s-early 1990s, DiMasi et al. (1991); 1990s-mid 2000s, DiMasi et al. (2003); 2000s-mid 2010s, Current Study

Fig. 3. Trends in capitalized pre-human, clinical and total cost per approved new drug.

5.6. Total capitalized cost per approved drug

Total cost estimates are the sum of pre-human and clinical period cost estimates. Our base case total out-of-pocket cost per approved new drug is $1395 million, while our fully capitalized total cost estimate is $2558 million (Fig. 2). Time costs (differences between capitalized cost and out-of-pocket cost) account for 45% of total cost. This share is down from the share in our previous study (50%) and that for the study that preceded it (51%). This is due in part to a shorter pre-human period and a lower discount rate.

5.7. Trends in R&D costs

Fig. 3 presents capitalized pre-human, clinical, and total cost per approved new drug for the previous three studies in this series and for our current study. In constant dollars, total capitalized cost increased 2.31 times for the second study in comparison to the first, 2.53 times for the third study in comparison to the second study, and 2.45 times for the current study in comparison to the third study. However, the samples for these studies include drugs that entered clinical testing over periods that are not uniformly distributed. In addition, while the samples were chosen on the basis of when drugs entered clinical testing, changes over time in the average length of the development process make ascribing differences in the study periods according to the year of first human testing problematic. An alternative is to determine an average approval date for drugs in each study's sample and use the differences in these dates to define the time differences between the studies. Our previous study described this approach and presented the corresponding annual growth rates between successive studies for the first three studies.

Drugs in the current study sample obtained FDA marketing approval from 2005 to 2013. The mean and median approval dates for drugs in the current study's sample were both in 2008. For the previous study, we reported that the average approval date was in 1997. Thus, we used 11 years as the relevant time span between the studies and calculated compound annual rates of growth between the two studies accordingly.

Using the period differences described here and in our previous study, we determined the compound annual growth rates between the studies for out-of-pocket and capitalized cost per approved drug for pre-human, clinical, and total costs (Table 5). Compared to the growth rate for the results in the previous study, the growth rates for total out-of-pocket and capitalized costs for the current study are somewhat higher (9.3% and 8.5% per year). The results for the current study in comparison to those for the previous study are also noteworthy in that, after a substantial decline in the growth rate for real pre-human costs described in the previous study and presented in Table 5, pre-human costs for the current study resumed a much higher rate of growth. Conversely, the growth rates for clinical period expenditures declined from the very high rates for the previous study, although they are still substantial.

5.8. Cost of post-approval R&D

As we did for our most recent study, we develop indirect estimates of post-approval R&D costs. Post-approval R&D consists of efforts subsequent to original marketing approval to develop the active ingredient for new indications and patient populations, new dosage forms and strengths, and to conduct post-approval (phase IV) research required by regulatory authorities as a condition of original approval. We follow the methodology that we used in previous study.[23] We utilize our pre-approval estimates together with aggregate pharmaceutical industry data regarding the drug development process to construct an estimate of the cost of post-approval R&D, which together with our pre-approval estimates, provide estimates of average total R&D cost per new drug covering the entire development and product life-cycle. The data that we collected from the survey firms on company annual aggregate expenditures on biopharmaceutical R&D show that over the study period these firms spent 73.1% of their prescription biopharmaceutical R&D expenditures on investigational self-originated new compounds,[24] 10.2% on investigational compounds that were licensed-in or otherwise acquired, and 16.5% on improvements to drugs that have already been approved.[25]

We cannot, however, use the percentage of aggregate R&D expenditures spent on post-approval R&D on a current basis and apply it to a pre-approval cost estimate to obtain an appropriate estimate of the cost of post-approval R&D per approved compound. The reason is that pre-approval costs occur years before post-approval costs. We used our aggregate annual firm R&D data to obtain an appropriate ratio by building in a reasonable lag structure between pre-approval and post-approval costs.

For our base results we used, as we did for the previous study, a 10-year lag for the aggregate data (which is the approximate time between median pre-approval development costs and median post-approval costs, given an 8-year post-approval expenditure period), we assumed that post-approval R&D cost per approval is the same, on average, for licensed-in and self-originated compounds, and we determined the percentage of approvals for the cost survey firms that are self-originated to estimate the ratio of post-approval R&D cost per approved compound to pre-approval cost per approved compound. The data indicated that this share was 33.4%. Applying this ratio, we estimated the out-of-pocket cost per approved compound for post-approval R&D to be $466 million (Fig. 4). Since these costs occur after approval and we are capitalizing all costs to the point of marketing approval, our discounted cost estimate is lower ($312 million). Thus, out-of-pocket cost per approved compound for post-approval R&D is 25.0% of

[23] We refer to the discussion in DiMasi et al. (2003) and an accompanying Appendix A for more detail on the method.

[24] This figure includes expenditures on biologics, vaccines, and diagnostics. The self-originated share for therapeutic investigational drugs and biologics was 71.2%.

[25] These expenditure shares are similar to those found for the previous study for the 1980 to 1999 period. The results here are also similar to figures that the trade association Pharmaceutical Research and Manufacturers of America (PhRMA) has published for its member firms for the years 2003 and 2005 to 2010. Those data do not separate out expenditures on existing products, but they do distinguish between self-originated and licensed products. Aggregating across those years, the shares for self-originated, licensed, and uncategorized were 74.3%, 17.6%, and 8.1%, respectively.

Table 5
Compound annual growth rates in out-of-pocket and capitalized inflation-adjusted costs per approved new drug.[a]

Approval periods	Out-of-pocket			Capitalized		
	Pre-human	Clinical	Total	Pre-human	Clinical	Total
1970s to 1980s	7.8%	6.1%	7.0%	10.6%	7.3%	9.4%
1980s to 1990s	2.3%	11.8%	7.6%	3.5%	12.2%	7.4%
1990s to early 2010s	9.6%	9.2%	9.3%	8.8%	8.3%	8.5%

[a] Costs for 1970s approvals are from Hansen (1979), costs for 1980s approvals are from DiMasi et al. (1991), costs for the 1990s to the early 2000s are from DiMasi et al. (2003), and costs for the 2000s to early 2010s are from the current study.

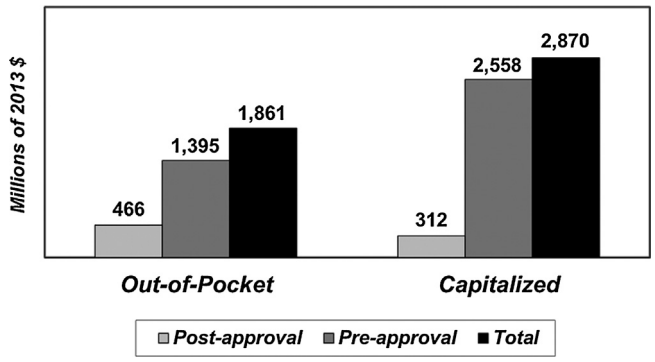


Fig. 4. Out-of-pocket and capitalized total cost per approved new drug for new drugs and for improvements to existing drugs.

Table 6
Capitalized pre-human, clinical, and total costs per approved new drug (in millions of 2013 dollars) by discount rate.

Discount rate	Pre-human	Clinical	Total
1.0%	472	1012	1476
2.0%	517	1044	1561
3.0%	567	1086	1653
4.0%	621	1129	1750
5.0%	679	1175	1854
6.0%	742	1222	1964
7.0%	811	1271	2082
8.0%	885	1322	2207
9.0%	965	1376	2341
10.0%	1052	1431	2483
11.0%	1145	1489	2634
12.0%	1246	1549	2795
13.0%	1355	1612	2967
14.0%	1473	1677	3150
15.0%	1600	1744	3344

total R&D cost (pre- and post-approval), while capitalized cost for post-approval R&D is 10.9% of total cost.

5.9. Extensions to the base case

We can extend the base case results on drug development costs prior to original approval in a number of interesting ways. The sample dataset includes information on compound-level costs for both chemical compounds (small molecules) and biologics (large molecules). As reported in the online supplement (Appendix B), we examined investigational compounds by molecule size for differences in individual clinical phase costs. Since the distributions of compounds across therapeutic classes differ for large and small molecules, we conducted a regression analysis of phase costs for investigational compounds for each of the three clinical phases, while controlling for molecules size and therapeutic class. Sample sizes were somewhat limited when cut by both sample size and therapeutic class, but we found statistically significant higher phase II costs for large molecules. However, we found that clinical approval success rates for large molecules are substantially higher than for small molecules. As a result, clinical period cost per approved compound was appreciably higher for small molecules, with the ratio of costs nearly the same as we had estimated in a previous paper for an earlier period (DiMasi and Grabowski, 2007). Compete results are given and discussed in the online supplement (Appendix B).

The base case results on full R&D costs link expenditures on drug failures to the costs of drugs that attain regulatory success. We can also estimate the clinical period cost of taking a successful drug all the way to approval by examining the data for just the approved drugs in the sample. Focusing on that subsample also allowed us to examine evidence on the costs for the more therapeutically significant drugs (according to what is known at the time of approval) by using an FDA prioritization system for reviewing drugs submitted to the agency for marketing approval. We found that clinical period costs were substantially higher for the approved compounds in the sample relative to our results for the sample as a whole, and that costs were lower (although not at a statistically significant level) for compounds that the FDA had designated for a priority review (compounds thought to represent a significant gain over existing therapy). These results are presented in full and discussed in the online supplement (Appendix B).

6. Sensitivity analysis

We examined how sensitive the results were to extreme values in the data and to changes in certain critical parameters. In particular, we focus in detail in this section on variation in the discount rate used to calculate capitalized costs. We also determine the extent to which key cost drivers (cash outlays, risks, time, and the cost of capital) explain the increase in total cost per approved drug found for this study relative to our previous study.

In addition, since all of the parameters are subject to sampling error, we conducted Monte Carlo simulations, reported on in detail in the online supplement (Appendix C), allowing all parameters to vary according to their sampling distributions (using Crystal Ball™ software). For the full capitalized pre-approval cost estimate, 80% of the simulation forecasts (set of 1000) varied between $2.3 billion and $2.8 billion. All of the forecasts varied between $1.9 billion and $3.2 billion.

Finally, we also conducted an outlier analysis to determine the impact of the most extreme values in the dataset. The results show that drugs with high and low costs have a fairly small impact on cost estimates. For example, if all cost data for the drugs with the highest and lowest aggregate clinical costs are dropped from the analysis, then the full capitalized cost estimate falls by only 3.0% (3.5% if only the drug with the highest aggregate cost is dropped). The online supplement (Appendix D) further describes in detail various outlier analyses, including those that examine results when a number of high and/or low values for each clinical phase are excluded even though no one drug has uniformly high or low values across all clinical phases.

6.1. Effects of variation in the discount rate

Table 6 shows how pre-human, clinical, and total capitalized costs would vary by discount rate at one percentage point intervals. The values for a zero percent discount rate are out-of-pocket costs. In the neighborhood of our base case discount rate (10.5%), clinical cost changed by approximately $30 million, pre-human cost changed by approximately $45 million, and total cost changed by approximately $75 million for every half of one percent shift in the discount rate. In our previous study, the base case discount rate was 11.0%. At an 11.0% discount rate, total capitalized cost here was $2634 million or 3% higher than our base case result. At more extreme values for the discount rate, Table 6 indicates that total capitalized cost with a 15% discount rate was $3334 million, or 30% higher than our base case result. Similarly, a 3% discount rate (a figure often used as a social discount rate) yielded a total capitalized cost per approved new drug of $1561 million, or 39% lower than the base case result.[26]

6.2. Impact of cost drivers

As noted in the previous section, the full cost estimate is a function of numerous parameters that interact in a non-linear (often multiplicative) manner. That makes it difficult to isolate the extent to which changes in individual parameters alone drive changes in total costs. However, we can get a sense for which parameters had the greatest impacts, in either direction, on the change in total R&D cost between the previous study and the current one by calculating what R&D costs would have been if only a single parameter (or a set of related parameters) had changed from what it was for the previous study to what we found it to be for the current study period.

Table 7 shows our results for these thought experiments for the major parameters categorized into four groupings (direct pre-human and clinical average phase cash outlays, technical risks, average development and approval times, and the cost of capital). The base result is total cost per approved new compound for the DiMasi et al. (2003) study in year 2013 dollars ($1044 million). The current study full cost estimate is 145% higher than the base result. That change reflects the cumulative effect of all parameter changes. For the table, we examined parameter-by-parameter changes from the parameter values for the DiMasi et al. (2003) study to those values found for the current study.

The largest impact on the change in costs between the studies was driven by changes in average out-of-pocket clinical phase costs, which resulted in an 82.5% increase in full cost.[27] Considering also the small difference between the studies in the estimated ratio of pre-human to clinical costs, the impact of the change in direct out-of-pocket phase costs was an increase in total cost of 85.5%. The increase in total cost was also driven to a substantial extent by much higher development risks. The overall clinical approval success rate declined from approximately one-in-five to approximately one-in-eight. That change alone accounts for a 57.3% increase in total cost. However, the impact of a lower clinical approval success rate was mitigated to a small extent by a shift in the distribution of failures to earlier in development. Taking both effects into account resulted in an increase in total cost of 47.3%. Changes in the development and approval timeline had a relatively small depressing effect on total cost. This impact was driven by a shorter pre-human testing phase and a shorter average approval phase. Average clinical development time increased modestly, and this had a relatively small impact on total cost. Overall, the effect of changes in the development and approval timeline was a 5.6% decrease in total cost. Finally, the small change in the cost of capital had a 3.1% depressing effect on total cost. The aggregation of the direct impacts across the four cost factor groupings accounted for a 124% increase in costs between the two studies. We attribute the residual increase (21%) to interaction effects.

Table 7
Impact on total capitalized cost per approved new drug due to changes in individual cost drivers (current study factor effect relative to prior study[a] cost).

Factor category	Factor (change to current study values)	Capitalized cost (millions of 2013 $)	Percentage change in cost
Direct cash outlays			
	Out-of-pocket clinical phase costs	1905	82.5%
	Pre-human/clinical cost ratio	1061	1.6%
	Overall out-of-pocket costs	1937	85.5%
Risk			
	Clinical approval success rate with prior study distribution of failures	1643	57.3%
	Distribution of failures with prior study clinical approval success rate	981	−6.0%
	Overall risk profile: clinical approval success rate plus distribution of failures	1538	47.3%
Time			
	Pre-human phase	993	−4.9%
	Clinical phase	1046	0.2%
	Regulatory review	1013	−3.0%
	Overall development timeline	985	−5.6%
Cost of capital			
	Discount rate	1012	−3.1%

[a] DiMasi et al. (2003). In 2013 dollars the capitalized cost per approved new drug for the prior study is $1044 million.

7. Critiques, sample representativeness, and validation

Our prior study results have been questioned on a number of methodological and data grounds (Angell, 2005; Goozner, 2004; Light and Warburton, 2005a,b; Love, 2003; Young and Surrusco, 2001). We have rebutted each of these criticisms in detail in a number of venues (e.g., DiMasi et al., 2004, 2005a,b). We review the critics' main arguments only briefly here.

Goozner (2004) and Angell (2005) reject opportunity cost calculations because they, in essence, deny that industrial pharmaceutical R&D expenditures can be viewed as investments at risk.[28] These points are addressed more fully in DiMasi et al. (2004). Clearly, industrial pharmaceutical R&D meets the criteria for being considered investments that have opportunity costs. In any event, an estimate with no opportunity costs is simply the out-of-pocket cost estimate.

[26] The appropriate social rate of discount for government backed expenditures has been analyzed and debated extensively in the economics literature. See for example, Moore et al., 2013 and Burgess and Zerbe, 2013. A standard reference in the cost-effectiveness literature (Gold et al., 1996) recommends 3% as the base case rate in comparing alternative medical therapies ("Therefore, we recommend that the base rate of 3% and an alternate rate of 5% be retained for a period of at least 10 years.", p.233).

[27] Given the methodology, higher out-of-pocket clinical phase costs also get associated with higher out-of-pocket pre-human phase costs.

[28] In the case of Goozner (2004), the claim is made that R&D expenditures are expenses rather than investments, because accountants have traditionally treated them as such for tax purposes (failing to recognize practical measurement problems underlying why this has been the practice, such as great uncertainty regarding future regulatory and commercial success). The basis offered for rejecting opportunity costs in Angell (2005, p.45) is simply the claim that pharmaceutical firms "have no choice but to spend money on R&D if they wish to be in the pharmaceutical business".

A number of the critiques question how representative the data were for prior studies, whether tax deductions and credits must be included, and whether any FDA application for product marketing approval (as opposed to the active ingredient that is at the core of all such applications) should be taken as the unit of observation. As noted, we have addressed all of these issues in earlier publications as they relate to our prior studies. In this section we examine the representativeness of the survey firms and data used for this study, what the level of tax credits has been in relation to R&D expenditures in recent years, an analysis of molecules that have been approved for orphan drug indications recently, and we outline a variety of methods using independent data that can be used to validate our results (full details of the methods and analysis can be found in our online supplement).

7.1. Representativeness of the survey firm data

Questions about data representativeness should be framed in terms of the population from which the sample was selected. In particular, it is relevant to compare characteristics of the investigational drugs in our cost survey sample and for our cost survey firms generally to those of all drugs in our database of top 50 pharmaceutical firms, which is the relevant population.[29] This is the main focus of the analysis in this section.

Smaller research-oriented firms may have a comparative advantage in the discovery and pre-human stages because they often have scientific researchers with close ties to the basic research underlying new classes of therapies and technology platforms. Even if this is the case, the literature indicates that smaller firms also tend to have significantly higher costs of capital, especially when they are start-ups financed by venture firms. The literature also indicates that firms with larger R&D pipelines and greater R&D experience have a higher probability of success during the costly clinical stages of drug R&D. It is not evident, therefore, that the R&D costs for compounds originating in smaller firms, whether developed internally or in alliances would be systematically lower than those originating in mid-sized and large firms. We discuss what is known about R&D metrics for small firms in Appendix E of the online supplement.

As noted, the appropriate comparator dataset for our cost survey sample is the population of investigational compounds of the top 50 pharmaceutical firms over the relevant period. There are 1442 compounds in the top 50 firm database that met our study inclusion criteria. Of these, 510, or 35.4% belonged to nine of our 10 cost survey firms.[30] Thus, the cost survey sample ($n = 106$) constitutes 20.8% of the survey firm compounds and 7.4% of the population compounds.

We determined the therapeutic class distribution for the drugs in the larger dataset for the four largest therapeutic classes and one miscellaneous class (with a wide variety of drug types) for drugs in the dataset that met our study inclusion criteria and compared it to the therapeutic class distribution for our cost sample. The population shares for antineoplastic, cardiovascular, central nervous system (CNS), and systemic anti-infective drugs were 21.5%, 8.7%, 19.0%, and 8.5%, respectively. The corresponding shares for the cost survey sample were 19.8%, 9.4%, 24.5%, and 8.5%, respectively. We used a chi-squared goodness-of-fit test to compare the therapeutic class distributions for cost survey firm drugs and for the drugs of the entire set of 50 firms in the database, and found no statistically significant differences in the class shares ($\chi^2 = 2.4257$, df = 4).

We also examined the degree to which the top 50 firms in aggregate and the sample of cost survey firms agreed in terms of how molecule type (biologic versus small molecule) and the sourcing of compounds are distributed. For the set of top 50 firms, 14.6% of their self-originated investigational compounds over the study period are large molecules, compared to 13.7% for the survey firms ($p = 0.3933$). In terms of the share of investigational compounds for the study period that are self-originated (as broadly defined here), we found the share to be 74.1% for the cost survey firms and 71.1% for all top 50 firms ($p = 0.1039$).

Finally, we also examined the phase transition and overall approval success rates for the cost survey firms and compared them to the corresponding estimates for the larger dataset. The phase transition rates for just the cost survey firms were 58.0% for phase I to phase II, 36.0% for phase II to phase III, 58.2% for phase III to regulatory review, and 89.5% for regulatory review to approval. The corresponding figures for the population, as shown in Fig. 1, are 59.5%, 35.5%, 62.0%, and 90.4%. The overall clinical approval success rate for just the cost survey firms implied by the phase transition rates is 10.9%, which compares to 11.8% for the entire dataset.

7.2. Orphan drug development

Some past critiques have focused to some extent on orphan tax credits, which can provide incentives to develop some drugs for a class of indications. We examine the extent to which these tax credits and other tax issues are empirically significant in the context of drug development as a whole in the next section. Here we briefly discuss the nature of development of molecules that are approved for orphan indications and the distinction between costs for orphan drug indications and the full development costs for molecules with orphan drug indication approvals.

Compounds developed for orphan indications may well have lower clinical development costs for those indications, as trial sizes tend to be lower.[31] The share of U.S. original new drug approvals from 2000 to 2014 for drugs with an orphan indication was 27%, and has increased in relative terms over the last 3 years of that period.[32] The most recent approval experience aside, the share of approvals sponsored by the set of population firms (top 50) matches closely the historical average for all approvals from 1987 to 2010 (22% for top 50 firms versus 23% of all approvals).[33] The survey firms were nearly indistinguishable from the population non-survey firms by this metric (21% versus 23%).

[29] The data included in the top 50 firm dataset were curated primarily from information contained in two commercial investigational drug pipeline databases that are available after payment of subscription fees. Additional information was obtained from freely available web sites. See Section 4 above for a description of data sources.

[30] One of the participating firms was outside of the top 50.

[31] Drugs for these indications, with some notable exceptions, tend to garner lower sales given limited patient populations. This contention is supported by recent data analysis conducted by IMS Health (Divino et al., 2014). They found that sales in the United States for orphan indications varied from only 4.8% to 8.9% of total pharmaceutical sales over 2007–2013. The analysts also projected that growth in orphan drug expenditures would slow over 2014–2018.

[32] The result was calculated from information provided by the FDA on its website and included in a Tufts CSDD database of NME and therapeutically significant biologic approvals. The share of new drug approvals with orphan indications has increased very recently. The *Orphan Drug Act* was enacted in 1983, but it took several years for an appreciable number of such approvals to appear. From 1987 to 1999 the orphan drug share of all new drug approvals was 23%; the same share as for the 2000–2010 period. The orphan drug share was, however, unusually high for 2014 (41%), and above-average for 2011–2013 (approximately one-third of approvals).

[33] An FDA analysis of Center for Drug Evaluation and Research (CDER) marketing applications for NMEs and new biologics for 2006 to 2010 found that approximately one-third of the applications were sponsored by small firms, and that 75% of the applications for first-in-disease therapies for orphan indications came from small firms (Lesko, 2011). Such firms may find a low R&D cost orphan disease oriented strategy attractive, given that typical sales and operating profit levels may still be sufficient to increase their market valuations.

Table 8
Number of indications tested clinically prior to initial U.S. regulatory marketing approval for therapeutic compounds approved[a] in 2014 by orphan drug status.

	Mean	Median	Range	% multiple indications
Orphan ($n=17$)	8.5	7.0	1–4	88%
Orphan cancer ($n=9$)	10.9	9.0	1–24	89%
Non-orphan ($n=22$)	2.7	2.0	1–7	73%
All approvals ($n=39$)	5.3	3.0	1–24	79%

[a] Therapeutic new molecular entities (NMEs) and new biologic entities (NBEs) approved by the Center for Drug Evaluation and Research (CDER) of the United States Food and Drug Administration (FDA).

The cost survey sample contained two compounds that were approved originally for orphan indications.[34] The average clinical period cost for these two compounds was nearly the same as the average for all sample approved compounds (94% of the overall average). One of the compounds, though, was relatively low cost, while the other was relatively high cost. This may reflect the experience of molecules approved for orphan indications generally, as total molecule cost depends not only on the approved indication, but, critically, on the total number of indications (orphan and non-orphan) pursued.

To investigate this point further, we examined the development histories of all new therapeutic drugs and biologics approved in the United States in 2014. We studied the records for these compounds in two commercial pipeline database (*IMS R&D Focus* and *Cortellis*), as well as the clinicaltrials.gov website. Table 8 demonstrates that, even with a conservative notion of what constitutes different indications,[35] molecules approved for orphan indications were investigated in a substantial number of indications prior to original marketing approval. This was particularly true for compounds approved for treating orphan cancer indications, and, in general, the orphan drugs tended to be investigated in many more indications prior to approval than was the case for non-orphan compounds.

7.3. Taxes and R&D expenditures

As in our previous studies, the cost estimates presented here are pre-tax. Our objective was to measure the level of and trends in the private sector real resource costs of developing new drugs and biologics. As discussed in DiMasi et al. (2003), if one is calculating after-tax rates of return for R&D one would need to include the effect of taxes. Under current U.S. corporate income tax accounting practices, firms are able to deduct R&D expenses at the time they incur the costs. This is in contrast to many other investments, such as plants and equipment, which must be amortized and depreciated over a longer time period. This treatment reflects the difficulty of appropriately depreciating an intangible asset such as R&D. Later, when the company earns profits from the sales of approved pharmaceuticals it cannot depreciate the R&D investment for income tax purposes. The advantage for R&D investment over investment in plant and equipment is the timing of tax payments on net income. If one were calculating the rate of return on R&D investments one would need to take into account the tax implications. Making these adjustments is complicated by the fact that major firms operate in multiple tax jurisdictions.

In DiMasi et al. (2003) we also discussed several tax credits available in the United States to firms in the biopharmaceutical industry. In particular, we examined the Research & Experimentation tax credit for increasing qualified research expenditures, which we concluded had little impact on large multinational pharmaceutical firms.[36] Since then, the Qualifying Therapeutic Discovery Project tax credit was created as part of the Patient Protection and Affordable Care Act of 2010 (http://grants.nih.gov/grants/funding/QTDP_PIM/; accessed 14.08.14). However, it is quite restrictive in that it applies to discovery projects for small firms with a limit of $5 million per taxpayer. Recently, the U.S. Congress Joint Committee on Taxation (2013) estimated tax expenditures for fiscal years 2012–2017 for the credit for increasing research activities, the Qualifying Therapeutic Discovery Project tax credit, and the advantage from expensing, as opposed to amortizing, research and experimental expenditures to be, in aggregate, in the range of $10 billion to $12 billion per year for fiscal years 2012–2017 across all U.S. corporations engaged in research activities. It is not clear how much of this is accounted for by the biopharmaceutical industry.

We also examined in DiMasi et al. (2003) the impact of tax credits for orphan drug research, and found them to be quite small in relation to total R&D expenditures for large pharmaceutical firms. The reporting requirements for orphan drug credits are such that many companies do not take the credit. The major financial incentive of the orphan drug program appears to be the intellectual property protection that is created from the granting of 7 years of marketing exclusivity. With respect to the magnitude of orphan drug tax credits utilized in the United States, the U.S. Congress Joint Committee on Taxation (2013) estimated that expected tax credits for orphan drug research are fairly small at between $700 million and $1 billion per year from fiscal years 2012–2017.

To put these tax credits and tax advantages in perspective, Battelle and R&D Magazine's 2014 Global R&D Funding Forecast (http://www.battelle.org/docs/tpp/2014_global_rd_funding_forecast.pdf?sfvrsn=4; accessed 14.08.14) estimates that approximately $79 billion will be spent in the United States on R&D by the biopharmaceutical industry.[37] Some other countries also have a number of tax credit incentives in place for R&D. However, it seems unlikely that, in aggregate, their value in relation to R&D expenditures for the biopharmaceutical industry is disproportionately higher than is the case for the United States. The Battelle and R&D Magazine's prediction of global R&D spending by the biopharmaceutical industry is approximately $171 billion. In sum, in aggregate the value of R&D tax credits and the tax advantage of expensing versus amortizing R&D expenditures for the biopharmaceutical industry appear to be no more than one-sixth of total industry R&D expenditures (and perhaps significantly less than that).

7.4. Validation

We gathered publicly available data and performed a number of independent analyses on those data to corroborate our results. Details on methodology and data are provided in Appendix F of our online supplement. The validation efforts can be grouped into those

[34] Analyzing orphan drug status for investigational compounds is problematic because the designation may be granted at any point during the development process. Thus, some compounds that might have been granted orphan drug status can be abandoned before that would occur.

[35] Indications may be defined quite narrowly. We chose a broad definition that would limit the number of different indications pursued. Specifically, we considered all trials for the same disease and that applied to the same organ system as testing on the same indication. For example, oncology compounds may be tested as first-line treatment, second-line treatment, for refractory patients, as a monotherapy, in combination with other compounds, or for special patient populations. These cases were considered to be the same indication if they applied to the same organ (e.g., breast cancer or prostate cancer).

[36] The impact may be greater for small firms if their R&D expenditures are growing more rapidly.

[37] The report estimates that the industrial life sciences sector will spend $92.6 billion on R&D in the United States in 2014. However, the report also indicates that approximately 85% of all life sciences industrial expenditures are accounted for by the biopharmaceutical industry.

that utilize micro data on elements of the development process that are then used to develop growth rate estimates for portions of the process, and those that use publicly available aggregate financial time series data and compound approval statistics for biopharmaceutical firms as a check on our estimate of overall cost.

On a micro level, we examined survey data from the National Science Foundation (NSF), published estimates of trends in clinical trial complexity and clinical trial costs per subject, and published trade association times series data on R&D employment levels. Utilizing external data on costs per subject, along with clinical trial sizes and estimated clinical approval success rates from our analyses over time, we found a compound annual growth rate in real clinical trial costs between the study periods for our previous study and the current study of 9.9%, which is close to our clinical period cost growth rate of 9.2% for out-of-pocket costs shown in Table 5. We also examined measures of clinical trial complexity (number of procedures per trial) in the published literature (Getz et al., 2008; PAREXEL, 2005) and found a compound annual growth rate of 10.0% over our study period. Finally, we utilized trade association and 10-K information on R&D scientific and professional staff employment levels and NSF data on salary levels to estimate that labor costs increased at a rate of 8–9% per year across our study periods.

We examined PhRMA time series data on the R&D expenditures of its member firms. The reported growth rate for cost survey firms was 4.9%, compared to 4.2% for the PhRMA time series data for the portion of the survey period that could be compared.[38] We also used the industry time series data, as we had in the previous study, in two ways to get a sense for the magnitude of overall costs per approved new molecule. In one approach, we estimated the portion of the reported time series expenditure levels that could be attributed to self-originated compound development. Next we determined the annual number of approvals of PhRMA-member firms that were self-originated. Finally, we used our study estimated time-expenditure profile to link aggregate R&D expenditures to approvals. For reasons expounded upon in the supplement, this will likely yield an upper bound estimate. Using this approach we found our out-of-pocket cost per approved molecule estimate to be 56% of the estimate derived from aggregate published industry data. The second approach focuses on the published industry self-originated R&D expenditure level for a single year, assumes that every self-originated member-firm approval (inclusive of failures) costs what we found to be our average out out-of-pocket cost estimate, and uses our estimated time-expenditure profile to spread costs out over time to explain reported total R&D expenditures for the year considered. As with the previous method, the outcome would be problematic if using our average out-of-pocket cost estimate explained more than the reported aggregate R&D expenditure level. We found that this approach explained 57% of the reported expenditures.

Company total biopharmaceutical R&D expenditures reported for the cost survey are consistent with the audited financial statements of the firms in that the annual values are equal to or lower than company R&D expenses found in the financial statements.[39] As another check on our overall results, we examined what survey company total biopharmaceutical R&D expenditures would be given our estimate of out-of-pocket cost per approved molecule and assuming that entry rates to survey company pipelines are in a steady state. That figure can then be compared to R&D expenditure levels reported for these firms for our cost survey (which, as noted, match audited financial statements). Full details of these calculations are in Appendix F of the supplement. Depending on assumptions, we found that we could account for between 51% and 94% of the reported total annual biopharmaceutical R&D expenditures in this way. Thus, all three approaches using aggregate R&D expenditure data suggest that our estimate of out-of-pocket cost per approved molecule is, if anything, conservative.

8. Conclusions

Studies of the cost of developing new drugs have long been of substantial interest to drug developers, drug regulators, policy makers, and scholars interested in the structure and productivity of the pharmaceutical industry and its contributions to social welfare. The interest has been strong and growing over the last few decades during which cost containment pressures for drugs approved for marketing have expanded and concerns have been raised about industry productivity in an environment in which industry structure has been evolving (Munos, 2009; Pammolli et al., 2011). The changing industrial landscape has featured consolidation among large firms, growing alliances among firms of all sizes, and the growth of a small firm sector.

We have conducted the fourth in a series of comprehensive compound-based analyses of the costs of new drug development. In the last study we reported average out-of-pocket and capitalized R&D costs of $403 million and $802 million in 2000 dollars ($524 million and $1044 million in 2013 dollars), respectively. For our updated analysis, we estimated total out-of-pocket and capitalized R&D cost per new drug to be $1395 million and $2558 million in 2013 dollars, respectively. To examine R&D costs over the entire product and development lifecycle, we also estimated R&D costs incurred after initial approval. This increased out-of-pocket cost per approved drug to $1861 million and capitalized cost to $2870 million. We validated our results in a variety of ways through analyses of independently derived published data on the pharmaceutical industry.

Our pre-approval out-of-pocket cost estimate is a 166% increase in real dollars over what we found in our previous study, and our capitalized cost estimate is 145% higher. Roughly speaking, the current study covers R&D costs that yielded approvals, for the most part, during the 2000s and early 2010s. Our previous study (DiMasi et al., 2003) generally involved R&D that resulted in 1990s approvals. The compound annual rates of growth in total real out-of-pocket and capitalized costs between the studies are 9.3% and 8.5%, respectively. These growth rates are both somewhat higher than those we found for the two previous studies (7.6% and 7.4%, respectively). Growth in out-of-pocket clinical period costs have moderated some from the 1990s, but the growth rate is still high at 9.2%. While the compound annual growth rate for out-of-pocket pre-human costs declined substantially for the previous study (from 7.8% to 2.3%), this study showed a substantially higher growth rate for pre-human costs in the new century (9.6%).

The success rate found for this study is nearly 10 percentage points lower than for the previous study. The overall change in the risk profile for new drug development by itself still accounted directly for a 47% increase in costs. It is difficult to know definitively why failure rates have increased, but a number of hypotheses worthy of testing come to mind. One possibility is that regulators have become more risk averse over time, especially in the wake of high profile safety failures for drugs that have reached the marketplace (most notably, Vioxx™, but there have been others as well). It may also be the case that the industry has generally focused more in areas where the science is difficult and failure risks are high as a result (Pammolli et al., 2011). Finally, the substantial growth in identified drug targets, many of which may be poorly validated, may have encouraged firms to pursue clinical development of more

[38] As explained in the Supplement, the growth rate for the PhRMA time series may somewhat underestimate the true growth rate.

[39] Biopharmaceutical R&D expenditures may be less than total company R&D expenditures if the firm engages in non-biopharmaceutical R&D.

compounds with an unclear likelihood of success than they otherwise would.

As can be seen from results cited in the supplement developed external to this study, as well as our own data, out-of-pocket clinical cost increases can be driven by a number of factors, including increasing clinical trial complexity (Getz et al., 2008), larger clinical trial sizes, inflation in the cost of inputs taken from the medical sector that are used for development, and possibly changes in protocol design to include efforts to gather health technology assessment information and, relatedly, testing on comparator drugs to accommodate payer demands for comparative effectiveness data. The expansion of the scope of the clinical trial enterprise during our study period is illustrated by the finding in Getz and Kaitin (2015) that for a typical phase III trial information had been gathered by sponsors on nearly 500,000 data points in 2002, but more than 900,000 data points in 2012.

Finally, it is difficult to assess whether and how regulatory burdens may have impacted changes in industry R&D costs over time. However, occasionally, an exogenous shift in the types and amount of information perceived as necessary for regulatory approval for particular classes of drugs can be instructive. For example, during our study period the FDA issued guidance (Food and Drug Administration, 2008) for the development of drugs to treat diabetes in late 2008 that highlighted a need to better assess and characterize cardiovascular risks for this class of compounds, after a number of cardiovascular concerns emerged regarding a previously approved drug (Avandia®). A number of development metrics positively related to R&D costs can be examined pre- and post-guidance. DiMasi (2015), for example, found that average U.S. clinical development times increased from 4.7 to 6.7 years for diabetes drugs approved in the United States from 2000–2008 to 2009–2014, respectively. In addition, Viereck and Boudes (2011) found that the number of randomized patients and patient-years in NDAs for diabetes drugs approved from 2005 to 2010 increased more than 2.5 and 4.0 times, respectively, before and after the guidelines were issued. Our sample data show that diabetes drugs were among the most costly (particularly for phase III [92% higher than the overall average]).

Our analysis of cost drivers indicates that the rate of increase observed in the current study was driven mainly by increases in the real out-of-pocket costs of development for individual drugs and by much higher failure rates for drugs that are tested in human subjects, but not particularly by changes in development times or the cost-of-capital. Continued analysis of the productivity of biopharmaceutical R&D should remain an important research objective.

Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhealeco.2016.01.012.

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EXHIBIT B

EMBO reports

viewpoint

Accelerating drug discovery

Although the evolution of '-omics' methodologies is still in its infancy, both the pharmaceutical industry and patients could benefit from their implementation in the drug development process

Sandra Kraljevic, Peter J. Stambrook & Kresimir Pavelic

Drug development, from initial discovery of a promising target to the final medication, is an expensive, lengthy and incremental process. The ultimate goal is to identify a molecule with the desired effect in the human body and to establish its quality, safety and efficacy for treating patients. The latter requirements ensure that the approved medication improves patients' quality of life, not only by curing their illness, but also by making sure that the cure does not become the cause of other problems, namely side effects (Snodin, 2002). It also means that this is a particularly costly and prolonged process. At present, bringing a single new drug to market costs around US$800 million, an amount that doubles every five years. According to the US Food and Drug Administration (FDA), it takes, on average, 12 years for an experimental drug to progress from bench to market. Annually, the North American and European pharmaceutical industries invest more than US$20 billion to identify and develop new drugs, about 22% of which is spent on screening assays and toxicity testing (Michelson & Joho, 2000). In addition to costs, administrative hurdles have become problematic, which contributes to the high failure rate of new drug candidates. Of 5,000 compounds that enter pre-clinical testing, only five, on average, are tested in human trials, and only one of these five receives approval for therapeutic use (Fig 1). It is not surprising that, while development costs have increased, the absolute number of newly approved drugs has constantly decreased for several years. These trends—increasing costs for drug development and testing and greater scrutiny of the approval process—create a growing problem both for the drug industry and for patients who are desperately waiting for new drugs to treat their illnesses. It is therefore timely to consider how new technologies, namely functional genomics, proteomics and the related field of toxicogenomics, can help to speed up drug development and make it more efficient.

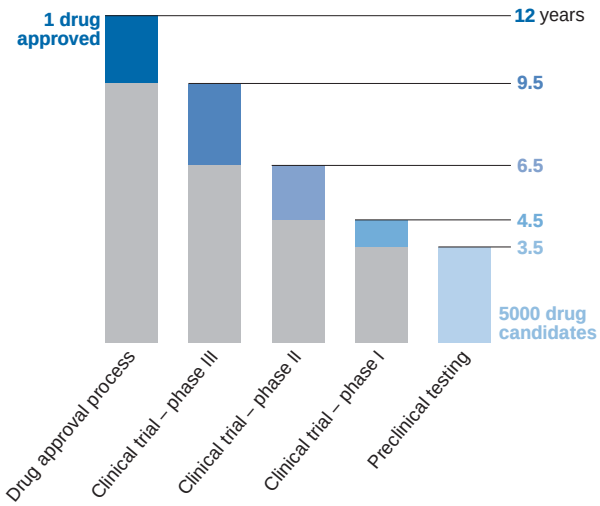

Fig 1 | Current time-scale of drug approval process. New drugs are developed through several phases: synthesis and extraction of new compounds, biological screening and pharmacological testing, pharmaceutical dosage formulation and stability testing, toxicology and safety testing, phase I, II and III clinical evaluation process, development for manufacturing and quality control, bioavailability studies and post-approval research. Before testing in humans can start, a significant body of pre-clinical data must be compiled, and appropriate toxic doses should be found for further *in vivo* testing to ensure human safety. Toxicology, pharmacology, metabolism and pharmaceutical sciences represent the core of pre-clinical development.

The current process of identifying a new drug and bringing it to market involves several lengthy steps (Fig 2). It starts with the synthesis of small molecules to target specific proteins or enzymatic activities in living cells. The next step is to identify those compounds that have the best chance of survival in clinical trials. These drug candidates are then subjected to a battery of *in vitro* tests to investigate potential class- and compound-specific toxicity; it is in these early stages that most candidates fail. Compounds that make it through this stage are then subjected to acute and short-term *in vivo* toxicology studies. All information gathered in these pre-clinical stages is then used as a guide for subsequent clinical trials in human volunteers and patients. It is on these pre-clinical and clinical tests that new technologies could have the largest impact.

Functional genomics, which includes proteomics and transcriptomics, is an emerging discipline that represents a global and systematic approach to identifying biological pathways and processes in both normal and abnormal physiological

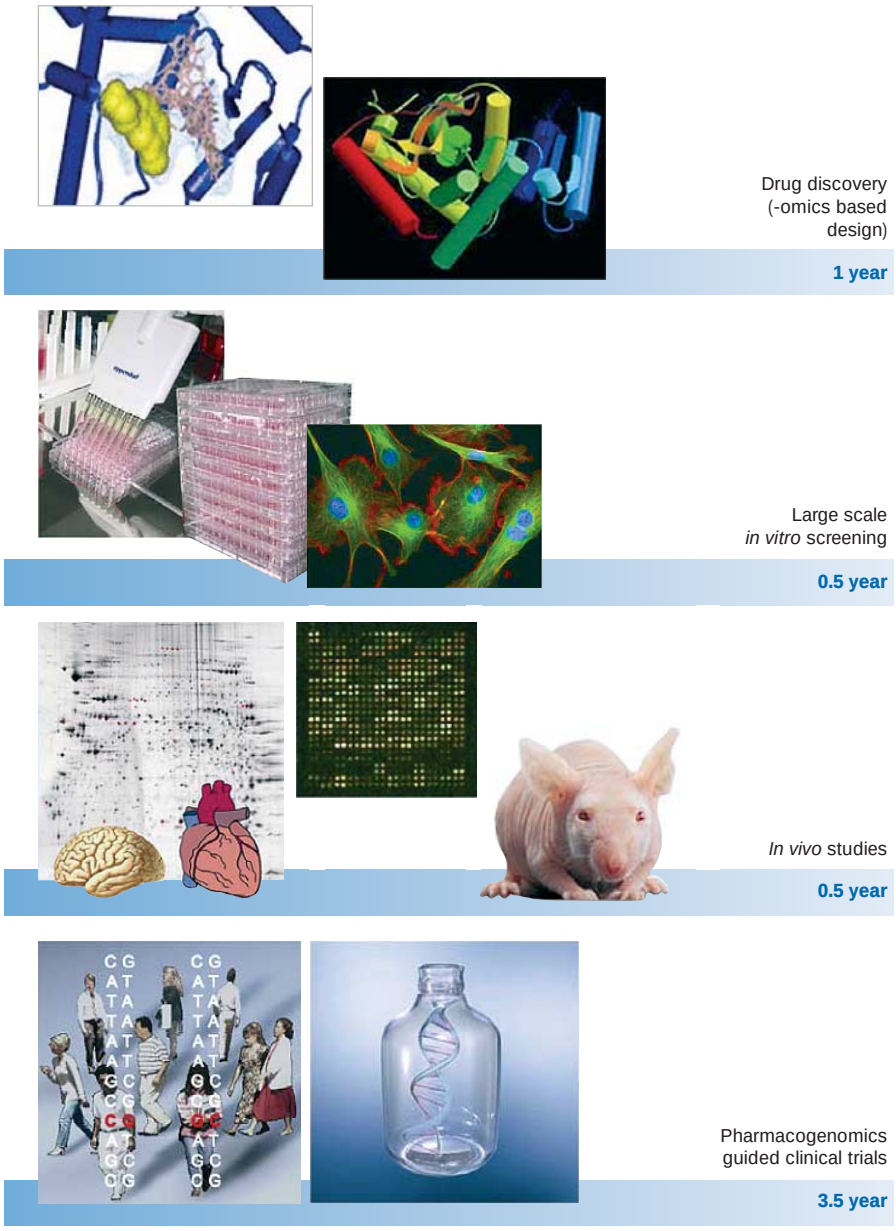

Fig 2 | The increasing availability of quantitative biological data from the human genome project, coupled with advances in instrumentation, reagents, methodologies, bioinformatics tools and software, are transforming the ways drug discovery and drug development are performed. The ability to combine high-throughput genomic, proteomic, metabolomic and other experimental approaches with drug discovery will speed up the development of safer, more effective and better-targeted therapeutic agents. Functional genomics approaches should be exploited throughout the entire drug development process. Particularly, combinatorial chemistry, *in silico* structure prediction, new scaffold-like molecular weight compounds targeting conserved regions of multiple protein family members, accompanied by high-throughput X-ray crystallography and proteomic-based drug target discovery, will reduce the time required for drug discovery. Large-scale (robotics) *in vitro* screening using cultured human cell lines and *in vivo* studies on 'humanized' mouse models combined with functional genomic analysis of different organs will speed up testing. Finally, pharmacogenomics-guided clinical trials, followed by toxicogenomics-based analyses should shorten the clinical phase of testing by as much as 3–4 years.

states. It uses high-throughput and large-scale methodologies combined with statistical and computational analyses of the results. The fundamental strategy of functional genomics is to expand biological investigations beyond studying single genes and proteins to a comprehensive analysis of thousands of genes and gene products in a parallel and systematic way. Given that about 30% of the open reading frames in the human genome have as yet unknown biological functions, scientists have begun to shift from using genome mapping and sequencing for determining gene function towards using functional genomic approaches, which have the potential to rapidly narrow the knowledge gap between gene sequence and function, and thus yield new insights into biological systems.

In transcriptomic studies, DNA microarray analyses have already become standard tools to study transcription levels and patterns in cells (Gershon, 2002; Macgregor, 2003). Furthermore, advances in two-dimensional gel electrophoresis and mass spectrometry are providing new insights into the function of specific gene products (Banks *et al*, 2000; Jungblut *et al*, 2001; Lefkovits, 2003). Full understanding of the proteome, however, requires more than gene expression levels as many proteins undergo post-translational modifications that dictate intracellular location, stability, activity and ultimately function. Relying exclusively on mRNA levels to measure protein function can therefore be misleading (Choudhary & Grant, 2004), and thus requires additional information about protein levels and modifications as well as signalling pathways and metabolite concentrations and distribution. These large-scale approaches, aided by using bioinformatics to analyse the data, now generate more biological information than previously possible.

The application of functional genomics to drug discovery provides the opportunity to incorporate rational approaches to the process (Fig 2). Combinatorial chemistry—using high-throughput technologies to rapidly synthesize a huge range of new compounds—and computer-assisted drug design, together with information from emerging proteomics methodologies, are now being exploited to identify new drug targets. The expectation is that combinatorial chemistry, along with computer analysis of the 30,000 or so human genes and their protein products, will yield new

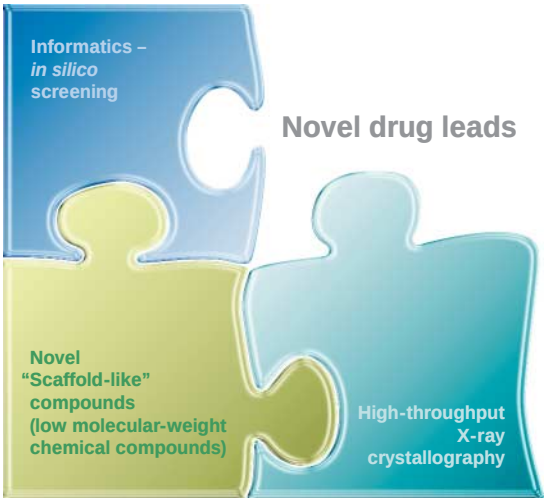

Fig 3 | New chemical approaches and biological assays combined with bioinformatics provide a general ability to globally assess many classes of cellular and other molecules. Such attempts are likely to expand the repertoire of potential therapeutics directed towards a particular molecular target in the near future.

information on hitherto unidentified drug targets. Because traditional high-throughput screening of drug candidates is inherently inefficient, virtual screening of libraries of existing compounds should be an excellent method for *in silico* prediction for active therapeutics (Dolle, 2002; Jorgensen, 2004). Plexxikon, a drug company in Berkeley (CA, USA), is already exploiting this approach by synthesizing new low-molecular-weight 'scaffold-like' compounds that interact broadly with many members of a protein family and target their conserved regions. By combining low-affinity biochemical assays and high-throughput X-ray crystallography, the company identifies promising scaffold compounds for lead development. This platform is unique in that it combines high-throughput co-crystallography, parallel biochemical assays, informatics, screening of compound libraries and chemistry, all combined to accelerate the drug discovery process (Fig 3).

Notwithstanding these novel approaches, large-scale methodologies will become an indispensable tool for understanding drug responses and will provide a rational basis for predicting toxicological outcomes. These new tools should therefore reduce the time and costs required for identifying mechanisms of drug action and possible toxic effects, thereby facilitating the speed with which a new potential drug reaches the market. Better understanding the processes by which drug candidates affect the human body and identifying the cellular factors and processes with which these compounds interact will be the key to improved therapeutics. This particular application of functional genomics to toxicology is defined as toxicogenomics. It allows researchers to identify the toxic effects of a given compound at the level of mRNA translation and gather additional valuable information on protein function and modifications as well as metabolic products (Aardema & MacGregor, 2002; Boorman *et al*, 2002; Lindon *et al*, 2004; Robosky *et al*, 2002).

Microarray-based toxicogenomic experiments to describe changes in gene-expression profiles induced by a toxic compound may help to establish signature markers of toxicity that are characteristic for a given compound. Recent studies have shown that chemicals with similar mechanisms of toxicity induce characteristic gene-expression profiles (Burczynski *et al*, 2000; Waring *et al*, 2001). The microarray data may also provide supporting evidence for potential mechanisms of toxicity (Amin *et al*, 2004; Hamadeh *et al*, 2002; Newton *et al*, 2004; Waring *et al*, 2001). Two related approaches have been used to classify toxicants on the basis of changes in expression profiles. The first focuses on identifying specific genes whose expression is altered by exposure to a toxicant, so that these can be used as a standard for toxicity tests. The second aims to classify chemicals on the basis of their capacity to alter transcriptional profiles similarly to known toxicants. These strategies may eventually lead to targeted, specific toxicity arrays, which could lower experimental costs and provide better mechanistic data. As public gene-expression databases grow, more toxicological markers will be added and will contribute to greater predictive capacity.

There is considerable interest in using gene-expression profiling to define markers both for desired pharmacological activities and for toxic effects. Such markers can be used to characterize drug candidates and select those with optimal properties for further development. Similarly, proteomics offers a comprehensive overview of the cellular protein complement and can provide useful data about alterations in protein expression after exposure to a toxicant (Fountoulakis & Suter, 2002; LoPachin *et al*, 2003). A toxicant can act on proteins at many levels: by affecting gene expression, it can induce changes in protein levels, and toxicant-induced oxidative stress can cause secondary damage to proteins. Furthermore, toxicants acting directly or indirectly on their protein targets can alter important post-translational modifications or enhance or decrease stability. All these processes individually or collectively can lead to the disruption of normal protein function in a cell (LoPachin *et al*, 2003).

> Better understanding the processes by which drug candidates affect the human body and identifying the cellular factors and processes with which these compounds interact will be the key to improved therapeutics

Toxicogenomics is already moving from being a purely descriptive science towards being a predictive tool (Fig 4). The identification of more genetic, protein and metabolic toxicity markers allows predictive models of toxicity. Furthermore, these can be grouped into one or several experiments to test which markers are modified by exposure to the compound under investigation. Administration of several doses of a toxicant at different intervals then allows for the separation of pharmacological effects from toxic responses. But to achieve a level of predictability and reliability that is acceptable for drug development and testing, it will require identifying more true markers for toxic response and/or induced toxicity. Such a high confidence in marker prediction will be achieved only by comparing data from large reference databases, multiple doses, different treatment periods, post-exposure points and biological models for each condition.

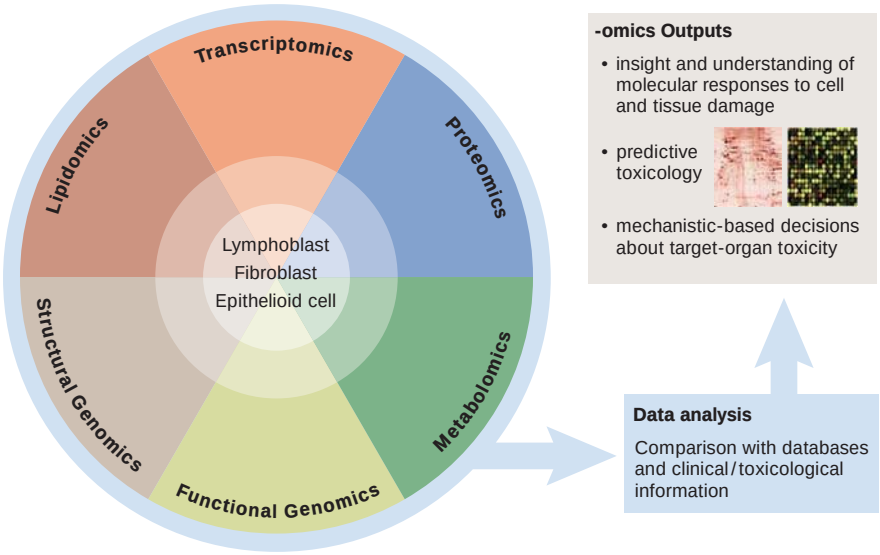

Fig 4 | The advantages of '-omics' approaches in the drug development process

The implementation of toxicogenomics in toxicology and eventual drug development depends on several factors. The first requires further advances in bioinformatics. Analysing and interpreting expression changes in hundreds of genes and modifications of proteins and metabolic pathways is a daunting task, even when dealing with a small number of samples. Biological pathways are highly complex and interconnected, and high-throughput experiments commonly generate many false-positive and false-negative signals. Advances in biocomputing and new analytical tools, however, are already improving the interpretation of large-scale expression data and contribute to mechanistic and predictive information that is indispensable for drug discovery and development. The second factor concerns the proprietary issues that result from costly large-scale studies on toxic effects performed by pharmaceutical companies. It is important that this information is made freely available for other companies and researchers to enable them to develop new predictive tests and models. The third challenge is the standardization of raw data deposition in data banks (Kramer & Kolaja, 2002). The minimum information content for microarray experiments, for instance, is already a topic for debate (Ball *et al*, 2002; Brazma *et al*, 2001). In brief, the application of functional genomics methodologies to toxicology should optimize the prediction of drug responses. Such a global analysis will lead to a better understanding of biological mechanisms that cause toxic responses. As Castle and colleagues (Castle *et al*, 2002) argued, these global approaches will provide a better insight into human toxicology than current developments and have the potential to identify a toxicant earlier and faster in drug development.

Further down the development pipeline, toxicogenomics could also help to make clinical trials safer and more efficient by identifying either poor responders or those who are at particular risk of adverse side effects. One of the main functions of clinical research is to assess possible deleterious properties and side effects in humans of the drug under investigation. A central role in how humans react to a drug is played by the drug-metabolizing cytochrome P450 (CYP) enzymes in the liver. Patients with non-functional CYP alleles are at particular risk for adverse side effects, whereas those with additional copies respond poorly or not at all. The variability of CYP genes thus underlies the variable intensity of drug effects, adverse side effects, toxicity and duration of the toxic response for identical drug doses. In addition, many adverse drug effects are not due to single gene modifications but are polygenic in nature, and different combinations of haplotypes may thus exacerbate or attenuate a toxic response. Again, a toxicogenomic approach to identifying deleterious polymorphisms and the use of RNA expression profiles should help to overcome such problems. In this context, pharmacogenetics, the study of inherited variations in drug metabolism and drug response, could be used as a tool in clinical trials, either prospectively or retrospectively. Prospective genotyping may be used to include or exclude poor metabolizers or those at risk of adverse side effects. Retrospective genotyping can help to generate new hypotheses for further testing or explain unexpected events, such as outliers or adverse drug reactions. As the field of pharmacogenomics is relatively new, most experimental results are not yet suitable for regulatory decision-making; however, efforts to standardize methods and assays are already under way.

> Given that adverse drug reactions are the fifth leading cause of death in the USA … the application of pharmacogenomics to identifying those at risk before treatment has huge potential for using existing drugs more safely and efficiently

In addition, advances in toxicogenomics will also benefit patients in predicting the efficiency and side effects of existing drugs. It has been known for some time that different people in a population respond differently to a given drug. Genetic polymorphisms in genes that encode drug-metabolizing enzymes, transporters, receptors and other proteins are abundant and cause these individual differences in drug responses. For instance, specific variations in the gene that encodes thiopurine methyltransferase (TMPT)—the primary enzyme that metabolizes 6-mercaptopurine and a standard therapeutic for childhood leukaemia—may cause a life-threatening toxic reaction. Although these adverse reactions are well documented and understood, a recommendation for genetic testing before therapy has been vigorously opposed for several reasons: the tests are still rather complex and expensive, and their reliability needs to be improved. Also, training and familiarization of oncologists with genetic testing is needed to achieve a consensus on mandatory testing. Another

example of drug specificity is the use of Herceptin® to treat breast cancer, an effective drug for the 25% of patients who have a mutation in the HER2 receptor gene. A diagnostic test for mutations of the gene now helps to identify those patients who will respond positively to treatment with Herceptin.

There are numerous other benefits of using genetic markers, not only as a guide during drug development but also in treatment. Pharmacogenetics, for instance, promises a rapid elucidation of genetic inter-individual differences in drug disposition, thereby providing a stronger basis for optimizing drug therapy to each patient's genetic makeup. This will lead to individualized therapies in which risks are minimized and desired drug effects are maximized. Although it is financially impractical to design a drug specifically targeted to each patient's genetic constitution, it should be possible to target particular haplotypes and to increase a drug's efficacy or decrease its toxicity across a wider patient population (Evans & Johnson, 2001; Goldstein, 2003). This personalized approach would be based on molecular profiling and would thereby maximize benefit for the patient. Given that adverse drug reactions are the fifth leading cause of death in the USA, causing more than 100,000 fatalities each year (Lazarou *et al*, 1998), the application of pharmacogenomics to identify those at risk before treatment has huge potential for using existing drugs more safely and efficiently.

But we are not there yet. Large-scale approaches using microarray data analysis have come under criticism because of inter-laboratory, and sometimes even intra-laboratory, variability. This is mainly caused by the difficulties in identifying uncontrolled or unknown variables. Tissue heterogeneity and sampling error introduce additional variability to expression profiling. Tissues from individuals of different ethnicities lead to significant polymorphic noise between individuals, unrelated to the direct effect of the toxicant under study. The relative effect of these experimental variables on expression profiling in humans, including tissue source and patient ethnic background, is an important challenge for the design of better diagnostics (Novak *et al*, 2002).

> …pharmaceutical companies are still hesitant to integrate these methodologies because they fear that their use will engender new regulations for clinical trials

> Ultimately, it will be market forces that decide whether the pharmaceutical industry will start using the large-scale '-omics' approaches

In addition, the pharmaceutical industry is concerned that clinical trials could become even more costly if clinical pretesting is required to determine who should or should not participate. Identifying non-responders, however, has the potential to reduce the cost of drug development by making clinical trials more focused. It should be emphasized that the pharmaceutical industry is a profit-making industry, and that pharmaceutical companies are intent on reaching as many consumers as possible with an approved drug. Because only about one-third of patients benefit from any given prescription drug, companies have little incentive at present to develop tests that alert the remaining two-thirds of their customers to the fact that they are not benefiting. But we would argue that linking a new drug to a pharmacogenomic trait and implementing new functional genomics methods in drug discovery and drug development would ensure profit, while drug discovery and pre-clinical studies should be affected only minimally, if at all. First, true responders would be identified prospectively and properly dosed, which would also save healthcare money spent on adverse effects. It would also lower the risk of the ultimate and most damaging failure: that a company has to pull a drug from the market when serious side effects become known after approval, which not only creates huge losses in monetary terms but also in consumer trust and credibility, notwithstanding the threat of lawsuits. Second, toxicogenomic-guided preclinical studies and subsequent pharmacogenomic-focused clinical trials would shorten the drug development process and significantly lower costs (Fig 2). Despite these advantages, pharmaceutical companies are still hesitant to integrate these methodologies because they fear that their use will engender new regulations for clinical trials (Eisenberg, 2002; Lesko & Atkinson, 2001). Nevertheless, many pharmaceutical companies have joined the Single Nucleotide Polymorphisms Consortium, which will determine the frequency of certain disease-linked single-nucleotide polymorphisms (SNPs) in three major world populations. The aim is to draw a map of disease SNPs to improve the understanding of disease processes and thus facilitate the discovery and development of safer and more effective therapies. GlaxoSmithKline (Uxbridge, UK) has formed a partnership with Affymetrix (Santa Clara, CA, USA) for its GeneChip technology for the development of genechips for HIV to correlate virus variants with the efficacy of antiviral drugs and drug combinations. In addition, GlaxoSmithKline now uses genotyping in 50 clinical trials in the development of 15 compounds worldwide. This clearly shows that the pharmaceutical industry is responsive to the reality of inter-individual variability in its development of new drugs. Ultimately, it will be market forces that decide whether the pharmaceutical industry will start using the large-scale '-omics' approaches. If it leads to cost savings, as we believe it will, pharmaceutical companies will inevitably adopt them.

From the patients' and regulators' points of view, does the pharmaceutical industry have an obligation to adopt the new '-omics' methodologies? So far, their use is not required in seeking approval of a new drug, although the FDA is already drafting 'Guidance for Industry: Pharmacogenomic Data Submissions'. But before forcing companies to adopt these new technologies in pre-clinical research and clinical trials, it would be prudent to pause and take stock. So far, there is not sufficient assurance that these new methodologies and procedures are able to meet the requirements of safety,

> So far, there is not sufficient assurance that these new methodologies and procedures are able to meet the requirements of safety, accuracy and clinical validity

accuracy and clinical validity. The new techniques are in fact still inadequate to ensure safety and accuracy, because of a lack of uniformity in the use of new technologies between different laboratories, a lack of uniformity of data and a large variability in the interpretation of these data (Eisenberg, 2002). Before they can be implemented in standard drug development and testing, it is important to achieve consensus on, or at least acceptance of, issues such as standardized materials, standards for assay validation and specific regulatory guidelines for the validation of test results.

The evolution of '-omics' methodologies is still in its infancy, and it is important that these approaches are further developed and standardized before they are implemented in drug development for the benefit of the patients and the pharmaceutical industry alike. Nevertheless, they are powerful tools for understanding signalling and biochemical pathways and for elucidating the mechanisms in disease and drug disposition. For that reason, they will eventually facilitate the development of new drugs and the better use of existing ones. More importantly in the short term, they will help to make the drug development process faster and more efficient by eliminating flawed drug candidates early on and thus making sure that when drugs fail, they fail 'cheaply' and not after a long and expensive process of pre-clinical and clinical testing. This alone would mean a huge improvement in light of ever increasing costs for drug development, decreasing drug approvals and the fact that many diseases, cancers and others, cannot yet be treated efficiently and safely.

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doi:10.1038/sj.embor.7400236

EXHIBIT C

Pharmaceutical Price Regulation

Pharmaceutical Price Regulation

Public Perceptions, Economic Realities, and Empirical Evidence

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and
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The AEI Press
Publisher for the American Enterprise Institute
WASHINGTON, D.C.

Distributed to the Trade by National Book Network, 15200 NBN Way, Blue Ridge Summit, PA 17214. To order call toll free 1-800-462-6420 or 1-717-794-3800. For all other inquiries please contact the AEI Press, 1150 Seventeenth Street, N.W., Washington, D.C. 20036 or call 1-800-862-5801.

Library of Congress Cataloging-in-Publication Data

Vernon, John A.
Pharmaceutical price regulation : public perceptions, economic realities, and empirical evidence / John A. Vernon and Joseph H. Golec.
p. ; cm.
Includes bibliographical references.
ISBN-13: 978-0-8447-4277-9
ISBN-10: 0-8447-4277-5
1. Pharmaceutical industry—Government policy—United States.
2. Drugs—Prices—Law and legislation—United States. I. Golec, Joseph.
II. Title.

HD9666.6.V47 2008
338.4'361510973--dc22

2008049681

12 11 10 09 1 2 3 4 5

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Introduction

Over the past forty years, pharmaceutical innovation has saved countless lives and improved the quality of life for millions of people. Although these benefits are enormous, the costs of developing breakthrough medicines are staggering, and rarely appreciated. The average cost of bringing a single new drug to the marketplace—covering years or even decades of research and development, safety tests, clinical trials, and regulatory approval—is about $1 billion (DiMasi, Hansen, and Grabowski 2003). The process isn't just expensive, it's risky. For every blockbuster drug, dozens of other drugs fail to earn back their upfront investment.

What propels the pharmaceutical industry to keep taking these risks? It is the expectation that as physicians and consumers embrace the new medicines, the drug companies themselves will be able to make enough profit over time to justify their expensive effort.

Unfortunately, today drug development is under siege, both around the world and, increasingly, in the United States. The large profits earned on a relatively small number of successful, high-priced medicines have created a clamor for government-imposed price controls. At least ten developed countries control "launch" prices on new drugs. At least sixteen countries control reimbursement prices. Moreover, most of Western Europe, Canada, Australia, and New Zealand have imposed a system of indirect controls by requiring cost-effectiveness analysis (CEA) before approving payment for a drug. The United Kingdom has perhaps the most stringent form of CEA; it recently refused to pay for Alzheimer's drugs in all but the most severe cases, triggering a patient backlash.

So far, the U.S. Medicare program has not adopted a similar policy

(Neumann, Rosen, and Weinstein 2005). Doing so would be widely unpopular. Yet the Centers for Medicare and Medicaid Services (CMS) could soon yield to budget pressures from the new Medicare drug benefit and start formalizing reimbursement decisions using CEA methods. In 2006, the influential Institute of Medicine released guidelines (at the request of the U.S. Office of Management and Budget) on how best to implement and conduct these analyses (Miller, Robinson, and Lawrence 2006).

Regulators have questioned some drugs' effectiveness in treating life-threatening diseases, especially given their sky-high prices. In 2007 and again in 2008, the Food and Drug Administration (FDA) expressed concerns about Aranesp and Epogen, developed by Amgen, and Procrit, developed by Johnson & Johnson. Separately, members of Congress criticized the companies for aggressive marketing of the drugs. These drugs, used to treat anemia caused by kidney disease or chemotherapy, had combined sales of $10 billion in 2006 and were the single biggest drug expense for Medicare (Berenson and Pollack 2007).

Controversy swirls around pricing of some of the most high-profile, high-priced breakthrough drugs that have emerged from big-budget, high-risk R&D efforts. Look, for instance, at Genentech Inc.'s Avastin. Used to treat colorectal, lung, and other cancers, Avastin can cost $55,000 or more for a year's supply. Genentech is under increasing pressure from Congress and Medicare to curb prices, but Genentech's chief executive argues that the company must charge premiums on Avastin and other successful anticancer drugs to recoup the company's $1.8 billion annual R&D budget (Chase 2007).

Indirect forms of price controls are already on the rise across the United States, as exemplified by the ongoing controversy over legalized drug importation. Bills are pending in Congress that would legalize reimportation of pharmaceuticals nationally. As we will argue, allowing drug reimportation is a frontal assault on the future of pharmaceutical industry R&D. Drug importation undermines drug companies' efforts to charge different prices in different markets. This erosion of competition leads to a single worldwide price,

one that is simultaneously too high for many poorer countries and too low for drug companies seeking to recoup their upfront R&D investments.

Advocates in the United States and abroad believe that direct or indirect price controls such as CEA and drug reimportation can provide a free lunch. In their view, pharmaceutical companies can charge lower prices and still make enough profit to encourage them to develop future innovative medicines. Unfortunately, these advocates, as well as a large segment of the American public, have failed to grasp the connection between the temporarily high prices paid for new drugs and the level of R&D that takes place inside pharmaceutical and biotechnology companies. A random sampling of 1,006 Americans surveyed in 2005 indicated a telling lack of knowledge about the pharmaceutical R&D process:[1]

- Only 40 percent of the respondents believed that if the government controlled drug prices, R&D spending would drop. Nearly half said spending would be unchanged, and 15 percent thought it would rise.

- Only 27 percent of the respondents believed that allowing drug importation from Canada would result in a drop in R&D expenditure. Moreover, 48 percent "strongly" disagreed that importation would hurt research.

- Nevertheless, the survey turned up strong evidence that Americans want pharmaceutical R&D to continue. Given a choice between lower prices on existing drugs and continued R&D, 55 percent voted for continued research and only 36 percent favored lower costs.

This monograph will argue that pharmaceutical price controls constitute a short-sighted, wrong-headed, and possibly dangerous policy. The prices set by the free market are the signals that corporations need in order to decide whether to undertake expensive, risky research into new drugs. Free-market pricing is essentially a

voting mechanism, whereby consumers can send signals to producers about what they value.

As we will argue, there is an unmistakable historical connection between price controls and lower levels of drug R&D. By extension, price controls ultimately lead to the introduction of fewer new, and potentially life-saving, medicines. In short, there is no free lunch in drug pricing. Pharmaceutical price regulations reduce pharmaceutical R&D spending, and this monograph will demonstrate the fallacy of believing otherwise.

Europe's experience with price controls is one proof of our point. The European Union (EU) has largely controlled prices, and R&D spending has dropped as a result. Between 1985 and 2004, the European Union's price controls resulted in a near-zero drug inflation rate, with a cumulative 4 percent increase in prices over a twenty-year period (Golec and Vernon 2006). But this tight control over drug spending led to very sharp restraints on drug R&D spending. In the mid-1980s, Europe's drug R&D spending exceeded that of the United States by 24 percent. But since 1986, Europe's pharmaceutical industry R&D has grown at merely one half the rate of America's. By 2004, Europe's spending trailed U.S. spending by 15 percent.[2]

This reversal occurred at a time when U.S. drug prices rose by 51 percent, when U.S. firms' profit margins far exceeded those of EU firms, and when stock market returns of U.S. pharmaceutical companies were double those of their European counterparts. These are, we argue, the key ingredients of a robust R&D culture. Our models over this time horizon suggest that EU-type price controls in the United States would have led to a decline of about 40 percent in R&D spending over that eighteen-year span.

This monograph will also show that America's mere flirtation with strict government price controls—the Clinton health plan of 1993—took a heavy toll on the very companies that conduct the most intensive R&D into new drugs. Our research into the stock market effects of the Clinton plan shows that the more intensely R&D-focused a drug company, the more its stocks dropped in the aftermath of the plan's announcement. Small biotechnology firms' stock prices fell the most, and recovered only slowly.

Our strong contention is that the U.S. pharmaceutical market is relatively free and has worked reasonably well. For example, the early success (and profits) of Merck's Mevacor led to the introduction of other statins such as Merck's Zocor, Bristol-Myers Squibb's Provachol, Pfizer's Lipitor, AstraZeneca's Crestor, and Schering-Plough's Zetia. Each drug represents an advance, and through price and sales, the producer and the consumer signal one another about just how advanced and useful it is, and how desired.

Critics argue that drug companies invest billions of dollars in frivolous "lifestyle" drugs. Even if this is so, it raises a valuable question: what kinds of drug development would likely be starved by price controls? Our evidence suggests that it would *not* be the so-called lifestyle drugs that would suffer, but instead life-saving drugs, such as Gleevec (for the treatment of leukemia), because they tend to be higher priced.

Some believe that free-market prices do not work well for pharmaceuticals because consumers cannot properly judge the value of complex, high-technology goods. But consumers often rely on experts (e.g., financial advisers, lawyers, consultants) to help them to judge the effectiveness of many complex goods in areas where they lack expertise. For pharmaceuticals, consumers rely on physicians and pharmacists, and even trusted health care Web sites such as WebMD.

Free-market prices certainly work quite well for many other high-tech products. For example, consumers signaled to all potential producers of mobile communications devices that they were willing to pay a high price (and support high profits) for a device like the Blackberry Smartphone. Blackberry maintained its relatively high price until a better product (iPhone) came along. Blackberry's response to the emergence of a superior product has been to lower its own price.

It is possible to object that the market for drugs differs from the market for mobile communications devices. Consumers in the latter market may accept high prices, which signal high value and often exclusivity—that is, only those willing and able to pay the price may possess the good. Unlike iPhones, however, health care is

often regarded as a necessity rather than a luxury, a basic human entitlement that should be available to all at a "fair" (i.e., government-controlled) price.

But this argument fails to consider that even low-priced, generic drugs rely on unrestricted budgets for pharmaceutical R&D. Without initial high prices to cover large R&D costs, few new breakthroughs would be forthcoming. Fewer competitor medicines would follow at lower prices, and fewer cheap generics would follow these. The virtuous cycle of R&D spending, innovation, and competition grinds to a halt when governments constrain prices, because low initial prices mean investors will not earn the high return required to encourage high-risk R&D investment.

Lastly, it's worth mentioning that in the United States, some areas of drug R&D, such as vaccines, have been largely abandoned by big pharmaceutical companies—at least partly because the U.S. government, as the sole or most important buyer, has insisted on paying rock-bottom prices. Friedrich Hayek (1945) eloquently explained long ago why free market prices are the best mechanisms for determining production and consumption. Alternative social mechanisms have failed time and again. Yet an effort is afoot to replace the free market with the wisdom of government bureaucrats.

These bureaucrats want to measure how much more effective one drug is than another, and how much the incremental effectiveness is worth in terms of price. Drugs judged to be breakthroughs will get the "right" price that will encourage future breakthroughs. In other words, government controls propose to better the market through product-information aggregation, consumer-benefit measurement, and relative pricing.

Another effort to improve on the free market would have the government "negotiate" a free-market price with pharmaceutical producers, because it pays a large fraction of the pharmaceutical bill. But government negotiation is likely to become government dictation, as prices reflect political forces such as government budgets. With continuously tight budgets, prices offered by the government may no longer reflect the value of a medicine's effectiveness but instead reflect budget demands to reduce expenses. The short-run

benefit is lower prices, but the long-run costs are fewer new medicines for current and future generations.

As health care rises to the top of the national agenda in the United States, and with fiscal budget deficits growing, drug pricing will soon likely emerge as a vital issue for policymakers. It is alarming to us that so few American consumers can at this crucial stage envision the disturbing consequences of government price controls for new drugs. Few American consumers understand the value of initial high drug prices. Even sophisticated consumers don't see the connection between prices, R&D spending, and new drugs.

Chapter 1 lays out a model of how drug companies decide to move forward with drug development, pointing out that even after launch, only about 30 percent of new drugs eventually earn back their investments. This chapter also shows the many factors that increase the cost and risk of new drug launches. Among them are the delays in product launch that occur as companies and governments haggle over prices.

Chapter 2 explains the effects of financial incentives and government price setting on the level of pharmaceutical R&D spending and the introduction of new medicines. Budget-constrained governments are likely to show a bias toward low-priced, low-value pharmaceuticals as opposed to high-priced, high-value ones. This is unlikely to be corrected through voting, especially in the short run, because the benefits of current lower prices are easy to see, while the costs of forgone future medicines are not.

There is little doubt that consumers need some intermediary to guide them in their decisions about which pharmaceuticals are best for them. But there is little reason to believe that consumers should rely on government bureaucrats to represent their interests properly in selecting pharmaceuticals. This is because bureaucrats' incentives are driven by the exigencies of budgets and not by the needs of consumers.

Chapter 3 discusses the artificial mechanisms employed by some government bureaucracies to select among pharmaceuticals and to rationalize price controls. Although some are quite technical they are unlikely to produce optimal results. This is because governments

often succumb to short-term political fixes, i.e., lower prices today. Budget constraints have led many policymakers to adopt a goal of zero real pharmaceutical price inflation, without any economic rationale for why prices for superior goods like pharmaceuticals should exhibit no real increase.

Chapter 4 offers a summary of our conclusions and makes recommendations. We oppose legislation that would permit large-scale or wholesale drug reimportation. We urge the Centers for Medicare and Medicaid to refrain from imposing European-style price controls on—or applying cost-effectiveness analysis to—drugs administered under their programs.

We believe that the present system of drug pricing in the United States works quite well. Despite its flaws, it is better than any other in existence in countries with single-payer (i.e., government) systems. Some of these countries enjoy lower drug prices, but the trade-off is rationing, a paucity of development, and poor market signals about what's valued by patients and their doctors. Above all, we conclude that all too often, governments and voters choose short-term gains, in the form of lower prices, while ignoring the great long-term benefits that flow from temporarily higher prices and profits.

1

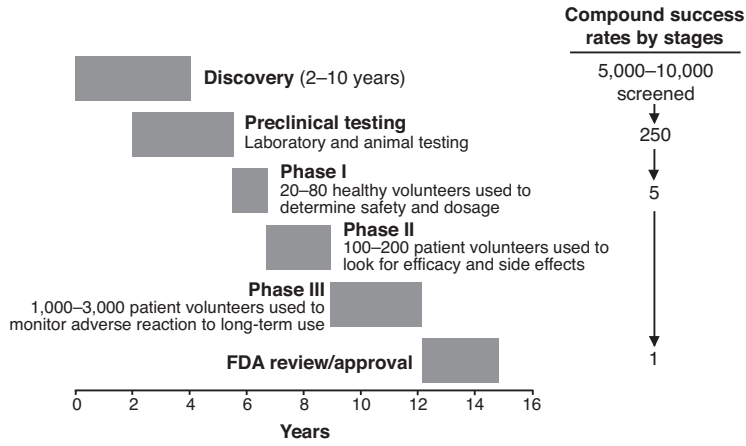
R&D Investment in New Drugs: How It Works, and How It Is Harmed by Price Controls

In this chapter, we will explain how pharmaceutical companies make their investment decisions. We will put forth a detailed model of how executives make a series of "go/no-go" decisions regarding expensive drug development. We will then show how government price controls tilt the decision toward the negative, reducing drug companies' incentive to decide "go" and putting in place obstacles that make it more compelling to decide "no go."

In the final section of the chapter, we will demonstrate that this model of corporate R&D investment is based on long-term payoffs. As such, it is vulnerable to attack from politicians and voters, who often prefer short-term gains in the form of immediate lower prices, not fully understanding how this imperils the long-term goal of getting better drugs in the future.

In many respects, drug development is similar to the wildcatter's search for oil, with its many dry holes and uncertainty. Drug "prospecting" is an arduous task, involving long development times, high costs, and low probabilities of technical success. Before an investigational new compound ultimately reaches the market, it must advance through several stages of research and clinical development: preclinical testing in animals and three phases of successful clinical testing in humans. It must then receive FDA approval. This process is heavily regulated, and attrition rates are high. On average, only one out of several thousand investigational compounds goes on to become a marketed drug. The vast majority fail

FIGURE 1-1
THE DRUG DEVELOPMENT PROCESS



SOURCE: PhRMA, based on data from Center for the Study of Drug Development, Tufts University, 1995.

at some point in the development process, whether because of safety concerns, or because the compound doesn't work as well as hoped, or because the prospects for profitability are too low. The average length of time from discovery to market launch is approximately fifteen years (DiMasi, Hansen, and Grabowski 2003). The pharmaceutical R&D process is illustrated in figure 1-1.

On average, firms must invest in many unsuccessful R&D projects before they find a successful one; that results in a marketed product. The costs associated with failed R&D projects are thus unavoidable and must be factored into the average cost of drug development. One recent estimate places this cost on a pretax basis at $802 million per FDA-approved drug (new chemical entity) in year 2000 dollars (DiMasi, Hansen, and Grabowski 2003), although both higher and lower estimates exist. On an after-tax basis, assuming the firm has sufficient revenues to capture the tax benefits of R&D, or is in a position to sell these tax benefits, the estimated cost of developing an average drug is $480 million (Grabowski, Vernon, and DiMasi 2002).

It is important to emphasize that these figures don't simply measure the cost of drugs that become successes in the marketplace. They factor in, as they should, the cost of failures, as well as the cost of developing drugs that ultimately reach the marketplace but never earn back their initial development costs.

In fact, only three out of ten marketed drugs earn back their investments. Because the decision to market a drug is made after R&D costs are incurred, some drugs are marketed despite being unprofitable. Having already sunk many millions of dollars into development, drug companies often decide it is better to earn low revenue rather than kill the product and get zero revenue. Usually, drug companies take this course if their expected revenue will exceed the marginal cost of merely producing and selling the drug, after the R&D phase.

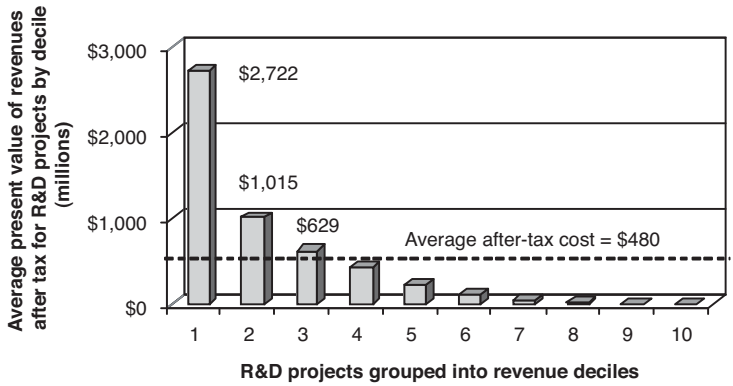
As figure 1-2 shows, the best-selling drugs—the top 10 percent of new drugs by sales—earn back their investment several times over. The next 20 percent also do fairly well, as their cumulative revenue over time is greater than the cumulative cost. But the bottom 70 percent fail to clear the bar, i.e., the cost of developing one of these drugs exceeds its total sales over the life of the drug. And of course, in many of these cases, the R&D money is spent but the drug never makes it to market, so the revenue is zero.

Figure 1-2 presents the skewed nature of revenues in pharmaceutical R&D. It assumes that the after-tax costs are fixed at $480 million, although they could be skewed as well.

Average net revenues adjusted for time value over all deciles is estimated to be $525 million, after taxes. At the time of product launch, the average economic value of pharmaceutical research and development activities is approximately $45 million ($525 – $480). This value is what provides incentives for investment in the pharmaceutical industry, and under current conditions it appears that, on average, there is an incentive for continued investment.

In a sense, this is good news. The pharmaceutical success stories more than compensate for the duds. Overall, then, it is rational for the drug industry to invest in R&D, because it recoups its costs, although not by the fantastic margins that some critics claim.

FIGURE 1-2
SKEWED DISTRIBUTION OF R&D PROJECT REVENUES



SOURCE: Grabowski et al., *PharmacoEconomics*, vol. 20, supplement 3, 2002.

The trouble, as we show in detail below, is that price regulation creates fewer potential "winners."

Conceptual Model and Theory of Price Regulation

Let's focus our attention on the first critical decision point in the life of a pharmaceutical product's development, the time of the Phase I "go/no-go" decision. This is the point at which a firm decides if a compound it has been studying in laboratories is ready for testing in humans. At this stage, all in vitro (test tube) and animal tests have been completed, the mechanism of action is reasonably well understood, and there is a general belief that the compound's medical benefits outweigh its risks in addressing a specific ailment. It is also at this point that the first financial modeling of the compound's commercial potential is conducted.

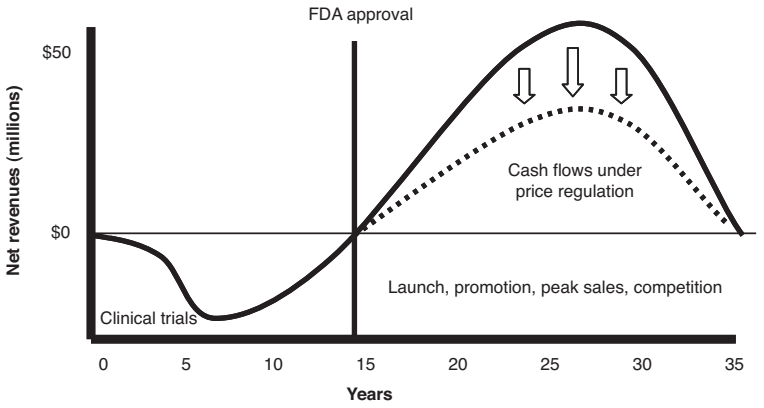
We'll use the net present value approach, which calculates investment return, in a somewhat simplified version, as follows: First, a company takes the sum of all expected future revenue from the drug.

Then, it calculates the accumulated costs, all the while adjusting for the fact that the company is deploying, over time, capital that carries a cost. Specifically, firms often fund R&D by selling stock to investors, who expect to earn a return that exceeds the return on a bond from the same company. While pharmaceutical companies seldom issue new bonds to finance their R&D projects, the required returns on stocks are analogous to the interest payments on bonds (only they come from stock price appreciation and dividends). A common practice is to include the returns required by investors on the capital that funds R&D, up until the year of FDA approval. This "capitalized" value, which incorporates expenditures on both successful and failed R&D projects, represents the true economic cost of bringing a new drug to market.

To move ahead with a drug, companies need to project that their accumulated sales will exceed their total costs, making sure to adjust for their own costs of funds over these years. Thus the firm makes the Phase I "go/no-go" decision by first calculating expected cash flows year by year—i.e., the difference between the cash revenues and production expenses expected in each year over the period of time when the drug will be marketed. These can be positive or negative, but we assume here that they are positive. We also assume FDA approval. Next, the cost of clinical trials is computed for each year until the point of FDA approval. These are all negative cash flows. Finally, the negative clinical cash flows are weighed against the positive net cash flows from future sales. But the cash flows are not simply added together, because each comes in a different year, and the value of a dollar in later years is smaller than in earlier years. Therefore, each cash flow is adjusted for time value. The time-value adjustment depends upon a firm's cost of stock and/or bond financing. The adjusted figures are summed together to produce a net present value, which, if positive, implies that the particular drug project is a "go." If negative, it's a "no-go."[1]

Now let's look at the effect of price controls. If government imposes a reduction in the price of a drug, overall revenues will very likely decline, as numerous studies have demonstrated that the demand for drugs is inelastic (Coulson and Stuart 1995; Santerre

FIGURE 1-3
THE EFFECT OF PHARMACEUTICAL PRICE REGULATION ON CASH FLOWS



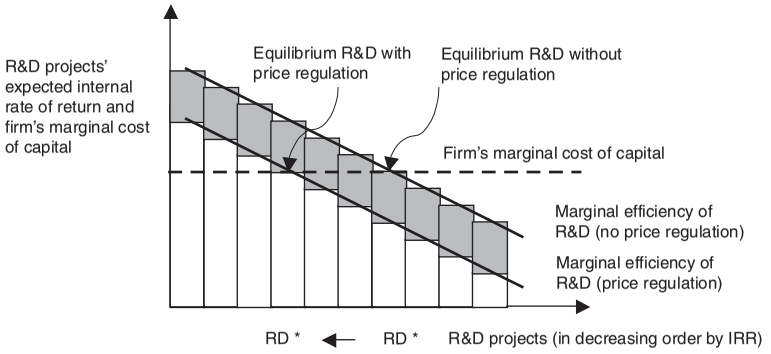
SOURCE: Adapted from Robert Helms, "The Impact of Pharmaceutical Price Controls on R&D," presentation, AEI-Brookings Joint Center for Regulatory Studies, May 16, 2005, http://www.aei.org/publications/filter.all,pubID.22650/pub_detail.asp.

and Vernon 2006). That is, price drops won't create a big rise in sales volume to produce a rise in overall revenue

Figure 1-3 illustrates how revenue declines in a government price-control scenario but the costs of clinical development do not. Clearly, the negative cash flows associated with clinical development do not change, while the positive expected future cash flows from sales fall significantly. If the positive expected future cash flows fall enough so that the total of positive cash flows no longer exceeds the total of negative clinical cash flows (after time-value adjustment), then the drug will not proceed into clinical trials.

Price regulation can have additional negative effects. Danzon, Wang, and Wang (2003) have shown that pharmaceutical price regulation often results in product launch delays due to government price negotiations. Launch delays would have the effect of shifting the dashed line in figure 1-3 to the right and truncating the period of peak sales by shortening the market exclusivity period.

FIGURE 1-4
THE EFFECT OF PRICE REGULATION ON A FIRM'S INTERNAL RATE OF RETURN (IRR) AND NUMBER OF R&D PROJECTS



SOURCE: Authors' diagram.

Credible threats of new price regulation will have similar effects (Golec, Hegde, and Vernon 2008). Firms must predict expected cash flows over many years; hence, they must consider the possibility that they will be forced to sell at regulated prices in the future, even if prices are not currently regulated. In other words, the percentage return a firm can expect to earn on its investors' capital (its internal rates of return) will drop under the threat of price regulation, thereby reducing the equilibrium level of R&D investment. This is illustrated in figure 1-4, where the gray boxes reflect the difference between a project's internal rate of return with and without price regulation and RD* is the firm's profit-maximizing level of R&D spending.

Figure 1-4 demonstrates that fewer R&D projects make financial sense under price controls. As prices and expected revenues drop (the slanted lines), fewer and fewer projects will be profitable. Firms will undertake the high return projects first (the vertical bars on the left-hand side of the chart)—and continue to undertake additional investment projects so long as the expected rate of return from the

next project exceeds the firm's marginal cost of capital, meaning that fewer of the projects further to the right will pay off. This is the classic supply and demand framework.

In economic terms, price regulation shifts the marginal internal rate of return schedule down, and fewer R&D projects meet the criterion of earning an internal rate of return that exceeds the cost of capital required to fund the project. Investors will not supply capital to fund the marginal projects whose internal rates of return fall below their required returns. These marginal projects could be minor medical advances or major breakthrough medicines. If one assumes that breakthrough medicines can command higher market prices, then price regulation is more likely to be applied to them. Indeed, the Clinton administration's Health Security Act proposed to regulate mostly high-priced breakthrough drugs. After all, there is little cost savings in constraining low-priced, seldom-used drugs.

Finally, figure 1-4 excludes the effects that internal cash flows have on capital supply to the firm. Cash flows exert a positive influence on the level of firm investment spending, but price regulation constrains this internal capital supply and thus reduces R&D investment.

Unfortunately, public debate on this issue can become problematic because firms sometimes proceed with drug development even though they will never earn back their total sunk costs. For many years, the mantra of some industry supporters was that pharmaceutical prices had to be "high" in order to recoup the high fixed costs of R&D. Not true. Firm managers are forward looking and seek to maximize profits; at the time of product launch, R&D costs are sunk and are irrelevant to the calculus of price determination. That is, once a drug reaches the market, its R&D costs have already been incurred and variable costs are the only costs relevant for decision making. Of course, in the long run, if a firm cannot cover its fixed costs, it will go out of business.

Even in cases where the new product is a financial success, the economically efficient and socially optimal market outcome is achieved through fierce competition in the product market, because this drives price down to marginal cost (in the case of perfect com-

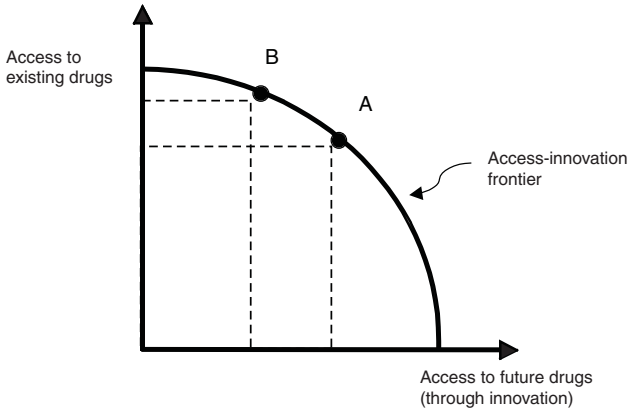
petition). However, precisely to the extent that competition achieves these efficiency gains, the economic incentives to invest in research for future technologies are diminished.

But the point here—and it's a vital one—is that drug companies take a long-term view toward investment in R&D and its payoff in the form of revenue and profit. (Paradoxically, these same companies are often characterized as short-sighted and self-serving, when in fact their interests are aligned with the interests of many current and future consumers.) This long-term orientation puts them in conflict with politicians, who serve current voters and their immediate concerns. These politicians speak, all too often, to short-term interests. If the interests of future voters were to be taken into account, government policy might be more evenhanded. However, prices set in the political arena will reflect current voters' wishes, as opposed to the full economic value that pharmaceuticals would attain in a free market.

Striking the optimal balance between the long-run benefits of future innovations and the short-run benefits of patient access to existing medicines is as difficult as it is important. This is due in large part to the fact that future medicines are not observable and are difficult to approximate. This difficulty in estimating long-run benefits may bias the emphasis toward short-run economic interests, which are tangible, straightforward to measure, and easy to grasp.[2] Political agendas of special interest groups are often advanced by false premises and flawed economic logic because it is easier to operate, intentionally or unintentionally, amid a backdrop of public confusion and economic illiteracy.

Figure 1-5 depicts the pharmaceutical trade-off society faces between current and future goods. A new price-control or importation policy (depending on its effectiveness in lowering average drug prices in the United States and the degree of influence of regulated foreign drug prices) will result in a movement from point A to point B. Society gives up some innovation in exchange for improved access to drugs already on the market. Yet the existence of this fundamental trade-off and economic reality has effectively, if not explicitly, been denied by Congress.[3]

FIGURE 1-5
THE TRADE-OFF BETWEEN ACCESS TO EXISTING MEDICINES AND ACCESS TO FUTURE MEDICINES



SOURCE: Authors' diagram.

The Challenge: Addressing the Real Issues

It is difficult to debate the merits of a new policy that shifts the balance between short- and long-run economic efficiency if both parties to the debate and the architects of the policy deny the very existence of this economic reality. The pharmaceutical industry's image problem has no doubt been exacerbated by the prevalence of economic illiteracy in the United States. This illiteracy is manifest in a political process that is messy and imprecise, so that the costs and benefits of alternative policies are often not fully valued. As we will argue, failure to fully measure the costs of pharmaceutical price controls may have a dire effect on future medical innovation.

2

Government Price Regulation and the Impact on Pharmaceutical R&D Spending

Governments around the world have developed many methods for controlling pharmaceutical prices. Some are direct; others are indirect. The effect of these policies has been striking. The EU in particular has succeeded in keeping the rise in drug prices down to the rate of inflation. That stands in sharp contrast to the experience in the United States, where price controls have been almost absent, and where real prices grew about 47 percent faster than EU pharmaceutical prices between 1985 and 2004 (Golec and Vernon 2006).

The bulk of this chapter will examine how these starkly different levels of drug pricing have led to equally striking differences in the levels of pharmaceutical R&D spending. As we will demonstrate, European drug R&D has fallen far behind levels in the United States. Where once Europe was a leader, it has in the past two decades become a notable drug-research laggard. Our research will show that there is more than merely a link between price controls and diminished R&D, but a compelling cause and effect relationship. That is, government controls that keep prices down also keep drug R&D down. By contrast, the dominance of free-market pricing in the United States has led to robust spending on drug R&D over the past twenty years.

We can study the effect of regulated prices on pharmaceutical R&D spending using three approaches. First, we can simply look at correlations between average industry prices and industry R&D over time. Second, we can explore the connection between changes

in prices and profits on the one hand and R&D spending on the other. Finally, we can show how price controls affect firms' stock prices, and then how stock prices influence R&D decisions. We argue below that because firms sometimes issue stock to finance R&D, lower stock prices result in lower R&D spending.

These different approaches point to the same conclusion: pharmaceutical price regulations reduce pharmaceutical R&D spending. We will offer evidence to support all three conclusions: lower prices, lower profits, and lower stock market valuations all create strong disincentives for drug companies to spend heavily on R&D.

We will also show that if the United States had adopted EU-type price controls, R&D spending in the United States would have been between 24 percent and 40 percent less during the period from 1980 to 2001—causing large but immeasurable harm, as fewer new medicines would have been developed.

Pharmaceutical Price Regulation and Real Pharmaceutical Price Inflation

Vernon (2003a) catalogues how methods of pharmaceutical price regulation vary from country to country. Table 2-1 provides a list of countries and the various methods they use. The most common methods of controlling pharmaceutical prices are setting rates at which governments reimburse health care providers, and compiling formulary lists of drugs to be dispensed to patients. Directly setting launch prices for medicines is also common. Note that all of the countries use more than one method. Multiple methods may afford them flexibility to fine-tune prices.

Controlling launch prices is a direct form of price setting. Using "reference" prices—that is, fixed prices based on the lowest prices already being paid by a comparison group—often has the same effect. The comparison price may be that of another price-regulated country, usually one where prices are already low. Controlling reimbursement prices or capping doctors' drug budgets theoretically allows consumers to pay more, or doctors to prescribe higher-priced medicines, but the indirect effect of this approach is to constrain

TABLE 2-1
METHODS OF PHARMACEUTICAL PRICE REGULATION BY COUNTRY

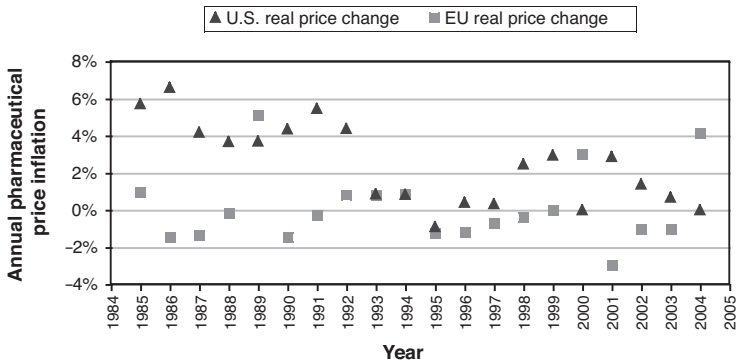
Country	Controls launch prices	Controls reimbursement prices	Uses reference prices	Caps profit rates	Uses positive/negative listings	Caps doctors' drug budgets
Austria	Yes	Yes			Yes	
Belgium	Yes	Yes			Yes	
Canada	Yes	Yes	Yes		Yes	
Denmark			Yes		Yes	
Finland		Yes			Yes	
France	Yes	Yes			Yes	Yes
Germany		Yes	Yes		Yes	Yes
Greece	Yes	Yes			Yes	
Ireland	Yes	Yes			Yes	Yes
Italy	Yes	Yes			Yes	
Japan		Yes		Yes	Yes	
Netherlands	Yes	Yes	Yes		Yes	
Norway		Yes	Yes		Yes	
Portugal	Yes	Yes			Yes	
Spain	Yes	Yes		Yes	Yes	
Sweden		Yes	Yes		Yes	
Switzerland		Yes			Yes	
United Kingdom				Yes	Yes	Yes

SOURCE: Vernon, J. A., "Drug Research and Price Controls," *Regulation* (Winter 2002/2003).

prices to actual or implied reimbursement rates. Formulary listings can be negotiating tools; if firms will not accept the regulated price, their medicine can be dropped from the list of medicines covered by the regulator. And setting maximum profit rates for firms can effectively cap prices.

These are tactics; they are means to an end. The ultimate goal for most of these countries is to keep pharmaceutical price inflation at or below the average level of consumer price inflation. Indeed,

FIGURE 2-1
COMPARISON OF ANNUAL REAL PHARMACEUTICAL PRICE INFLATION IN THE UNITED STATES AND THE EU



SOURCE: U.S. Bureau of Labor Statistics, Eurostat, and *OECD Health Data*.

when President Clinton proposed pharmaceutical price regulations in 1993, he referred to the goal set by many European countries of zero real pharmaceutical price inflation.

Figure 2-1 shows that the EU countries have indeed attained that goal. Using U.S. Bureau of Labor Statistics, Eurostat, and OECD health data, the figure plots the difference between the annual percentage of change in pharmaceutical prices and the annual percentage of change in the consumer price index, for both the EU and the United States.[1] U.S. prices represent relatively free prices, allowing us to judge the level of price control in the EU. In most of the twenty years between 1985 and 2004, the annual real inflation rate for pharmaceuticals in the EU is close to zero. Cumulative real pharmaceutical inflation over the twenty years is about 4 percent for the EU compared to about 51 percent for the United States. The real inflation rate in the United States exceeds or equals the rate in the EU in all but three years.

Note that the real pharmaceutical inflation rate in the United States dropped sharply in 1993, the year of President Clinton's proposed

price regulations to limit the real rate to zero. Ellison and Wolfram (2006) document how U.S. pharmaceutical firms started to moderate their price increases during that period to convince Congress that government price controls were not needed. In fact, since then, U.S. real pharmaceutical price inflation has remained moderate, particularly in the presidential election years of 1996, 2000, and 2004. This illustrates how U.S. pharmaceutical prices are not immune to political threats of price regulation.

Indeed, since 1993, pharmaceutical pricing has become more politicized even though it is not federally regulated. To show that the Clinton plan marked a significant change in how closely the U.S. public (as reflected in the press) watches pharmaceutical price inflation, we searched for articles in the *Wall Street Journal* that discussed average drug price inflation. We found only three articles from 1984 until 1992. But during the period when Clinton developed and proposed price regulations in his Health Security Act (1992–93), twelve such articles appeared. Then, from 1994 through 2005, forty-two articles appeared. Most of these articles focused on the political dimension of the debate.

The U.S. government, as an important buyer of pharmaceuticals, has served to keep a lid on prices even without directly regulating them. The historical evidence is overwhelming that when Uncle Sam enters the picture as buyer, prices are held down. If this influence has been a factor in the past, it will be even more important in the future, especially given the Medicare Modernization Act, which will greatly increase the share of drug purchasing by the U.S. government.

Santerre, Vernon, and Giaccotto (2006) analyze the effect of growing government purchasing on prices. Drawing on extensive databases of actual prices paid, we determined that between 1962 and 2001, every 10 percent rise in the share of government as purchaser of a drug resulted in a 1.2 percent decrease, per year, in prices paid for the drug. In recent years, increased government purchasing has had a much more significant effect. Admittedly, other factors, such as the rise of pharmacy benefit managers (third parties who administer prescription drug programs for insurance companies), have also played a role in capping prices. Yet we estimate that

between 1992 and 2001, a 10 percent increase in government purchasing caused annual real pharmaceutical prices to decrease by about 5.83 percent. It's important to note that these are price drops *per year*, so the compounding effect is very large over time.

Looking to the immediate years ahead, pricing pressure on drugs is bound to accelerate, as Medicare Part D, the Medicare drug-benefit program, sharply raises the share of drugs paid for by the U.S. government. Catlin, Cowan, Hartman, and Heffler (2008) show that the public share of drug spending rose to 36 percent in 2006, up from 28 percent in 2005.

The Link between Pharmaceutical Prices and R&D Spending

Not everyone agrees that lower drug prices will trigger drops in R&D spending. Public Citizen (2001, 2003), Angell (2004), and Sager and Socolar (2004) suggest that R&D could be unaffected or even *increase* if drug prices were lower. Their arguments have amounted at times to mere hostile sentiments toward drug companies: they have suggested that Big Pharma is claiming a drug price–R&D link in order to mask a strategy of me-too products and mergers designed to cut competition and expenditures for marketing and advertising (Sager and Socolar 2004).

The fact is, lower prices do affect R&D. And the contrasting experience of Europe and the United States in R&D spending is clear evidence that price-limiting policies have huge effects on research.

Public Citizen (2001) claims that EU firms have maintained their R&D spending despite facing strict price regulation in their home markets. This is misleading. EU firms' growth in real R&D spending is quite slow compared to U.S. firms' (only 2.8 percent vs. 7.6 percent in recent years [Golec and Vernon 2006]).

Golec and Vernon (2006) show that EU price controls have helped EU consumers to pay less for pharmaceuticals than U.S. consumers between 1986 and 2004. But during the same period, the U.S. pharmaceutical industry's R&D spending has grown about twice as fast as that of the EU. As noted above, in 1986, EU-based pharmaceutical R&D spending exceeded U.S. spending by about 24 percent ($4,790

million vs. $3,875 million), but by 2004, EU spending trailed U.S. spending by about 15 percent ($26,725 million vs. $30,644 million).

Between 1986 and 2004, EU price controls were increasingly adopted and strengthened. And these years were similarly marked by huge drop-offs in drug research and development. The truly important issue, however, is what the forgone R&D spending in Europe has meant in terms of new drug development. We estimate that reduced R&D from price controls during that period resulted in about fifty fewer new drugs and about seventeen hundred fewer scientists employed in the EU. And whereas EU firms introduced about twice as many new medicines as U.S. firms between 1987 and 1991, they introduced about 20 percent fewer than U.S. firms between 2000 and 2004 (EFPIA 2002, 2005).

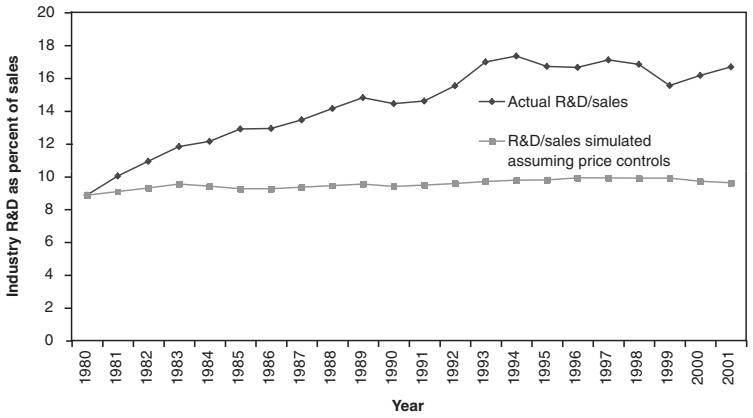
To put the issue even more starkly, let's imagine what would have happened to U.S. R&D if the United States had adopted EU-style price controls over the past two decades. The possibilities are disturbing, to say the least. As we pointed out earlier, a regulatory policy that decreases real pharmaceutical prices by 10 percent would likely decrease industry R&D by 6 percent.[2] Using these results and other models (Giaccotto, Santerre, and Vernon 2005), we simulate what would have happened from 1980 to 2004 in the United States if EU-type price controls had limited U.S. pharmaceutical price inflation to average U.S. consumer price inflation. Figure 2-2 illustrates those effects.

First, note that total industry R&D spending is standardized by dividing by industry sales to eliminate the extraneous effects on total dollar sales of such influences as demand increases from population aging. Second, the figure shows that between 1980 and 2001, the U.S. pharmaceutical industry increased the percentage of sales revenue that it devoted to R&D from 9 percent to about 17 percent. Perhaps because of favorable pricing or technology trends, firms were willing to devote more resources to R&D. Under hypothetical price controls, however, the proportion of sales devoted to R&D would have stayed roughly the same, at 9 percent.

Giaccotto, Santerre, and Vernon (2005) use the simulation to calculate how much total R&D spending and how many new

FIGURE 2-2

ACTUAL R&D AS A PERCENTAGE OF SALES COMPARED TO SIMULATED R&D AS A PERCENTAGE OF SALES ASSUMING ZERO REAL PHARMACEUTICAL PRICE INFLATION

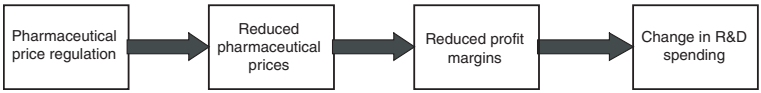


SOURCE: Giaccotto, Santerre, and Vernon, *Journal of Law and Economics*, May 2005.

pharmaceutical introductions would be forgone. They estimate that from 1980 to 2001, between $265 and $293 billion of capitalized R&D expenditures would have been lost. This is about 28 to 31 percent of the actual total capitalized R&D expenditures during the period. Using the estimate of $802 million average R&D cost per new medicine, they calculate that between 330 and 365 new medicines would have gone undeveloped between 1980 and 2001. One cannot be sure whether lifestyle medicines (e.g., Claritin, Nexium, or Viagra) or life-saving drugs (e.g., Avastin, Gleevec, or Epogen) would have been sacrificed; however, price controls could have greater impact on R&D investment decisions for life-saving drugs, because those drugs typically have higher prices.

Ominously, the ill effects associated with price controls have already begun to take hold and to deliver, as theory predicts, less R&D funding into next-generation drugs. Total sales of pharmaceuticals continue to grow as the world population ages and incomes rise.

FIGURE 2-3
THE RELATION BETWEEN PHARMACEUTICAL PROFIT MARGINS AND R&D SPENDING



SOURCE: Authors' diagram.

These factors and industry economics should support strong growth in R&D and many new pharmaceuticals. But even U.S. R&D growth is slowing, falling from 9.9 percent between 1981 and 1986, to 7.6 percent between 1999 and 2004.

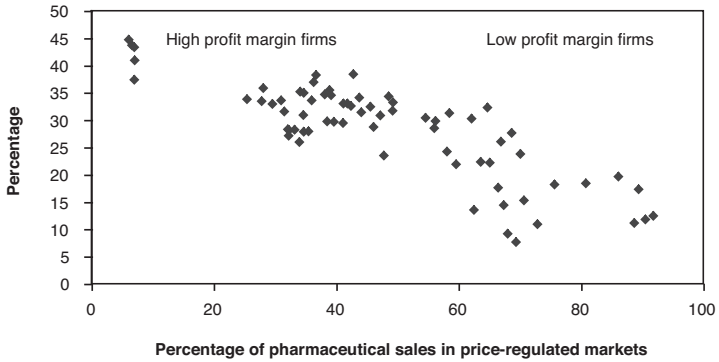
We believe a significant portion of the R&D spending slowdown is due to tighter pharmaceutical regulations worldwide. Because most firms sell their medicines internationally, they all face price restrictions to some degree. The costs of these restrictions quickly compound into significant forgone R&D spending, and many fewer new medicines.

The Effects of Pharmaceutical Prices on R&D through Profit Margins

Another approach to testing the relationship between drug price regulation and R&D spending is to focus on an intermediate step between pharmaceutical prices and R&D spending. A number of studies examine how price regulation lowers firm profit margins, i.e., reduces the returns to R&D investment, which in turn reduces a firm's incentive to invest in R&D, at least at the margin. This approach is illustrated in figure 2-3. This formulation gives us a more refined test of the line of causation between price regulation and R&D spending.

The first issue to consider is whether price regulation significantly affects profit margins. Some critics have suggested that pharmaceutical firms can maintain profit margins even with lower regulated prices by

FIGURE 2-4
THE RELATION BETWEEN FIRMS' PROFIT MARGINS AND SALES VOLUME IN PRICE-REGULATED MARKETS

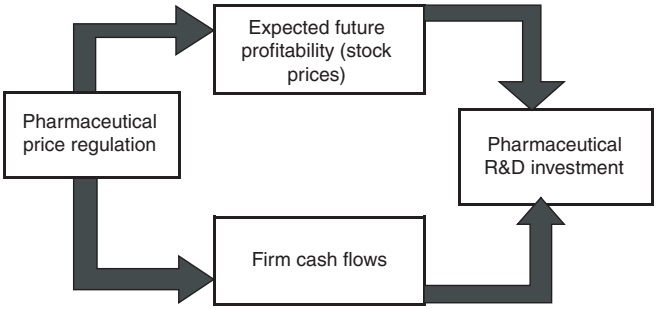


SOURCE: Vernon, J. A., "The relationship between price regulation and pharmaceutical profit margins," *Applied Economic Letters* 10: 467–70.

cutting waste, marketing, or other expenses (Angell 2004; Public Citizen 2001). If that were so, why is there such a tight relationship, as we have found, between price levels and profits? In 2003, we examined data from eleven firms, and, estimated each firm's profit margins on sales in price-controlled and free markets respectively (Vernon 2003b). We discovered that the more a firm sells in price-controlled markets, the lower its profit margins, and vice versa. Figure 2-4 illustrates this negative relation.

Some research has taken this analysis a step further and found that internally generated cash is more likely to spur R&D than externally generated funds (such as those gained by floating stock or incurring debt). Vernon (2005) utilizes firm-level profit margin data to estimate models of the determinants of firm R&D investment. This study also includes cash-flow effect to capture the financing advantage of internally generated funds compared to externally generated funds. Results show that price-regulated firms would spend between 23 and 33 percent less on R&D than unregulated firms.

FIGURE 2-5
THE RELATION BETWEEN CAPITAL MARKET FINANCING AND R&D SPENDING



SOURCE: Authors' diagram.

Scherer (2001) documents a close link between gross pharmaceutical profitability and R&D investment at the industry level. The relationship holds tightly, this study suggests, partly because internally generated cash flows from higher sales exert a positive influence on firm R&D spending. Price regulation would negatively affect pharmaceutical profitability and cash flows, and would be expected to reduce industry R&D investment.

The Effects of Pharmaceutical Prices on R&D through the Capital Market

Many recent studies use firms' stock prices to proxy for expected future profitability. We know from basic finance that firms (and investors) will react immediately to expected future profits. When expected profits are high, stock prices are high, and firms can fund R&D by issuing stock. This is particularly important for the pharmaceutical industry, where firms typically use mostly equity financing. The effects of expected future profitability and current cash flows on R&D are illustrated in figure 2-5.

Lichtenberg (2004) shows that although both current profits and stock prices are related to R&D spending, stock prices do a better job than current profits in explaining R&D. His statistical analysis indicates that stock prices explain more variation in R&D across firms and across time.

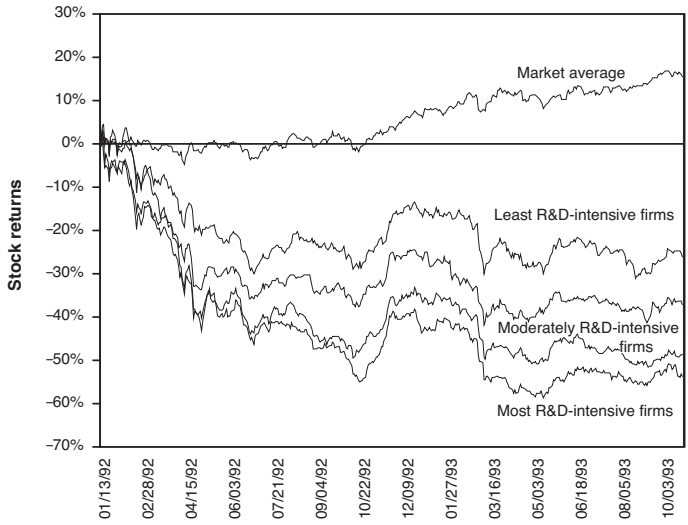
Lichtenberg and other scholars have studied how the mere threat of government price controls has sent stock prices spiraling downward, and thereby crimped R&D spending. The premiere case of this threat—and its very real consequences for R&D—came in 1993 with the Health Security Act of the first Clinton administration.

Ellison and Mullin 2001 is an exhaustive "event study" of the sixteen major political events leading up to the day that the Health Security Act was delivered to Congress. An event study measures the stock price changes caused by surprise events. For example, when Clinton leaked his plan to regulate drug prices to the *New York Times*, which reported it on February 16, 1993, pharmaceutical stock prices fell by about 3 percent (after adjustment for the general market return that day). Investors reacted to the new information that price controls could be on the horizon by reducing stock prices.

Ellison and Mullin 2001 finds that eighteen large pharmaceutical company stocks suffered an average 38 percent cumulative loss over all of the Health Security Act events. Golec, Hegde, and Vernon 2008 also finds large negative returns for a wider array of 111 pharmaceutical and biotechnology companies. More important, this study finds that firms that spent proportionately more on R&D suffered larger losses. The top quarter of firms lost 60 percent on average. These firms were mostly small biotechnology firms.

Figure 2-6 shows the stock returns for the market average compared to pharmaceutical stocks grouped by how much they spend on R&D per dollar of their assets (R&D intensity). The start date is January 13, 1992, five trading days before presidential candidate Bill Clinton issued his vague health care white paper. The end date is October 3, 1993, when Hillary Clinton presented the final plan to Congress. The figure shows the severe drop in pharmaceutical firms' stock prices during the period, and makes clear that R&D-intensive firms, many of them biotech firms, suffered the most.

FIGURE 2-6
STOCK RETURNS FOR THE MARKET AVERAGE VS. PHARMACEUTICAL FIRMS GROUPED BY R&D INTENSITY



SOURCE: Generated from Center for Research in Securities Prices Database.

The stock market in general did not fall during this period; therefore, one cannot attribute the pharmaceutical industry's stock price declines to general market conditions.

Golec, Hegde, and Vernon (2008) show that the more a firm's stock price fell during this period (which ends in 1993), the more the firm reduced R&D spending in 1994 from what it would have been otherwise. This relation is statistically significant and supports a significant link between the expected net present value of future cash flows (as reflected in stock prices) and R&D spending. Furthermore, because firms' stock prices did not quickly recover when the act did not pass Congress, we know that the threat of future price controls continued to have an effect.

Other event studies have also shown that new government regulations, or threats of regulation, influence firms' share prices. For

example, Dowdell, Govindaraj, and Jain (1992) and Dranove and Olsen (1994) show that the introduction of more stringent production, testing, and compliance regulations significantly decreased pharmaceutical firms' stock prices. Although current profits were not affected, investors expected future costs to rise, making pharmaceutical stocks worth less.

Perhaps this is not so surprising, given our understanding of the effects of profit margins and stock prices on R&D spending. Golec and Vernon (2006) show that U.S. firms' profit margins exceeded those of EU firms by an average of five percentage points from 1986 through 2004. And from 1993 to 2004, the percentage return on U.S. pharmaceutical stocks exceeded the return on EU pharmaceutical stocks by 100 percentage points. Relatively high U.S. stock prices have allowed many U.S. biotech firms to raise significant amounts of equity capital to fund R&D spending.

Bias toward Price Controls for Short-Term Benefits

In the previous section, we noted that because U.S. firms sell more of their medicines at U.S. prices, they have higher profit margins and their investors earn higher returns compared to EU firms. It is no surprise that U.S. firms also increase their R&D more than EU firms. The evidence is clear: free pricing yields higher profit margins, higher stock prices, and more R&D projects. This economic dynamic is very much consistent with the predictions of neoclassical economic theory.

The political dynamic, however, clashes with the economic dynamic. In the next chapter, we will show how pharmaceutical price controls are an easy solution for politicians at a time of rising government budget deficits. That's especially true when neither the public nor the politicians see much immediate connection between price controls and R&D spending.

The issue can be traced, as we have said, to the tension between short-term political agendas and the long-term payoff from pharmaceutical research. The substantial negative effects of price controls appear only after many years, making it difficult to tie the price controls to the R&D effect. But Golec, Hegde, and Vernon (2008) show

that negative effects on R&D come even before controls are adopted. Investors discount pharmaceutical firms' share prices as the probability of future price controls increases, and firms start fewer R&D projects because discounted stock finances fewer projects. When price controls are actually adopted, the immediate response in R&D is negative but muted because some of the negative effect has already occurred, and because many current projects will remain profitable under price controls.

We now turn to the rising political clamor to deploy those controls.

3

Government Intervention and the Threats to Drug R&D

In the multibillion dollar market for pharmaceuticals, there are two basic ways that prices can be controlled. One is the marketplace itself. The other is government intervention, by officials who often use complex measures of costs and benefits to rein in drug prices, or who discourage the use of drugs by refusing to pay for them.

The marketplace mostly works quite well, and much the way theory suggests it should. Theoretically, free-market pricing should generate higher prices for breakthrough medicines over incumbent drugs. Lu and Comanor (1998) find that medicines representing important new therapeutic advances are priced between two and three times higher than incumbents. Equally if not more important, me-too medicines or generic versions of breakthrough medicines create a market-based version of price control. They can be cheap to develop and eventually compete with original breakthroughs to keep prices down. Also, new medicines that are therapeutically equivalent to incumbents are priced at the level of incumbents. These results demonstrate that the U.S. market distinguishes between medicines, awarding proportionately higher prices for proportionately more effective medicines.

Outside the United States, however, many governments believe they have found better ways to keep prices under control—by directly tinkering with the market. They think that they have found the drug-pricing equivalent of a free lunch: they establish drug-pricing regimes that provide incentives equal to or better than free-market incentives, but with lower prices on average.

Technology assessment and cost-effectiveness analysis (CEA) are governments' preferred new methods. These largely replace the much cruder government rules of the past, such as insistence on zero real price increases. As we shall see, however, these new tools are fraught with problems. At best, they create profound uncertainties for drug companies, because the firms can't fathom the basis for the rules. At worst, they create for governments more sophisticated weapons to get prices where they want them—low—by manipulating the various assumptions on which their cost-effectiveness analysis is based.

The new techniques have perhaps reached their most sophisticated application in the United Kingdom. Yet, as the ongoing and highly controversial case of the UK's partial ban on Alzheimer's treatments suggests, these new methods of CEA have created a cloud of uncertainty for the makers and marketers of these drugs. That's because the new wave of CEA analysis—the weighing of a drug's costs against its health benefits as measured by its effect on the length or quality of patients' lives—can operate like a bureaucratic black box and serve to confuse and discourage the development of breakthrough drugs.

The National Institute for Clinical Excellence (NICE) in January 2001 decided to fund Alzheimer's disease (AD) drugs under the UK's National Health Service only for patients in the most severe stages of the disease. The decision prompted an immediate backlash from patients and their families, who were suddenly denied their £2.50-per-day reimbursement for several anticholinesterase drugs, including Novartis's Exelon, Shire's Reminyl, and Aricept, a widely prescribed treatment offered by Pfizer Inc. and Japan's Eisai Co. Ltd. (Whalen 2005).

Pfizer and Eisai have led an all-out fight against the NICE decision, arguing that NICE based its denials on a secret cost-benefit formula that it refused to disclose. In May 2008, the drug companies won a round in the legal fight when a British appeals court ruled that NICE had to disclose the computer model of its cost-effectiveness analysis to the drug companies (Jack 2008).

Lack of transparency is hardly the only problem with these emerging new methods. The more basic problem is that of trusting

bureaucrats to outperform the markets. To outperform the market, the new methods require bureaucracies to have the resources and incentives to gather the proper information, the technical skills required to interpret the information, and the negotiating skills of specialized intermediaries such as pharmacy benefit managers and health maintenance organizations (HMOs). If this is even possible, it is surely expensive to administer, and we are skeptical that governments will provide enough funding to make it work.

Now let's turn to a more detailed analysis of these new methods for controlling drug prices.

Current Approaches to Technology Assessment and Cost-Effectiveness Analysis

Various countries with national health plans are trying explicit methods of technology assessment and cost-effectiveness analysis to guide reimbursement and rationing decisions for new pharmaceuticals. Certain health and cost thresholds are set, and if they are not met, the new medicine is excluded from national health plans, just as in the UK the NICE refused to pay for Alzheimer's treatments.

Technology assessment begins with the assumption that market forces are imperfect price setters. Some argue, for instance, that drug companies use their patent protections to extract unseemly prices during the life of the patent, or that patients pay outrageous prices because their insurance companies or employers will actually foot the bill. Many believe the solution is to bring government analysis into the picture. Different analytical formats have been used, including cost-minimization analysis (CMA), cost-benefit analysis (CBA), and cost-effectiveness analysis (Eisenberg 1989).

While CBA has a two-century history in public finance and has several theoretical and practical advantages over CEA, it is seldom used in health care because of the reluctance to attach monetary values to health benefits. In addition, some believe that consumers and providers are too ignorant of new medicines' values, and that this type of analysis does not fit the public payer's budget-level perspective (Sloan 1995).

CEA is more prominent in health care policymaking in some countries because it entails a combination of economic theory, medical information, and empirical flexibility. But CEA still requires someone to assign a monetary value to health benefits. Assigning health benefit value was a contentious issue in the decision to restrict access to AD drugs in the UK. NICE determined that none of four AD drugs it considered met a threshold it had set for health value at their price levels. This threshold criterion can be used as a CEA mechanism for imposing indirect pharmaceutical price controls. Below, we briefly review the CEA method and then demonstrate how it can be used to control prices.

An Overview of Cost-Effectiveness Analyses

CEA involves comparing the ratio of the difference in marginal costs and benefits between a new therapy and the old or alternative therapy.

$$(1)\quad \frac{\Delta C}{\Delta B} = \frac{NewTherapyCost - AlternativeTherapyCost}{NewTherapyBenefit - AlternativeTherapyBenefit}$$

Costs are generally calculated as the difference between the new drug and the one it replaces. Benefits are measured in standardized units of health such as life years or quality-adjusted life years (QALYs). NICE guidelines, for example, recommend the use of QALYs. It is difficult enough to measure life years—that is, the benefit that occurs when a therapy extends someone's life by one year—but measuring QALYs adds another layer of complexity. QALYs are "weighted" life years. Everyone whose life is extended by one year is not considered equal, and the weight reflects the quality of life in a particular state of health. If a therapy prolongs life but the patient is in poor health during those years, CEA discounts those years. Treatments that improve both the duration and the quality of life get better QALYs (Torrance 1976). Of course, measuring life quality is itself problematic.

Consider the following example of a payer using CEA to evaluate a new therapy which provides an additional life year at a marginal cost of $100,000; that is, the therapy increases costs per patient by

$100,000 over the alternative therapy. For pharmaceuticals, this is reasonably easy to calculate as the difference in medicine prices (and possibly some ancillary costs). Now suppose that the new medicine also increases life years by one and that the payer agrees that an extra year of life is worth $125,000. Then:

$$\frac{\Delta C}{\Delta B} = \frac{\$100{,}000}{\$125{,}000} = 0.80$$

A ratio less than 1 ($\Delta C/\Delta B < 1$) implies that the costs are less than the benefits and the medicine would seem to be acceptable. But there are two complications. First, in order to be more confident that the benefits will exceed the costs, the payer could require a smaller ratio—less than 0.50, for example. Second, the payer could decide that this particular life year saved is not worth a full year. Perhaps it is worth only 0.50 years because the patient is an eighty-year-old cancer survivor who will spend his year in a nursing home. Under these conditions we calculate thus:

$$\frac{\Delta C}{\Delta B} = \frac{\$100{,}000}{(\$125{,}000) \times 0.5} = 1.60$$

Now, even if the payer only requires the ratio to be less than 1, the new medicine is not acceptable. A thorough CEA requires the payer to consider all alternative medicines. All viable medicines should be compared, and their cost-effectiveness results rank-ordered in a league table. The top medicine or medicines are reimbursed, perhaps at different rates.

A decision to cover and reimburse any of the medicines depends on the payer's willingness to pay, which is implicit in the choice of a ratio cutoff. In our example, we started with a natural cutoff of 1, but different payers can set different cutoffs. If a payer sets the cutoff at 0.50, for instance, far fewer drugs will clear the hurdle. A payer will cover only those medicines with CEA ratios below the cutoff, and will not cover those with ratios above the cutoff.

Determining the cutoff is crucial to the success of CEA used by

governments and national payers. The cutoff makes explicit the placement of a monetary value on health benefits. If set too high, almost any new treatment will pass; if set too low, almost none will. In addition, a cutoff set below the true economic value of a health benefit (e.g., a life year) will have the socially undesirable effect of reducing innovation incentives to levels below their socially optimal level. The converse is also true: cutoffs set above the true economic value of a health benefit will encourage too much R&D investment.

Most of Western Europe, Canada, Australia, and New Zealand use explicit or implicit forms of CEA (Jommi 2001; Gosling 2000). The UK's NICE adopted CEA in 1999 to ensure that health care funds are used efficiently, that policies on treatment choice are consistent across the country, and that pharmaceutical products deemed to significantly increase health system expenditures are evaluated for cost-effectiveness (Atkinson 2002).

In the United States, not only Medicare but managed care organizations and state Medicaid programs are considering the possibility of developing formal and informal cost-effectiveness evaluation mechanisms. Even if no explicit CEA system is used, concerns about rising premiums and federal and state budget deficits could cause U.S. payers to consider using CEA.

CEA helps payers to place an explicit value on a new technology. This method can be attractive to payers even if it is imperfect, because it can help convince patients that their health coverage is defined by objective criteria. But it also formally defines a payer's maximum willingness to pay for different pharmaceuticals. Firms can reverse-engineer a maximum price for a medicine when they know how a payer determines its QALYs and its cutoff. Payers may have to reveal QALYs and cutoffs to patients or patient representatives in order to defend their CEA computations. Even if all the details are unknown, firms can use a payer's reimbursement and coverage policies to probabilistically forecast product prices within a given confidence interval.

But one advantage of CEA for firms is that it can reduce the uncertainty in the development or license-acquisition process. CEA essentially sets up a formula that defines the rules of the game. Offer

a medicine that passes the cutoff, and product sales are nearly assured. Vernon, Hughen, and Johnson (2005) show how firms have started to make R&D product development and in-licensing decisions based upon the CEA signals being sent by foreign governments via their reimbursement and coverage decisions.[1] The signals to firms may be more reassuring, but they can produce socially suboptimal results if the value payers place on a life year in their budgeting is less than the true economic value of a life year. Research by Murphy and Topel (2003a) on the economic value of a life year suggests national payers are setting their willingness-to-pay thresholds too low.

Potential Indirect Price Controls: Consequences for R&D Investment

The greatest problem with CEA is that QALYs and cutoffs can be improperly set, discouraging certain R&D projects. A related problem with CEA is that governments can essentially game the system by adjusting the cutoff point, i.e., requiring costs to be so far below expected health benefits that only low-priced drugs survive the cut.

Suppose that the payer sets a cutoff of K and that the cost of a new medicine is its price, P. We can rewrite equation (1) as follows.

$$(2)\quad \frac{\Delta C}{\Delta B} = \frac{P - AlternativeTherapyCost}{NewTherapyBenefit - AlternativeTherapyBenefit} = K$$

Now rearrange equation (2) by solving for P.

$$(3)\quad P = K * (NewTherapyBenefit - AlternativeTherapyBenefit) + AlternativeTherapyCost$$

Equation (3) shows that a payer can essentially set prices by setting K appropriately, or by defining therapy benefits appropriately. It is reasonable to assume that therapy benefits can vary by disease category. But the payer could even define a separate K for different classes of medicines, arguing that some benefits in some disease

categories are more uncertain; hence, these categories would involve a smaller *K*. Given some fixed *K*, defining therapy benefits in a way that makes them appear smaller implicitly reduces *P*. A smaller *K* also reduces *P*. That is, if the payer measures small benefits or sets *K* low, only low-price medicines will be reimbursed (all else being equal). Pharmaceutical firms do not need to know the payer's implied *P*; they will rationally interpret the low *K* or small measured benefit as a signal to avoid starting R&D projects in a particular disease category.

Payers typically announce their choices for *K* and measurements of benefits. How these are determined (and perhaps who sets them) is therefore critical to implementing CEA in a way that is not equivalent to indirect price controls. So far, the objectivity of some payers is not encouraging. For example, the UK's NICE uses approximately $50,000 per QALY to measure benefits. Research by Hirth, Chernew, and Orzol (2000) and Murphy and Topel (2003a), however, suggests the value of a life year in the United States is much higher, closer to $175,000 in current dollars. These studies estimate QALY values using market data on how much people are willing to pay to avoid hazardous work (and increase their expected life span). Even with a cutoff set at 1, when the UK measures benefits at less than a third of what they may be, fewer pharmaceuticals will pass this criterion.

Some see CEA as essentially a rationing tool, even if it is touted as an improvement over free-market pricing. If CEA is to be adopted in the United States as a rationing device for the Medicare drug benefit, more research and considerable caution are needed. These rationing tools can be as complex and theoretic as policymakers want them to be, but the real question is whether free-market prices send better signals than the rationing tools. We remain skeptical that government rationing tools will perform as well as the free market. Hayek (1945) showed long ago that central planners cannot hope to capture all of the relevant information required to set efficient prices.

Price regulation and price controls in the United States can come in many forms: directly, through prices "negotiated" by the government, and perhaps indirectly, through poorly formulated CEA

polices, if CEA is in the U.S. health care system's future. Our concern is that CEA could be used as cover for price controls. Lastly, and very importantly, we see danger in the way the United States is essentially importing the price-control regimes of other countries by allowing large-scale drug importation.

Over the past four years, some U.S. politicians have warmed to drug importation, in part because some economists have argued that it offers a "free lunch"—lower drug prices *and* no harm to drug R&D. A study by Sager and Socolar (2004) in support of drug importation drew a flurry of media attention and was the subject of several press releases by prominent U.S. politicians. The excitement was based on the "finding" that legalized importation of pharmaceuticals from Canada, where prices are regulated by the government, could increase industry profits through higher sales volumes at the lower Canadian prices. Thus, the authors concluded that the industry's intense lobbying effort to defeat legalized importation from Canada (and Europe) was misguided—because importation from Canada could increase its profits.

In U.S. Congressman Rahm Emanuel's (D-IL) press release, issued the same day as the Sager and Socolar press release and report (April 15, 2004), the current chairman of the Democratic Caucus remarked: "This study debunks the profit myth, showing that drug companies can still profit while providing Americans access to lower priced drugs from other countries. . . . Importation is a win-win" (Emanuel 2004). The message was clear: drug companies and their management teams were inept—they couldn't see a good thing when it was directly in front of them. A flurry of legislative initiatives followed, including a Senate importation bill (S.2328), the Pharmaceutical Market Access and Drug Safety Act of 2004.

The claims by Sager and Socolar, parroted by members of Congress, are startling. They assume that pharmaceutical firms' management teams, whose job it is to know pharmaceutical markets, key economic and demographic trends, and product demand, don't in fact know what's best for drug companies. For-profit firms have a fiduciary duty to shareholders to maximize profits. The fact that firms are not pricing their products in the United States at Canadian

price levels, and are vehemently opposed to legalized importation, is *prima facie* evidence that such a policy would reduce their profits.[2]

If drug importation is legalized, then rational firm managers, acting on behalf of their shareholders, will divert resources away from pharmaceutical activity and into other, relatively more attractive investment activities. Pharmaceutical R&D will decline. What is uncertain is by how much. As we explained earlier, we believe that if U.S. prices were equivalent to those in price-controlled countries, R&D in the United States would drop by 25 percent to 30 percent.

The debate over these types of polices must recognize and weigh the unavoidable trade-offs and opportunity costs involved. Regulating pharmaceutical prices in the United States, however it might be achieved, will involve forgoing future innovations in order to improve current access to, and lower the cost of, existing medicines. While there is certainly a need for more economic research on the topic, and indeed room for debate, the existing evidence suggests that the trade-off would result in a net social cost to Americans, with future generations bearing a disproportionate share of these costs.

4

Summary and Conclusions: Why Public Policy Must Recognize the Trade-Off between Lower Prices Today and Life-Saving Medicines Tomorrow

In the previous chapters, we made a case against government price controls on drugs. We argued against direct control of prices at launch or at any time after drugs have been marketed. We also argued against indirect forms of price control, whether through cost-effectiveness analysis by government bureaucrats, or mass drug-importation programs sponsored by politicians responding to voter demands. The problem with all this government tinkering is that artificially lowered prices lead to lower revenues and lower profits, and hence to lowered willingness of pharmaceutical companies to keep pursuing the risky, expensive, and time-consuming search for new, breakthrough medicines.

In this concluding chapter, we delve more deeply into the issue that lies beneath the link between drug prices and R&D. Although we've mentioned it earlier, it is worth repeating: there's a trade-off at work here between lower prices today and more breakthrough drugs tomorrow. And unfortunately, all too often, governments and voters choose short-term gains in the form of lower prices, while ignoring the great long-term benefits that flow from temporarily higher prices and profits. Those benefits are the breakthrough drugs that have transformed the treatment of heart disease, slowed or even halted the progress of cancers, and made possible the ongoing effort to unlock the mysteries of Alzheimer's disease and many other intractable illnesses.

There are some reliable generators of increased R&D. They include stronger (or longer) patents and higher profits. Both will increase the economic incentives for R&D and innovation, but will simultaneously reduce access to existing drugs. There are also some reliable generators of a less desirable future, one that features less R&D and less innovation. Price controls and shorter patents (weaker intellectual property rights) will improve access to existing medicines but reduce incentives for R&D and innovation.

This trade-off gives rise to an intergenerational conflict, because the short-term benefits of lower prices help today's citizens in obvious ways, while long-run economic benefits—drugs that cannot be well understood because, for the most part, they don't exist yet—accrue systematically to different generations. For example, there are no significant drugs based upon stem cell science, but resources currently used for stem cell research could produce breakthroughs that benefit mostly future generations.

It's the role of public policy to strike the proper balance between the short term and the long term. Indeed, this balance should be the single most fundamental concern when considering and implementing new government regulations and policies. Regrettably, the long-term consequences of drug price controls are frequently ignored, or their existence denied, by political rhetoric, media sensationalism, and bad economics. Both pharmaceutical industry critics and advocates are guilty of this: some industry critics may deny or ignore the long-run social and economic consequences of a policy, and some industry supporters may ignore or minimize the short-run benefits.

Governments have a powerful incentive to favor the short run: it's cheaper. Favoring the short run will cut budget deficits at a time when the federal budget deficit is large, partly because of new government-sponsored drug benefits. With the new Medicare prescription drug benefit adding many billions more to the U.S. government budget along with Social Security, Medicare, and Medicaid, we suspect that it is only a matter of time before the U.S. government faces a budget crisis. When that time comes, if pharmaceutical price controls are proposed again, we hope that the full list of benefits and costs will be arrayed for the public and policymakers to weigh and compare.

Exacerbating this controversy is the contrast between the market-oriented health care system in the United States and the systems of socialized medicine in Europe, Canada, and elsewhere. These foreign policies are increasingly influential in the United States, as the lower prices abroad create a clamor for large-scale importation of these cheaper drugs.

The debate over drug importation is unlikely to go away. Any consumer can simply look up the price of her medicine at a Canadian pharmaceutical Web site; hence, the benefits to most people are highly tangible. As we argued in the previous chapter, buying drugs from other countries amounts to bringing those countries' price-control regimes to American markets. Rather than being an example of free markets at work, large-scale importation imposes the restrictive, price-controlling regimes of other countries on the United States.

We do not mean to minimize the emotionally charged element in this debate over drug prices. The pharmaceutical industry has an image problem, which has worsened recently. The public's negative perception of the pharmaceutical industry is probably due to two principal factors: (1) the belief that medicine should involve kindness, compassion, and empathy (Green 1995; Flower 1996); and (2) economic illiteracy: the failure of the general public to understand the connection between pricing and the profit incentives to spend on R&D.

Pharmaceutical firms are in the businesses of discovering, developing, marketing, and selling new drugs for a profit; many find this offensive. Politicians, media, special interest groups, and book authors often characterize industry pricing practices with rhetoric such as "unconscionable profiteering" and "price gouging." Consider the titles of three recent books about the pharmaceutical industry: *The Big Fix: How the Pharmaceutical Industry Rips Off American Consumers* (Greider 2003); *Profits Before People: Ethical Standards and the Marketing of Prescription Drugs* (Weber 2006); and *The Truth about the Drug Companies: How They Deceive Us and What to Do about It* (Angell 2004).

Pharmaceutical firms and financial markets, however, fully value the expected dollar "votes" of current and future users of their

products. This puts them in conflict with politicians, who largely serve current voters. If future voters could somehow be heard, government policy might be more evenhanded. Unfortunately, drug companies' consideration of future customers doesn't really register with the public, whose animosity is directed at Big Pharma. This is especially unfortunate considering that price controls will create the biggest disincentives in smaller and more innovative firms, which for many years have taken some of the biggest R&D risks, engaging in early-stage research without the infrastructure or financial stability of the bigger firms.

Chapter 2 showed that the mere threat of price controls drove pharmaceutical stock prices down significantly, with the largest declines suffered by R&D-intensive firms. These firms also happen to be the smaller, younger, innovative firms with little sales revenue and mostly early-stage R&D projects. A number of simulation models predict that, indeed, the firms most likely to be severely affected by price controls are the early-stage firms. These studies include Abbott and Vernon 2007, Filson and Masia 2007, and Vernon 2003c. They use evolutionary economic models of value-maximizing firms of various sizes and characteristics to simulate the effect of price controls on the structure of the industry. The large firms, which are more harshly criticized in the popular press and by citizens' action groups, have established products that help them limit the damage. They have the resources to adapt to the new regulated environment. Conversely, the studies show that the small early-stage firms often die off under price controls. This leaves a less healthy competitive environment because new innovative firms have less chance of start-up and survival, and large firms have less to fear from innovative upstarts.

Furthermore, Higgins and Rodriguez (2006) show that successful small firms are likely to be bought out by the large ones to fill their R&D pipelines. This strategy essentially outsources the uncertain R&D function, leaving small firms to bear the risk. Because price regulation reduces the payoff for risk taking, this is a rational strategy for large firms.

These effects do not create much of a political counterweight against regulation, because the decline of small innovative firms does

not happen immediately. Like the decline in innovative activity in the EU's pharmaceutical industry, the effects of price controls are not observed immediately; rather, they accumulate over time. Pharmaceutical R&D projects take fifteen years on average to bear fruit, and because most late-stage projects are still worthwhile even under price controls (their costs are already sunk), new products will continue to enter the market, albeit at a progressively slower rate. This makes it difficult for consumers and policymakers to tie the regulatory policy to its negative effects.

Benefits to consumers, however, are immediate and tangible. This produces an unfortunate political dynamic in which price-control policies yield immediate gains without showing immediate large costs. This could vindicate politicians' price-control policies, garnering them votes and reelection. The major costs come well after they leave office.

Pharmaceutical price regulation is also not good news for generic drug companies. Danzon and Chao (2000b) show that price regulation undermines price competition generated by generic firms. Therefore, if price regulations are adopted in the United States, one can expect fewer generic firms to survive and the remaining generic firms to become weaker competitors—that is, to charge higher prices. Indeed, Graham (2001) shows that in price-regulated Canada, generic pharmaceuticals sell for more than they do in the United States. Part of the reason that U.S. generics are less expensive is that entry into the U.S. market by generic firms has been eased since 1984, producing a strong, competitive generic market (see Grabowski and Vernon 1992). Furthermore, Danzon and Chao (2000a) show that the United States consumes proportionately more generic pharmaceuticals than most price-regulated countries. Hence, when properly weighted by the amounts consumed, average U.S. pharmaceutical prices are much closer to regulated-market prices than is typically assumed.

Many public action groups ask why pharmaceutical firms' productivity has declined; why firms produce so many me-too medicines; why they pay so much to market their products; why so few new vaccines or AIDS medicines are produced; and why so many

life-style medicines are produced. Behind each question is a suspicion of sinister intent on the part of large, profitable pharmaceutical firms. In truth, no one can be sure about the correct answers to each question.

This is the beauty of a free market. Firms, and the industry as a whole, are molded by their economic environment and respond to its incentives. Left to their own, most free markets are driven to produce the product consumers demand, at the best price. But poor or convoluted incentives can lead to poor outcomes, and the evidence shows that price controls for pharmaceuticals provide poor incentives. Why produce high-R&D breakthrough medicines when commensurate high prices are not allowed? Given the price controls that pharmaceutical firms face in most countries, and could soon face in the United States, what looks like "sinister" behavior to some may simply be an optimal response to misguided policy incentives.

Appendix
National Survey on Public Perceptions of the Pharmaceutical Industry and Economic Illiteracy

To gauge the prevalence of economic illiteracy among the general public with respect to the pharmaceutical industry, and to measure general public perception of the industry, we conducted a random national telephone survey. The survey questions were designed, and the polling was undertaken, in 2005. We obtained responses from 1,006 randomly selected Americans. Our results have not previously been published.[1]

We intended to measure the public's most basic understanding of the pharmaceutical industry. For example, we asked questions about whether the elimination of intellectual property rights and patents would affect drug companies' incentives for doing research. We also asked whether price controls would affect R&D spending. There were also numerous questions about people's impressions of drug research, the value of new pharmaceuticals, drug prices, and profits, etc.

We report only some of these results in this appendix (those most germane to the direct questions of economic literacy and public perception). We collected demographic data that revealed how different groups responded to the survey questions, but we report only aggregate survey responses here to give a broad overview of the public's understanding of the economics of intellectual property rights and their general views of the industry as a whole. Full survey results are obtainable from the authors.

One question we asked concerned the importance of patents as a means to incentivize research. After a brief description of what pharmaceutical patents are, and why they are important, we read the following question to survey subjects.

Question 1: *Do you think that pharmaceutical or drug companies would continue to do research and development for new drugs if they were not able to have these patents?*

The survey responses to this question are summarized in table A-1.

Another question we asked, one particularly germane to the discussion and examples of economic illiteracy previously covered, concerned the effect that pharmaceutical price controls in the United States might have on future R&D spending.

Question 2: *Suppose the government controlled the prices of prescription drugs. Do you think that pharmaceutical or drug companies would spend more, less, or about the same amount on scientific research to find new drugs?*

We found that a significant fraction of the general public is misinformed or confused when it comes to the economic realities of this issue. Perhaps this should not be surprising when high-profile economists, such as former FDA commissioner Mark McClellan, are harshly criticized for even suggesting that price controls might discourage incentives for R&D. Table A-2 summarizes the responses to this question.

In a related question, we asked whether importing drugs from Canada, where the government controls pharmaceutical prices, would have an effect on drug companies' R&D spending. The additional layer of complexity (importing price-regulated drugs versus direct U.S. price controls) resulted in a higher proportion of responders believing that R&D would not be affected. We asked subjects the following question.

Question 3: *Some people say that allowing Americans to buy prescription drugs imported from Canada will lead United States pharmaceutical*

TABLE A-1
WOULD PHARMACEUTICAL R&D CONTINUE WITHOUT PATENTS?

Survey response	Percent of responses
Yes	39
No	52
Don't know	8
Refused	0
Total count	**100**

TABLE A-2
HOW WOULD U.S. PRICE CONTROLS INFLUENCE R&D SPENDING?

Survey response	Percent of responses
Spend more	15
Spend less	42
Spend the same	40
Don't know	3
Refused	0
Total count	**100**

or drug companies to do less research and development. Do you agree or disagree?

The distribution of responses to this question is presented in table A-3.

These results may partially explain why importation, as a political strategy to control U.S. drug prices, has been more successful in Congress than more direct efforts. This is the case despite the additional concerns over drug importation safety. Over 70 percent of people surveyed did not see importation as a threat to firm R&D. This is compared to 55 percent of survey respondents who believed that direct government price controls in the United States would not be a threat, or might actually act as a stimulus for more R&D. It is possible that this difference is due to uncertainty about how an

TABLE A-3
WILL PHARMACEUTICAL IMPORTATION DECREASE R&D?

Survey response	Percent of responses
Strongly agree	11
Somewhat agree	15
Somewhat disagree	23
Strongly disagree	48
Don't know	2
Refused	0
Total count	**100**

importation policy might be implemented, to increased pressure on foreign governments to set prices differently, or to judgments about the eventual scale and volume of importation.

We also asked a series of questions that were intended to shed light on the public image of the pharmaceutical industry and to learn the public's opinions about pharmaceutical prices and profits as well as the value of pharmaceuticals and pharmaceutical R&D. These questions and answers are presented next.[2]

Question 4: *Would you say that prescription drugs are priced fairly or unfairly?*

Question 5: *Do you think that the profits pharmaceutical or drug companies make are too high, too low, or about right?*

Note that out of approximately a thousand randomly questioned Americans, not a single person thought pharmaceutical profits were too low. This by itself is not terribly surprising. What is intriguing is research by Kevin M. Murphy, Robert H. Topel, and other prominent economists suggesting that the United States may be investing too little in medical and pharmaceutical research (Murphy and Topel 2003a, 2003b). The economic benefits of increasing investment in medical research, through gains in life expectancy and good health, may be substantially greater than the cost of the research

TABLE A-4
ARE DRUGS PRICED FAIRLY OR UNFAIRLY?

Survey response	Percent of responses
Fairly	12
Unfairly	77
Depends	3
Don't know	7
Refused	0
Total count	**100**

TABLE A-5
OPINION OF DRUG COMPANY PROFITS

Survey response	Percent of responses
Too high	70
Too low	0
About right	21
Don't know	9
Refused	0
Total count	**100**

itself. Studies by Frank Lichtenberg (2002, 2005, 2007) have repeatedly suggested that the same is true for pharmaceutical R&D, at least historically. If this is true, then pharmaceutical profits may be "too low" because profits, and more specifically expected future profits, are what attract investment dollars into R&D.[3]

To probe the issue of pharmaceutical profits a little deeper, we also asked the following question, which consisted of three parts asked in a random order.

Question 6: *Sometimes when people find out new information they change their opinion and sometimes they don't. I'm going to read you a list of items. After you hear each, please tell me if you think that the*

profits pharmaceutical or drug companies make are too high, too low, or about right.

a) Drug companies earned about average profits compared to other brand-name companies of their size. Knowing this, please tell me if you think that the profits pharmaceutical or drug companies make are too high, too low, or about right.

b) Some drugs have actually lowered the overall cost of care by reducing hospital stays or invasive treatment. Knowing this, please tell me if you think that the profits pharmaceutical or drug companies make are too high, too low, or about right.

c) Lower prices today might mean that fewer new drugs are available in the future. Knowing this, please tell me if you think that the profits pharmaceutical or drug companies make are too high, too low, or about right.

Presenting survey respondents with qualifying statements on the pharmaceutical industry's profits relative to other U.S. industries, on the effect of drugs on overall health care costs, and on the trade-off between access to existing drugs and innovation in the future had only a moderate effect on their perceptions of profit levels in the pharmaceutical industry. This may simply reflect prior knowledge of the information provided, but given the responses to some of the earlier questions, it appears that the public's opinions about pharmaceutical firms' profits do not change even in light of new information.

The next question addressed the trade-off between short- and long-run economic benefits of pharmaceutical technology (albeit in a very blunt and imprecise manner). As is always the case with survey research, different respondents may have different interpretations of the question being asked. Nevertheless, the question has value in that it indirectly addresses whether the public recognizes the opportunity costs involved in trading short- and long-run economic benefits.

Question 7: *Is it more important for pharmaceutical or drug companies to lower the cost of the drugs they have already developed, or to continue to do research on new drugs for the future?*

TABLE A-6a
OPINION OF DRUG COMPANY PROFITS—QUALIFIED
("PROFITS ARE AVERAGE")

Survey response	Percent of responses
Too high	54
Too low	2
About right	39
Don't know	4
Refused	0
Total count	**100**

TABLE A-6b
OPINION OF DRUG COMPANY PROFITS—QUALIFIED
("DRUGS LOWER COST OF CARE")

Survey response	Percent of responses
Too high	49
Too low	3
About right	43
Don't know	4
Refused	1
Total count	**100**

TABLE A-6c
OPINION OF DRUG COMPANY PROFITS—QUALIFIED
("LOWER DRUG PRICES MEAN FEWER NEW DRUGS")

Survey response	Percent of responses
Too high	52
Too low	4
About right	39
Don't know	4
Refused	1
Total count	**100**

TABLE A-7
SHOULD DRUG COMPANIES LOWER COSTS OR CONTINUE RESEARCH?

Survey response	Percent of responses
Lower costs	36
Continue research	55
Don't know	7
Refused	2
Total count	**100**

The results in table A-7, which indicate that the public values new drugs in the future over lower costs today, are difficult to reconcile with those presented in table A-6c, which indicate that the public values lower costs today over new drugs in the future. Perhaps, as discussed earlier, the discrepancy can be explained by the negative connotation associated with profits in medicine. Question 7 addresses the trade-off between access and innovation without mentioning the intermediate role played by profits. Question 6c addresses profitability directly. As already noted, it may also simply be a reflection of how the question was interpreted; Question 7 may have been interpreted as a binary choice between lower drug prices and new research.

The final two survey questions for which we will present results dealt with overall impressions of the industry and with opinions about the contribution and value of pharmaceutical research and new drug innovation.

Question 8: *Do you have a favorable or an unfavorable opinion of pharmaceutical or drug companies that make prescription drugs?*

Question 9: *How important of a contribution do pharmaceutical or drug companies make by researching and developing new drugs and treatments?*

The last two questions seem to show that respondents recognize the value and importance of pharmaceutical research and innovation,

TABLE A-8
OPINION OF PHARMACEUTICAL FIRMS

Survey response	Percent of responses
Strongly favorable	14
Somewhat favorable	32
Somewhat unfavorable	21
Strongly unfavorable	19
Don't know	13
Refused	1
Total count	**100**

TABLE A-9
IMPORTANCE OF PHARMACEUTICAL FIRMS' RESEARCH AND INNOVATION

Survey response	Percent of responses
Very important	59
Somewhat important	36
Not too important	2
Not at all important	2
Don't know	1
Refused	0
Total count	**100**

but this favorable view of the activity does not translate into approval of such research. We suspect that this is due to the motivation underlying the research: profits.

Notes

Introduction

1. See the appendix for the results of our survey, previously unpublished.

2. Golec and Vernon (2006) compute these figures based upon data supplied by European Federation of Pharmaceutical Industries and Associations (EFPIA) for Europe and Pharmaceutical Researchers and Manufacturers of America (PhRMA) for the United States. Members of both organizations supply separate R&D figures for the United States and Europe. For example, Pfizer might report $2 billion R&D spending in the United States and $1 billion in Europe. The next year, if Pfizer relocates a U.S. R&D facility to Europe, it might report $1.5 billion of R&D in the United States and $1.5 billion in Europe.

Chapter 1: R&D Investment in New Drugs: How It Works, and How It Is Harmed by Price Controls

1. We denote the time of the Phase I "go/no-go" decision as $t = 0$. A profit-maximizing firm decides whether or not to extend an R&D project into Phase I clinical development as follows. Defining period t expected cash flows (negative values during drug development and positive values after launch) as $E(C_t)$, an R&D project with final-year product sales in period T will have the following expected NPV:

$$(1)\quad E(NPV_0) = \sum_{t=0}^{T} \frac{E(C_t)}{(1+r)^t} = E(C_0) + \frac{E(C_1)}{(1+r)^1} + \frac{E(C_2)}{(1+r)^2} + \frac{E(C_3)}{(1+r)^3} + \ldots + \frac{E(C_T)}{(1+r)^T}$$

The discount rate r in equation (1) is the firm's cost of capital and is assumed to be constant. Profit-maximizing firms will take the R&D project into Phase I clinical development if $E(NPV_0) > 0$; they will terminate

the project, however, if $E(NPV_0) < 0$. The project's expected internal rate of return, which we will discuss later in the chapter, is the value of r that results in $E(NPV_0) = 0$.

2. We made this point in testimony before the Senate Commerce, Science, and Transportation Committee (John A. Vernon: Hearing on the Policy Implications of Pharmaceutical Importation for U.S. Consumers) in March 2007 (http://commerce.senate.gov/public/index.cfm?FuseAction=Hearings.Hearing&Hearing_ID=777fd1ca-1393-45dd-a60b-0b46ee444fe3).

3. It is easier to understand why the general public—unfamiliar with some of the economic and regulatory nuances of the pharmaceutical industry—fails to recognize the opportunity costs and trade-offs associated with new public policies. New pharmaceuticals are essentially information products, much like computer software; as such, they require intellectual property rights in the form of limited-term patents to establish economic incentives for their discovery and development. Once a new molecular structure has been discovered and studied in clinical trials, to ensure it is both safe and effective in humans (a process that takes over a decade and may cost over $1 billion), the final result is essentially a massive dossier of clinical, pharmacological, and scientific information. Generic pharmaceutical markets in the United States are highly competitive for this reason, with prices being rapidly driven down to marginal costs (Saha, Grabowski, et al. 2006). The United States, unlike other countries, greatly facilitates competition in generic pharmaceutical markets and does not regulate its drug prices. As a result, Americans enjoy the lowest-priced generic drugs in the world.

Chapter 2: Government Price Regulation and the Impact on Pharmaceutical R&D Spending

1. U.S. pharmaceutical and CPI (all items price 1982–84 = 100) indexes are from the Bureau of Labor Statistics (www.bls.gov/cpi/home.htm#data). EU CPI is from Eurostat Harmonized Indices of Consumer Prices (all items) (epp.eurostat.ec.europa.eu/portal/page?_pageid=1090,30070682,1090_33076576&_dad=portal&_schema=PORTAL). The EU pharmaceutical price index is from Eurostat starting in 2001 and compiled from *OECD Health Data 2003* for the years before 2001.

2. Using different data, Lichtenberg (2007) estimates a similar size relation.

Chapter 3: Government Intervention and the Threats to Drug R&D

1. Vernon, Hughen, and Johnson (2005) describe the various methods used within this context by firm managers, especially for potential projects in the earliest stages of drug development.

2. Empirical research has also consistently revealed that the demand for pharmaceuticals is inelastic. See Coulson and Stuart 1995; Pauly 2004; Santerre and Vernon 2006.

Appendix: National Survey on Public Perceptions of the Pharmaceutical Industry and Economic Illiteracy

1. The University of Connecticut's Roper Center for Public Opinion Research conducted the survey on behalf of the authors.

2. Additional questions relating to direct-to-consumer advertising, insurance, and drug consumption and expenditures were also asked, but these questions are beyond the scope of this appendix.

3. Of course this possibility is not easily communicated because of the economic illiteracy surrounding the process by which R&D investment decisions are made (the subject of chapter 2). The following exchange between Joseph DiMasi, professor, Tufts Center for the Study of Drug Development, and Donald W. Light, professor, University of Medicine and Dentistry of New Jersey, in a series of recent *Health Affairs* eLetters demonstrates this point and the challenge to overcoming economic illiteracy (so the right questions and issues can be debated). Joseph DiMasi had asserted that "expected R&D (and other) costs [of developing new drugs] together with expected prices (and associated quantities demanded) determine expected profitability. Expected profitability, in turn, determines the incentive to develop new therapies." DiMasi is just saying what economists have known and been saying for over a century. Yet Light denies DiMasi's seemingly unobjectionable claim: "DiMasi asserts that expected R&D costs, prices, and demand determine expected profitability. No, they don't. How can an expected something, minus an expected something else, be said to determine anything?" (*Health Affairs* 2006). How about the price of a share of Pfizer stock? Expectations are the cornerstone of economic theory; Robert Lucas won a Nobel Prize in 1995 for his work on rational expectations. In the same letter, Light suggests that his exchange with DiMasi "would make good material for classroom discussion about pharmaceutical policy and argumentation." Indeed it would, but in an economics class.

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EXHIBIT D

More Prices, More Problems: Challenging Indication-Specific Pricing as a Solution to Prescription Drug Spending in the United States

Ryan Knox*

ABSTRACT

In the United States, high prices of prescription drugs and rapidly increasing prescription drug spending have caused public outrage and calls for action. There is bipartisan acknowledgement of the problem by lawmakers, but no agreement on how to fix it. Value-based pricing models have gained increasing support and have been suggested as one possible solution to controlling prescription drug spending. One proposed value-based pricing model is indication-specific pricing: linking the price of a multi-indication prescription drug with the indication for which it is prescribed to a patient. Indication-specific pricing is intended to incentivize using higher-value treatments and allocating prescription drugs to patients who will receive the greatest benefit. However, there are many barriers to implementing indication-specific pricing in federal health insurance programs in the United States. Further, as a policy matter, indication-specific pricing would likely not decrease overall prescription drug spending and could worsen the accessibility and affordability of prescription drugs. This Note argues that lawmakers should not pursue an indication-specific pricing regime as a means to decrease prescription drug spending. Instead, lawmakers seeking prescription drug reform should consider methods that will more likely decrease prescription drug prices and spending while also ensuring patients' access to medicines.

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INTRODUCTION

The high cost of prescription drugs is a matter of serious concern in the United States. Several drug pricing scandals have elicited public outrage.[1] Gilead Sciences priced a twelve-week course of treatment for its first two hepatitis C treatments, Sovaldi and Harvoni, at $84,000 and $94,500 respectively.[2] Turing Pharmaceuticals raised the price of Daraprim, a treatment for toxoplasmosis, by 5,000 percent, from $13.50 to $750 per pill, immediately after acquiring rights to the drug.[3] Many new cancer drugs have been released and priced at hundreds of thousands of dollars per year.[4] Amgen's cancer drug Blincyto was approved in 2014 at a price of $178,000[5] and Novartis' cancer treatment Kymriah was approved in 2017 at a price of $475,000.[6] The average cancer drug now costs four times the average household income.[7] Unaffordable prescription drugs can lead to patient non-adherence, worsening health outcomes and increasing use and cost of

1. *See, e.g.*, Peter J. Neumann & Joshua T. Cohen, *Measuring the Value of Prescription Drugs*, 373 NEW ENG. J. MED. 2595, 2595 (2015) ("Escalating drug prices have alarmed physicians and the American public and led to calls for government price controls."); Charles Ornstein & Katie Thomas, *Prescription Drugs May Cost More With Insurance Than Without It*, N.Y. TIMES (Dec. 9, 2017), https://www.nytimes.com/2017/12/09/health/drug-prices-generics-insurance.html (describing the current time period as "an era when drug prices have ignited public outrage and insurers are requiring consumers to shoulder more of the costs"); Andrew Pollack, *High Cost of Sovaldi Hepatitis C Drug Prompts a Call to Void Its Patents*, N.Y. TIMES (May 19, 2015), https://www.nytimes.com/2015/05/20/business/high-cost-of-hepatitis-c-drug-prompts-a-call-to-void-its-patents.html (on Sovaldi scandal) [hereinafter Pollack, *High Cost*]; Andrew Pollack, *Drug Goes From $13.50 a Tablet to $750, Overnight*, N.Y. TIMES (Sept. 20, 2015), https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html (on Daraprim scandal) [hereinafter Pollack, *$750 Overnight*].

2. *See*; Carolyn Y. Johnson & Brady Dennis, *How an $84,000 drug got its price: 'Let's hold our position . . . whatever the headlines'*, WASH. POST (Dec. 1, 2015), https://www.washingtonpost.com/news/wonk/wp/2015/12/01/how-an-84000-drug-got-its-price-lets-hold-our-position-whatever-the-headlines/?utm_term=.68eea7c17de8.

3. *See* Pollack, *$750 Overnight*, *supra* note 1.

4. *See* SUSAN DENTZER & TOM HUBBARD, VALUE-BASED CONTRACTING FOR ONCOLOGY DRUGS: A NEHI WHITE PAPER 10, 11 (2017) (discussing Keytruda, a $150,000 per year treatment for metastatic melanoma, and Kymriah, a $475,000 personalized treatment for pediatric and adult patients with a type of acute lymphoblastic leukemia); Emily K. White, *Killing U.S. Slowly: Curing the Epidemic Rise of Cancer Drug Prices*, 72 FOOD AND DRUG L. J. 189, 191 (2017) ("Over the past fifteen years, the average price of a cancer drug has increased ten to fifteen times, costing patients over $100,000 a year in 2012.").

5. *See* White, *supra* note 4, at 191.

6. *See* Denise Grady, *F.D.A. Approves First Gene-Altering Leukemia Treatment, Costing $475,000*, N.Y. TIMES (Aug. 30, 2017), https://www.nytimes.com/2017/08/30/health/gene-therapy-cancer.html.

7. Julia Belluz, *The Nobel Prize is a reminder of the outrageous cost of curing cancer*, VOX (Oct. 2, 2018), https://www.vox.com/science-and-health/2018/10/1/17923720/immunotherapy-cancer-cost.

other health services.[8]

The problem of high prescription drug prices goes far beyond these few surprising examples. On average the United States spends twice as much as other countries on prescription drugs.[9] Prescription drug spending accounted for approximately 17 percent of all healthcare spending in 2015 and is the fastest growing portion of the healthcare budget.[10] Total prescription drug spending in the United States rose 12 percent in 2015 and another 6 percent in 2016, reaching $450 billion.[11] These high and increasing prices are a result of several factors, including the higher prices paid for prescription drugs under patent compared to generics, weaker negotiating power of federal government payers, and rapid adoption of newly released prescription drugs in the United States.[12]

When polled in 2015, the public expressed that its top health policy priority

8. *See* White, *supra* note 4, at 190 (explaining the strategic choices of the pharmaceutical industry "have also left many Americans unable to afford their medications; particularly patients who are elderly, socioeconomically disadvantaged, or suffer from chronic diseases."); Steven G. Morgan & Augustine Lee, *Cost-related non-adherence to prescribed medicines among older adults: a cross-sectional analysis of a survey in 11 developed countries*, BMJ OPEN 1, 1 (2017); Peter B. Bach & Steven D. Pearson, *Payer and Policy Maker Steps to Support Value-Based Pricing for Drugs*, 314 J. AM. MED. ASS'N 2503, 2503 (2015); Aurel O. Iuga & Maura J. McGuire, *Adherence and health care costs*, 7 RISK MGMT. AND HEALTHCARE POL'Y 35, 37 (2014) ("Between $100 and $300 billion of avoidable health care costs have been attributed to nonadherence in the US annually, representing 3% to 10% of total US health care costs.").

9. *See* Margot Sanger-Katz, *Prescription Drug Costs Are Rising as a Campaign Issue*, THE UPSHOT (Sept. 21, 2015), https://www.nytimes.com/2015/09/22/upshot/prescription-drug-costs-are-rising-as-a-campaign-issue.html. *See also* DAVID O. SARNAK ET AL., PAYING FOR PRESCRIPTION DRUGS AROUND THE WORLD: WHY IS THE U.S. AN OUTLIER? 2 (2017). Interestingly, this is not the case for generic drugs, which are cheaper in the United States. *See* Tal Gross & Miriam J. Laugesen, *The Price of Health Care: Is the United States an Outlier?*, 42 J. HEALTH POLITICS, POL'Y & L. 771, 774 (2018). Humira, which costs on average $2,669 for a 28-day supply in the United States, costs just $1,362 in the United Kingdom and $822 in Switzerland. THE PEW CHARITABLE TRUSTS, PAYMENT POLICIES TO MANAGE PHARMACEUTICAL COSTS: INSIGHTS FROM OTHER COUNTRIES 9 (Mar. 2017). Similarly, Harvoni, which costs on average $32,114 for a 28-day supply, costs $22,554 in the United Kingdom and $16,861 in Switzerland. *Id.*

10. AARON BERMAN ET AL., CURBING UNFAIR DRUG PRICES: A PRIMER FOR STATES 4 (Aug. 2017). In 2014, after a period of relatively stable drug spending, prescription drug spending in the United States increased by 12 percent when adjusted for inflation. *See* Sanger-Katz, *supra* note 10.

11. Aaron S. Kesselheim, *Health Law Year in P/Review: Prescription Drug Prices* (Dec. 12, 2017), https://vimeo.com/247814795#t=27m14s.

12. THE PEW CHARITABLE TRUSTS, *supra* note 9, at 9-10; Aaron S. Kesselheim et al., *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 J. AM. MED. ASS'N 858, 860 (2016) ("Drug prices are higher in the United States than in the rest of the industrialized world because, unlike that in nearly every other advanced nation, the US health care system allows manufacturers to set their own price for a given product."). New prescription drugs often enter the market at extremely high prices: the average price of a new drug or biologic in 2016 was over $17,000 per month. *See* EXPRESS SCRIPTS, PRESCRIPTION DRUG PRICING: A PUBLIC POLICY ANALYSIS 5 (Feb. 2017).

was making prescription drugs more affordable.[13] Since then, politicians from both sides of the aisle have called for prescription drug pricing reform.[14] President Trump has asserted that he and Secretary of Health and Human Services Azar will decrease the price of prescription drugs.[15] Since then, the Trump Administration has made various proposals to combat high prescription drug prices. In his first proposal, President Trump focused on the high list prices, the lack of negotiating tools, high out-of-pocket costs, and the lower prices for drugs in other countries.[16] Another proposal suggested decreasing prescription drug prices and spending under Medicare Part B by changing the way physicians pay for and are reimbursed for drugs.[17]

The federal government has shown interest in exploring value-based payment

13. Erin Trish et al., *Medicare Beneficiaries Face Growing Out-Of-Pocket Burden For Specialty Drugs While In Catastrophic Coverage Phase*, 35 HEALTH AFF. 1564, 1564 (2016) ("the public's top health policy priority for the president and Congress is 'making sure that high-cost drugs are affordable to those who need them.'" (quoting *Kaiser Health Tracking Poll: October 2015*, KAISER FAM. FOUND. (Oct. 28, 2015), https://www.kff.org/health-costs/poll-finding/kaiser-health-tracking-poll-october-2015/). *See also* Karen Van Nuys et al., *Reining in pharmaceutical costs*, BROOKINGS (Aug. 3, 2017), https://www.brookings.edu/blog/up-front/2017/08/03/reining-in-pharmaceutical-costs/ ("Most Americans believe that President Trump and the Congress should make lowering the cost of prescription drugs a priority."); THE COUNCIL OF ECONOMIC ADVISERS, REFORMING BIOPHARMACEUTICAL PRICING AT HOME AND ABROAD 1 (Feb. 2018).

14. *See, e.g.*, Katie Thomas, *The Fight Trump Faces Over Drug Prices*, N.Y. TIMES (Jan. 23, 2017), https://www.nytimes.com/2017/01/23/health/the-fight-trump-faces-over-drug-prices.html ("During the campaign, Mr. Trump joined his Democratic opponents, Mr. Sanders and Hillary Clinton, in calling for the federal government to be allowed to negotiate the price of drugs."); Rachel Sachs et al., *Innovative Contracting for Pharmaceuticals and Medicaid's Best-Price Rule*, 42 J. HEALTH POLITICS, POL'Y & L. 5, 5 (2017) ("Even in today's polarized political landscape, a consensus has emerged: Americans deserve better value for their health care dollars. The focus on value sits well with liberals and conservatives, health insurers and pharmaceutical manufacturers, and a host of disparate stakeholder groups.").

15. Ike Swelitz, *Trump says new health secretary will 'get those prescription prices way down,'* STAT (Jan. 29, 2018), https://www.statnews.com/2018/01/29/trump-azar-drug-prices/; Katie Thomas & Reed Abelson, *Lower Drug Prices: New Proposals Carry Lots of Promises*, N.Y. TIMES (Feb. 9, 2018), https://www.nytimes.com/2018/02/09/health/trump-drug-prices-medicare.html. Former Food and Drug Administration Commissioner Scott Gottlieb has also expressed concern over high prescription drug prices and has been clearer with proposed policy solutions, including faster regulatory approvals and promoting increased generic drug market entry. *See* Sarah Jane Tribble & Liz Szabo, *FDA vows to combat high drug prices and companies 'gaming the system,'* CNN MONEY (Feb. 16, 2018), http://money.cnn.com/2018/02/16/news/economy/fda-drug-prices/index.html; Nathaniel Weixel, *FDA chief becomes point man on drug prices*, THE HILL (Mar. 14, 2018), http://thehill.com/business-a-lobbying/business-a-lobbying/378254-fda-chief-becomes-point-man-on-drug-prices.

16. *See generally* U.S. DEP'T HEALTH & HUMAN SERVS., AMERICAN PATIENTS FIRST: THE TRUMP ADMINISTRATION BLUEPRINT TO LOWER DRUG PRICES AND REDUCE OUT-OF-POCKET COSTS (2018) (hereinafter AMERICAN PATIENTS FIRST) (outlining President Trump's drug pricing priorities).

17. *See* Rachel Sachs, *Administration Outlines Plan To Lower Pharmaceutical Prices In Medicare Part B*, HEALTH AFF. BLOG (Oct. 26, 2018), https://www.healthaffairs.org/do/10.1377/hblog20181026.360332/full/.

models to reform prescription drug pricing. The Department of Health and Human Services suggested value-based pricing, including indication-specific pricing, as possible opportunities to decrease high prescription drug prices. With a growing number of prescription drugs indicated for the treatment of several different conditions, especially in oncology,[18] indication-specific pricing, one type of value-based pricing model, has received increased attention as a potential solution to high prescription drug prices.[19]

Indication-specific pricing, sometimes called indication-based pricing, is a value-based payment scheme where a prescription drug used to treat multiple conditions is priced based on the condition for which it is prescribed.[20] Indication-specific pricing sets higher prices for higher-value indications, and lower prices for lower-value indications.[21] This scheme intends for prescription drug prices to better reflect value received by an individual patient.[22] Despite its intent, an indication-specific pricing model may not actually accomplish the overarching policy goal of decreasing prescription drug spending and prices.[23] Further, there are several significant legal, regulatory, and policy barriers to implementing indication-specific pricing in the United States healthcare system.[24] This Note, therefore, will argue that lawmakers should not pursue an indication-specific pricing regime and should instead consider other methods to control prescription

18. *See* Peter B. Bach, *Indication-Specific Pricing for Cancer Drugs*, 312 J. AM. MED. ASS'N 1629, 1629 (2014). *See generally* STEPHEN D. PEARSON ET AL., INDICATION-SPECIFIC PRICING OF PHARMACEUTICALS IN THE UNITED STATES HEALTH CARE SYSTEM: A REPORT FROM THE 2015 ICER MEMBERSHIP POLICY SUMMIT (Mar. 2016) (analyzing the potential for implementing an indication-specific pricing regime in the United States).

19. *See also* Tara O'Neill Hayes, *Current Impediments to Value-Based Pricing for Prescription Drugs*, AM. ACTION F. (June 12, 2017), https://www.americanactionforum.org/research/current-impediments-value-based-pricing-prescription-drugs/ ("With the unprecedented number of specialty medicines and oncology treatments expected over the next few years, the cost of prescription drugs will continue to be a concern for all stakeholders. QuintilesIMS Institute finds that 28 percent of new drugs currently being developed are oncology medicines, and nearly half of all drug spending in the U.S. will be for specialty medicines by 2021.").

20. *See* PEARSON ET AL., *supra* note 18, at 2 (defining indication-specific pricing as "setting different prices for different indications or for distinct patient subpopulations eligible for treatment with a medication.").

21. *See* Amitabh Chandra & Craig Garthwaite, *The Economics of Indication-Based Drug Pricing*, 377 NEW ENG. J. MED. 103, 103-04 (2017).

22. *See id.*

23. *See id.* ("relative to uniform pricing, indication-[specific] pricing results in higher prices for patients who benefit the most, higher utilization by patients who benefit least, higher overall spending, and higher manufacturer profits"). *See also* Part III, *infra*.

24. *See generally* PEARSON ET AL., *supra* note 18 (analyzing the potential for implementing an indication-specific pricing regime in the United States and discussing the legal, regulatory, and policy barriers to implementation).

drug prices and spending.[25]

Part I provides background on value-based pricing models and defines indication-specific pricing of prescription drugs. Part II identifies and describes the legal and regulatory barriers to indication-specific pricing under Medicare, Medicaid, the 340B Drug Discount Program, and the Veterans Health Administration program. Part III presents the policy incentives raised by indication-specific pricing of prescription drugs in federal health insurance programs and discusses how it would impact the FDA regulatory system, off-label prescribing and promotion, and prescription drug prices. Ultimately, Part III argues that lawmakers should explore other methods, instead of indication-specific pricing, to decrease prescription drug prices and spending. Part IV suggests alternatives to indication-specific pricing that could be considered, introduces some initiatives that have already been raised, and recommends next steps for lawmakers.

I. VALUE-BASED PRICING MODELS AND INDICATION-SPECIFIC PRICING

A. Value-Based Pricing of Prescription Drugs

Currently in the United States, prescription drugs are generally reimbursed in a fee-for-service model.[26] Insurance companies reimburse per unit of the prescription drug without regard to outcome, indication, value to the patient, or any other factors. Critics of this payment model stress that not all patients receive the same benefit or value from a prescription drug even though they pay the same amount as patients who do benefit.[27] To avoid paying for ineffective treatments and to lower prescription drug prices, some advocates propose value-based pricing models.

Value-based pricing models link the price paid for a prescription drug with the expected or actual benefit to the patient.[28] There are several different types of

25. As the majority of prescription drugs for which indication-specific pricing is being proposed are high-priced brand name drugs with no generic alternative, typically for cancer treatment or other rare diseases, *see generally* Bach, *supra* note 18 (discussing indication-specific pricing for cancer drugs), this Note will focus only on the issues presented by indication-specific pricing of brand-name prescription drugs.

26. *See* Gregory Daniel et al., *Advancing Gene Therapies and Curative Health Care Through Value-Based Payment Reform*, HEALTH AFF. BLOG (Oct. 30, 2017), https://www.healthaffairs.org/do/10.1377/hblog20171027.83602/full/. This is sometimes referred to as a "price-per-dose basis." *See* Sachs et al., *supra* note 14, at 5.

27. *See* Sachs et al., *supra* note 14, at 6 ("[M]any patients receive little or no benefit from their prescription drugs—yet they pay precisely the same amount as those who do benefit.").

28. *See* Daniel et al., *supra* note 26 ("[Value-based payment models] are designed to link payment more explicitly to a treatment's value, expected or realized."). *See generally* Sachs et al., *supra* note 14, at 7-14 (discussing how different value-based payment models work for prescription drugs).

value-based pricing models, differentiated based on the types of value measured (considering various contexts, benchmarks, or outcomes) in the model.[29] Value-based pricing models apply the determination of value to ultimately calculate the value-based price. The overall goal of value-based pricing is to incentivize providers to choose higher value, more effective prescription drugs, resulting in better outcomes for patients and lower overall healthcare spending.[30] Value-based pricing models therefore also encourage manufacturers to develop more effective and more profitable prescription drugs.

While the general concept of value-based pricing is simple, determining the value-based price of a prescription drug is exceedingly challenging. Most difficult is deciding what constitutes value and what factors represent this definition of value.[31] Value is typically considered to be "the benefit of a treatment with respect to its cost,"[32] but various factors must be taken into account in calculating the magnitude of this benefit with respect to cost. The determination of value can be made with respect to an individual patient (did this specific patient receive the intended benefit from this prescription drug?), to a sub-population (did the sub-population with a specific characteristic receive the intended benefit?),[33] or to a population as a whole (did this prescription drug lower the overall mortality or improve a health outcome to a predetermined benchmark related to clinical trial demonstrations?).[34] The value could be based on clinical measures, for example, a final treatment outcome, achieving a benchmark outcome in the course of treatment, or the disease requiring treatment.[35] This value could also be more subjective and include patient-centered benchmarks, such as patient satisfaction, increased quality of life, or decreased pain.

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29. This Note focuses on indication-specific pricing, discussed in detail in Part I.B, *infra*. Other types of value-based payment models include outcome-based payment, drug licenses, and drug mortgages. For a detailed description of these value-based payment models, *see* Sachs et al., *supra* note 14, at 10-14.

30. *See* Daniel et al., *supra* note 26.

31. *See id.* at 2595-97 ("Value is an elusive target, and there's no consensus about what dimensions should be taken into account."). Several organizations have developed their own methodologies of evaluating prescription drugs and calculating their value to patients. *See id.* For example, Memorial Sloan Kettering Cancer Center's framework focuses on the cancer drug's mode of action, efficacy, and toxicity. *Id.* By contrast, the Institute for Clinical and Economic Review's framework primarily looks at a prescription drug's cost effectiveness in terms of cost per quality-adjusted life year and overall budget impact, but also looks at clinical effectiveness and other benefits in context. *Id.*

32. Bach, *supra* note 18, at 1629.

33. *See id.* ("What is the right price for any particular level of benefit? How should benefit be determined? What if the condition is rare? What if the average benefit is small but a subgroup of patients derives a large benefit?").

34. *See* Hayes, *supra* note 19 (describing value-based payment agreements where the benchmarks were based on the results observed in clinical trials).

35. *See* Sachs et al., *supra* note 14, at 10-14 (discussing types of value-based pricing models).

B. Indication-Specific Pricing of Prescription Drugs

Prescription drugs are often used to treat more than one disease state or indication.[36] For example, Keytruda treats two different types of cancers and Avastin treats both cancer and macular degeneration.[37] However, despite the varied effectiveness of individual prescription drugs for different indications, prescription drug companies must charge the same price for the prescription drug regardless of the indication for which it is prescribed to a patient.

Indication-specific pricing would change this scheme by linking the price of the prescription drug to the condition for which it was prescribed.[38] In indication-specific pricing models, prescription drug manufacturers are paid more when their prescription drug is used to treat an indication for which the product is more effective or has a higher value (high-value indications) than when it is used to treat an indication for which the product is less effective or has a lesser value for the patient (low-value indications).[39] For example, in an indication-specific pricing regime, Keytruda would cost a different price when it is prescribed for the treatment of advanced non-small cell lung cancer than it is for advanced melanoma, based on its effectiveness in treating the condition.[40] The determinations of value or effectiveness are typically based on the data collected during clinical trials.[41] Depending on an individual's prescription drug coverage, these higher prices for high-value indications are likely less affordable and less accessible as a result.[42] Conversely, indication-specific pricing sets lower prices for lower-value indications, resulting in them being more affordable, more accessible, and used more by patient populations who receive a comparatively lesser benefit from them.[43] Indication-specific pricing models can be a pure indication-specific pricing regime, meaning that each different indication has a different price, or a partially indication-specific pricing regime, generally meaning

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36. *See* PEARSON ET AL., *supra* note 18, at 6 ("A multi-indication medication is a drug that is approved or prescribed for more than one condition or for a single condition with multiple identifiable patient sub-groups that have important differences in baseline risk and/or treatment outcomes."); Chandra & Garthwaite, *supra* note 21, at 103 ("in oncology, for instance, response to a treatment varies with the type of tumor and stage of disease.").

37. *See* Sachs et al., *supra* note 14, at 7-8.

38. *See* Sachs et al., *supra* note 14, at 7-8; Chandra & Garthwaite, *supra* note 21, at 103; PEARSON ET AL., *supra* note 18, at 2 (defining indication-specific pricing as "setting different prices for different indications or for distinct patient subpopulations eligible for treatment with a medication.").

39. *See* Chandra & Garthwaite, *supra* note 21, at 103.

40. *See* Sachs et al., *supra* note 14, at 7-8; KEYTRUDA ® (pembrolizumab), KEYTRUDA.COM (Nov. 2017), https://www.keytruda.com (listing the FDA-approved indications of Keytruda)

41. Hayes, *supra* note 19.

42. *See* Chandra & Garthwaite, *supra* note 21, at 103-04.

43. *See id.*

that indication-specific prices are combined into a weighted-average price.[44]

Some countries have implemented indication-specific pricing regimes for prescription drugs, either in part or in a pure form.[45] Italy has adopted a pure indication-specific pricing regime for some prescription drugs, including some cancer drugs and an anti-inflammatory prescription drug, through the use of managed entry agreements.[46] Managed entry agreements are contracts between payers and a pharmaceutical company that allows a prescription drug to be covered subject to certain conditions.[47] Italy permits three types of managed entry agreements, each involving some sort of refund to the payer for insufficient outcomes.[48] Some of these managed entry agreements consider different outcomes (and thus different refunds) for different indications, resulting in a *de facto* indication-specific price.[49] Even with some indication-specific pricing and outcomes-based pricing arrangements, Italy has not seen any resulting decrease in the cost of prescription drugs.[50] Other countries have incorporated the value of each indication of a drug into their prescription drug prices, resulting in a partially indication-specific pricing regime. Australia has used weighted-average prices for prescription drugs with multiple indications, combining the different value-based prices for each indication into a single weighted average price.[51] The United Kingdom allows prescription drugs to increase their reimbursement price once if a prescription drug manufacturer identifies a new high-value indication.[52]

In theory, indication-specific pricing may help better allocate prescription drugs, incentivizing prescribing high-value indications instead of less effective treatments and incentivizing prescription drug manufacturers to develop more effective treatments and support their products with demonstrations of effectiveness.[53] However, indication-specific pricing would face several legal barriers to implementation in federal health insurance programs in the United

44. *See* PEARSON ET AL., *supra* note 18, at 11-12 (describing different variations of indication-specific pricing models).

45. *See id.* at 12.

46. *See id.* at 13; Mathias Flume, et al., *Feasibility and Attractiveness of Indication Value-based Pricing in Key EU Countries*, 4 J. MARKET ACCESS & HEALTH POL'Y (2016).

47. Jacoline C. Bouvy et al., *Managed Entry Agreements for Pharmaceuticals in the Context of Adaptive Pathways in Europe*, 9 FRONTIERS IN PHARMACOLOGY 280, 280 (2018).

48. *See* Flume, et al., *supra* note 46.

49. *See id.*

50. *See* Noemie Bisserbe, *For New Trump Drug Plan, a Cautionary Tale in Italy*, WALL ST. J. (Apr. 17, 2018), https://www.wsj.com/articles/italy-serves-cautionary-lesson-for-new-trump-drug-plan-1523959644 (discussing the results of outcomes-based contracts).

51. *See* PEARSON ET AL., *supra* note 18, at 13 (describing different variations of indication-specific pricing models).

52. *See id.*

53. *See generally* Susan Abedi, *Indication-Based Pricing- The Good, The Bad, and the Ugly*, IMS CONSULTING GROUP (June 2016), http://www.ehcca.com/presentations/PharmaMM/abedi_c.pdf.

States.[54] Additionally, the policy effects of indication-specific pricing are debated.[55] There are several reasons advocates support indication-specific pricing, including having prescription drug prices better reflect their value to patients and incentivizing manufacturers to develop high-value treatments. Supporters of indication-specific pricing assert that this regime would decrease spending for high-cost prescription drugs, while critics claim it will increase spending.[56]

The remainder of this Note will detail the legal, regulatory, and policy barriers to implementing an indication-specific pricing regime in the United States, particularly in federal health insurance programs.[57] Further, this Note will demonstrate that although these barriers may not be insurmountable, indication-specific pricing is not the appropriate solution to high prescription drug spending and prices in the United States.

II. INDICATION-SPECIFIC PRICING IN FEDERAL HEALTH INSURANCE PROGRAMS

Implementing an indication-specific pricing regime would require rethinking the prescription drug pricing and reimbursement models of federal government health insurance programs. The federal government pays for healthcare, including prescription drugs, through several independent health insurance programs. Each program has, among other things, different eligibility requirements, different benefits packages, and different means of determining the price, provision, and reimbursement of prescription drugs. These systems pose different barriers to indication-specific pricing. This Part introduces four of the major federal health insurance programs purchasing prescription drugs (Medicare, Medicaid, the 340B Drug Discount Program, and the Veterans Health Administration); describes how each program structures pricing, reimbursement, and payment for prescription drugs; and discusses the barriers to implement an indication-specific pricing

54. *See* Part II, *infra*. *See also* Bach, *supra* note 18, at 1630.

55. *Compare* Bach, *supra* note 18, *with* Chandra & Garthwaite, *supra* note 21.

56. *See* Part III, *infra*. *See also* Chandra & Garthwaite, *supra* note 21, at 103 ("Supporters hope that such a system will re-duce prices for low-value indications but that prices for high-value indications will not increase." (citing Bach, *supra* note 18, at 1629-30)); Chandra & Garthwaite, *supra* note 21, at 103-04 (arguing that indication-specific pricing would increase overall drug spending); PEARSON ET AL., *supra* note 18, at 8-10 (listing the risks and benefits of indication-specific pricing of prescription drugs to payers and prescription drug manufacturers).

57. In considering indication-specific pricing as a solution to high prescription drug prices and spending, this Note assumes that if an indication-specific pricing model were allowed or adopted, all prescription drugs purchased in the United States by federal health insurance programs would now be subject to an indication-specific price. Further, this indication-specific price would reflect the value of the treatment to a patient population relative to other treatments. While this is ideally the case, adopting this policy does not guarantee that the negotiated price would in fact accurately reflect the actual value of a treatment received by a patient. This may affect the degree of the impact and incentive effects of indication-specific pricing. Regardless, the legal and regulatory barriers to indication-specific pricing and the policy incentives identified remain significant.

regime for prescription drugs in each program.

A. Medicare

Medicare provides health insurance coverage for people age sixty-five and over, some younger people with disabilities, and people with end-stage renal disease.[58] Medicare currently provides health insurance for approximately fifty-five million people in the United States,[59] covering $672.1 billion in healthcare services in 2016.[60] Medicare alone comprises approximately 40 percent of the pharmaceutical market in the United States.[61]

The Medicare program covers different healthcare services under different parts of the program.[62] Medicare Part A, sometimes referred to as Hospital Insurance, covers healthcare during certain inpatient stays.[63] Prescription drugs used during a hospital stay are included in the broader reimbursement for the inpatient stay.[64] Medicare Part B primarily covers services provided in a doctor's office.[65] Prescription drugs administered during a physician office visit or in a hospital outpatient clinic are included under Medicare Part B.[66] Medicare Part C, also called Medicare Advantage Plans, provides coverage for Medicare Part A and Medicare Part B benefits, and often prescription drug coverage, through a private company contracting with Medicare.[67] Medicare Part D provides prescription drug

58. *See What's Medicare*, MEDICARE.GOV: THE OFFICIAL U.S. GOVERNMENT SITE FOR MEDICARE, https://www.medicare.gov/sign-up-change-plans/decide-how-to-get-medicare/whats-medicare/what-is-medicare.html; *Health Policy Brief: Medicare Part D*, HEALTH AFF. (Aug. 10, 2017), https://www.healthaffairs.org/do/10.1377/hpb20171008.000172/full/healthpolicybrief_172.pdf [hereinafter *Medicare Part D Brief*].

59. *See Health Policy Brief: Implementing MACRA*, HEALTH AFF. (Mar. 27, 2017), https://www.healthaffairs.org/do/10.1377/hpb20170327.272560/full/ (55 million people on Medicare) [hereinafter *MACRA Brief*]. *See also The Medicare Part D Prescription Drug Benefit*, KAISER FAM. FOUND, (Oct. 2, 2017), https://www.kff.org/medicare/fact-sheet/the-medicare-prescription-drug-benefit-fact-sheet/ (59 million people on Medicare).

60. *NHE Fact Sheet*, CTRS. FOR MEDICARE & MEDICAID SERVS. (Dec. 6, 2017), https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata/nhe-fact-sheet.html.

61. *See* Greg D'Angelo, *The VA Drug Pricing Model: What Senators Should Know*, HERITAGE FOUND.: WEBMEMO (Apr. 11, 2007).

62. *See What's Medicare*, *supra* note 58.

63. *See id.* (explaining Medicare Part A "covers inpatient hospital stays, care in a skilled nursing facility, hospice care, and some home health care.").

64. *See Health Policy Brief: Medicare Part B*, HEALTH AFF. (Aug. 10, 2017), https://www.healthaffairs.org/do/10.1377/hpb20171008.000171/full/healthpolicybrief_171.pdf [hereinafter *Medicare Part B Brief*].

65. *See What's Medicare*, *supra* note 58 (explaining Medicare Part B covers "certain doctors' services, outpatient care, medical supplies, and preventive services.").

66. *See Medicare Part B Brief*, *supra* note 64; *Medicare Part D Brief*, *supra* note 58.

67. *See What's Medicare*, *supra* note 58.

coverage through contracts with private companies and Medicare Advantage Plans.[68] Each part of Medicare calculates prescription drug prices and reimbursement rates differently, posing various challenges to indication-specific pricing. As the majority of prescription drug spending through Medicare occurs under Parts B and D,[69] the following sections further detail their prescription drug pricing schemes.

1. Medicare Part B

Medicare Part B covers prescription drugs prescribed and administered in outpatient clinics and physician's offices.[70] These include prescription drugs administered by injection or intravenously in a physician's office or hospital outpatient setting and some oral cancer drugs that also have intravenous forms.[71] Medicare Part B must cover all prescription drugs that are "reasonable and necessary for the diagnosis or treatment of illness or injury;" price cannot be taken into account while deciding reimbursement coverage.[72] Medicare Part B spending on prescription drugs totaled approximately $25 billion in 2015, at least half of which was spent on cancer drugs.[73]

Prescription drug manufacturers participating in Medicare Part B are required to report prescription drug prices to the federal government on a per-unit basis without a reported indication.[74] Prescription drugs provided under Medicare Part B are reimbursed at the average sales price to a non-federal government payer plus 6 percent paid as a handling fee to doctors.[75] Patients are personally responsible for paying a 20 percent co-insurance for all prescription drugs under Medicare Part

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68. *See id.*
69. *See* Rachel E. Sachs, *Delinking Reimbursement*, 102 MINN. L. REV. 2307, 2314 (2018).
70. *See Medicare Part B Brief*, *supra* note 64; *Medicare Part D Brief*, *supra* note 58.
71. White, *supra* note 4, at 194-95.
72. *See* Sachs, *supra* note 17 (quoting 42 U.S.C. § 1395y(a)(1)(A))).
73. Sachs, *supra* note 69, at 2314.
74. *See* Daniel et al., *supra* note 26. Manufacturers must report the average sales price and average wholesale price of their products quarterly by the National Drug Code (NDC), and physicians report the NDC and/or the Healthcare Common Procedure Coding System (HCPCS) code for the product administered, but the indication for which the prescription drug was eventually prescribed by physicians is not reported. *See* DEP'T OF HEALTH & HUMAN SERVS., OFFICE OF INSPECTOR GENERAL, AVERAGE SALES PRICES: MANUFACTURER REPORTING AND CMS OVERSIGHT 3-4 (Feb. 2010); Report to the Congress: Medicare and the Health Care Delivery System (June 2016). *See also* CTRS. FOR MEDICARE & MEDICAID SERVS., HEALTHCARE COMMON PROCEDURE CODING SYSTEM (HCPCS) LEVEL II CODE MODIFICATION REQUEST PROCESS 2019 UPDATE (APR. 2017), https://www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/Downloads/HCPCS-Application.pdf (briefly advising on HCPCS coding through Medicare for prescription drugs).
75. *See* 42 U.S.C. § 1395w-3a (dictating average sales price methodology); 42 C.F.R. § 414.804 (providing further regulations on average sales price methodology); *Medicare Part B Brief*, *supra* note 64.

B with no upper limit on out-of-pocket spending.[76]

Medicare Part B poses a few significant challenges to adopting an indication-specific pricing model. First, the price reporting requirements for prescription drug manufacturers could cause a compliance issue; as indication-specific pricing by definition is not a price-per-unit model, this regulation would have to be modified in order for an indication-specific pricing model to be possible.[77] The regulation could be changed to require a price-per-unit-per-indication model, or otherwise repealed or modified to allow indication-specific pricing. Further, because prices are reported by product, not indications for the product,[78] the current reporting regime would need to be amended in order to include the indication for the reported code. Second, there is no requirement for physicians to report the indication for which they prescribe a prescription drug. In order for an indication-specific pricing regime to be implemented, a law or regulation mandating physicians to report the indication associated with each prescription would be necessary. Third, Medicare Part B reimburses based on the average sales price not differentiated by indication.[79] Average sales price would have to be redefined as average sales price per indication, or the formula would have to be otherwise modified for an indication-specific pricing regime to be implemented.

An indication-specific pricing scheme also would not address the questionable policy incentives for physicians under Medicare Part B. The 6 percent handling fee for physicians incentivizes physicians to prescribe prescription drugs with higher costs.[80] The prescription drug with the higher price would theoretically be the most effective treatment for the specific indication. This could effectively ensure that physicians make rational choices and maximize the value of their prescribing. However, with further incentives for doctors to prescribe the higher-priced prescription drug, prescription drug spending may not decrease under an indication-specific pricing model. In order to lessen the incentive for physicians, the Centers for Medicare and Medicaid Services (CMS) proposed a demonstration

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76. *See id.*; Bach & Pearson, *supra* note 8, at 2503 ("the current policy of flat 20% co-insurance without an upper limit has put some highly effective but expensive drugs out of reach for the roughly 6 million Medicare beneficiaries who have no supplemental insurance.").

77. *See* Daniel et al., *supra* note 26 ("Value-based payment arrangements by definition depart from a per-unit price, but current statutory and regulatory provisions are not designed to capture such arrangements. Manufacturers could be exposed to compliance risk when they seek to reflect a value-based arrangement in their price reporting, and reflecting a value-based arrangement in a per-unit metric could result in unintended reimbursement and payment consequences.").

78. *See National Drug Code Directory*, FOOD AND DRUG ADMIN. (Nov. 2017), https://www.fda.gov/drugs/informationondrugs/ucm142438.htm. *See also* MEDICARE PAYMENT ADVISORY COMM'N, REPORT TO THE CONGRESS: MEDICARE AND THE HEALTH CARE DELIVERY SYSTEM 131 (June 2016) (listing multiple indications in relation to one HCPCS code).

79. *See* 42 U.S.C. § 1395w-3a (dictating average sales price methodology not taking into account indication); *Medicare Part B Brief*, *supra* note 64.

80. *See Medicare Part B Brief*, *supra* note 64.

project in 2016 (which was never implemented) that would have changed physician reimbursement for prescription drugs under Medicare Part B to a flat handling fee of $16.80 plus 2.5 percent of the average sales price.[81] This proposal was intended to maintain the same aggregate prescription drug spending under Medicare Part B while increasing the handling fee for lower priced prescription drugs.[82] President Trump has also proposed a similar reform.[83] While changing this formula would address physician incentives to some extent, it would do little to help beneficiaries afford prescription drugs. Reforms to prescription drug pricing under Medicare Part B must consider this formula and the existing reimbursement model so as not to exacerbate the existing incentives for physicians to prescribe high priced prescription drugs and increase drug spending.

2. Medicare Part D

Medicare Part D is the largest federal program paying for prescription drugs.[84] Medicare Part D covers exclusively prescription drugs purchased at pharmacies by consumers.[85] Medicare Part D plans are run by private companies contracting with the federal government.[86] Medicare pays private companies running the Medicare Part D plans a fixed grant to help pay for all prescription drugs used by covered beneficiaries instead of paying for specific prescription drugs.[87] Everyone on Medicare has access to Medicare Part D and in 2017 over forty million people enrolled in Medicare Part D plans.[88] The largest Medicare Part D plans represent approximately 21 percent of Medicare Part D recipients.[89] Consumers eligible for both Medicare and Medicaid receive their prescription drug coverage under Medicare Part D.[90] Total drug spending under Medicare Part D in 2015 was

81. *See id. See also* Deborah Schrag, *Reimbursing Wisely? CMS's Trial of Medicare Part B Payment Reform*, 374 NEW ENG. J. MED. 2101, 2101 (2016).

82. *See Medicare Part B Brief*, *supra* note 64.

83. *See* Sachs, *supra* note 17.

84. *See Medicare Part D Brief*, *supra* note 67.

85. *See id.*

86. Michael Adelberg & Marissa Schlaifer, *The Other Side of Managed Competition: The Tension Between Protection And Innovation In Medicare Advantage And Part D Benefits*, HEALTH AFF. BLOG (Dec. 8, 2017), https://www.healthaffairs.org/do/10.1377/hblog20171205.156064/full/ ("Medicare Advantage and Medicare Part D are prime examples of managed competition markets, where the government provides services by contracting with private entities to serve program beneficiaries in a regulated market.").

87. *See Medicare Part B Brief*, *supra* note 64.

88. *See The Medicare Part D Prescription Drug Benefit*, *supra* note 59 (42 million people enrolled on Medicare Part D plans).

89. *See Medicare Part D Brief*, *supra* note 67.

90. *See The Medicare Part D Prescription Drug Benefit*, *supra* note 59. This allocation of Medicaid-eligible individuals to Medicare Part D prescription drug coverage raises its own prescription drug spending problems, as on average "Medicare Part D pays . . . 73% more than

approximately $135 billion.[91]

CMS requires all Medicare Part D plans to cover at least two prescription drugs in each therapeutic class and all drugs in six classes, called protected classes, which include antidepressants, antiretrovirals, antipsychotics, anticonvulsants, immunosuppressants (to prevent organ transplant rejection), and antineoplastics (a type of cancer treatment).[92] There is still substantial variation between Medicare Part D plans with regard to drugs included on the formularies and copayments (or cost-sharing amounts for which patients are responsible at the point of service).[93] The formularies of Medicare Part D plans generally tier drugs, differentiating preferred prescription drugs (which are associated with lower copayments) from more expensive non-preferred prescription drugs.[94] Beneficiaries cover 25 percent of prescription drug costs until the catastrophic cap of $4,950 in beneficiary spending.[95] After reaching the catastrophic cap, under a provision of the Affordable Care Act to be implemented by 2020, beneficiaries are responsible for 5 percent of prescription drug costs, with the Medicare Part D plan covering 15 percent and a federal government reinsurance subsidy covering the remaining 80 percent.[96]

Medicare is prohibited by law from negotiating or setting prices for Medicare Part D.[97] However, individual Medicare Part D plans can and do negotiate prices

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Medicaid and 80% more than [the Veterans Health Administration] . . . for the same brand-name drugs." Micah Vitale, Note, *The Rise in Prescription Drug Prices: The Conspiracy Against The Cure*, 20 QUINNIPIAC HEALTH L. J. 75, 92 (2017) (quoting MARC-ANDRÉ GAGNON & SIDNEY WOLFE, MIRROR, MIRROR ON THE WALL: MEDICARE PART D PAYS NEEDLESSLY HIGH BRAND-NAME DRUG PRICES COMPARED WITH OTHER OECD COUNTRIES AND WITH U.S. GOVERNMENT PROGRAMS 12 (2015), http://carleton.ca/sppa/wp-content/uploads/Mirror-Mirror- Medicare-Part-D-Released.pdf.) (alteration in original). Because Medicare Part D pays more for drugs than Medicaid, the system has essentially chosen to spend more for prescription drugs than is necessary. Some scholars have proposed that consumers eligible for both Medicare and Medicaid, sometimes called "dual-eligibles," should be moved back to Medicaid for their prescription drug coverage, arguing that it would lead to lower prescription drug spending and better access to prescription drugs for patients. *See* Kevin Outterson & Aaron S. Kesselheim, *How Medicare Could Get Better Prices on Prescription Drugs*, HEALTH AFF. W832, w834-35 (2009).

91. *See* Sachs, *supra* note 69, at 2314.

92. *Medicare Part D Brief*, *supra* note 67; CTRS. FOR MEDICARE & MEDICAID SERVS., MEDICARE PRESCRIPTION DRUG BENEFIT MANUAL 28 (2016), *available at* https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Part-D-Benefits-Manual-Chapter-6.pdf.

93. Adelberg & Schlaifer, *supra* note 86.

94. *See Medicare Part D Brief*, *supra* note 67.

95. *See id.*

96. *See id.*

97. 42 U.S.C. § 1395w-111(i) (2012). *See also Medicare Part D Brief*, *supra* note 67; Sachs, *supra* note 69, at 2325-26 ("Often referred to as the noninterference clause, the statute provides that the Secretary of Health and Human Services (HHS) " may not interfere with the negotiations between drug manufacturers and pharmacies and [Prescription Drug Plan] sponsors and "may not require a

with prescription drug manufacturers.[98] The cost-sharing model and the competition between Medicare Part D plans, both in attracting consumers and in bidding for federal government contracts, incentivize them to negotiate prescription drug prices as low as possible.[99] Prescription drug spending, including for high-cost brand name prescription drugs, is a concern under Medicare Part D. In 2013, while the top ten drugs paid for by Medicare Part D plans were all generics (306.6 million claims totaling $4.14 billion), the top ten most expensive were all brand name prescription drugs (54.63 million claims totaling $19.78 billion).[100]

The barriers to implementing indication-specific pricing in Medicare Part D are perhaps more formidable than those present in Medicare Part B. The laws forbidding Medicare from negotiation with prescription drug manufacturers would pose a challenge to implementing an effective indication-specific pricing scheme in Medicare Part D. Because Medicare cannot negotiate as a whole, even though individual Medicare Part D plans can negotiate with prescription drug manufacturers, Medicare Part D plans cannot leverage the buying power of the whole Medicare population.[101] This negotiation model weakens the bargaining power of Medicare Part D to lower prescription drug prices, likely making prices higher than they would be if Medicare negotiated as a whole. However, this limitation alone is not the most substantial barrier to lowering prescription drug prices and spending.

The requirement that Medicare Part D plans cover all prescription drugs in six protected classes, which includes cancer drugs, further challenges the ability for indication-specific pricing to lower prescription drug spending.[102] This regulation significantly weakens Medicare Part D plans' negotiating power, leaving the prescription drug manufacturers with all the bargaining power and forcing manufacturers to accept high prices for these drugs.[103] Even if the indication-

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particular formulary or institute a price structure for the reimbursement of covered part D drugs.").

98. *See Medicare Part D Brief*, *supra* note 67.

99. *See* Theodore T. Lee et al., *The Politics of Medicare and Drug Price Negotiation (Updated)*, HEALTH AFF. BLOG (Sept. 19, 2016), https://www.healthaffairs.org/do/10.1377/hblog20160919.056632/full/.

100. *See* Nicole M. Gastala et al., *Medicare Part D: Patients Bear The Cost Of 'Me Too' Brand Name Drugs*, 35 HEALTH AFF. 1237, 1238 (2016) (citing *Press release, CMS releases prescriber-level Medicare data for first time*, CTRS. FOR MEDICARE & MEDICAID SERVS. (Apr. 30, 2015), https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2015-Fact-sheets-items/2015-04-30.html)).

101. *See Medicare Part D Brief*, *supra* note 67.

102. *See id.*

103. *See* Thomas, *supra* note 14 ("'You get your largest negotiating power from your ability to walk away,' said Dr. Aaron S. Kesselheim, an associate professor at Harvard Medical School who has written frequently on drug prices."). *See also* Sachs, *supra* note 69, at 2326 ("Medicare might be able to achieve some savings where there is already market competition and where Medicare is permitted to cover two drugs in that class, although it is difficult to see why private plans have not negotiated such deals already. But for the six protected classes in which Medicare must cover all

specific price somewhat lowered the prices, the lack of negotiation power undermines the ability of Medicare Part D plans to negotiate a price truly reflecting the value. With this mandate still in place, not only would insurers be unable to demand an indication-specific price for a high-cost cancer drug based on its value to a patient population, but they would still be forced to accept inflated prices for prescription drugs in these protected classes.

While the negative physician incentives present in Medicare Part B are not present in Medicare Part D, the negative incentives for patients are significant. Instead of the 20 percent co-insurance under Medicare Part B, beneficiaries under Medicare Part D are responsible for a 25 percent co-insurance up to the catastrophic cap of $4,950 and then 5 percent co-insurance after reaching the catastrophic cap.[104] As many prescription drugs cost more than the catastrophic cap,[105] many consumers face a significant and possibly prohibitive out-of-pocket spending requirement. An indication-specific pricing regime would do nothing to address the cost to patients unless the indication was less effective. If the relevant indication of the prescription drug was a relatively less effective than other treatments, it would cost relatively less and be more affordable to the patient at the point of service. However, high-cost, high-value indications of prescription drugs would remain expensive to both consumers and to the system, and an indication-specific pricing model would give manufacturers and patients no incentives to lower prices or seek better care options.

In addition to not addressing the affordability of drugs for patients, an indication-specific pricing regime would do nothing to decrease the government's overall prescription drug spending. Under Medicare Part D, a federal government subsidy pays for 80 percent of prescription drug costs after the catastrophic cap is reached; the reinsurance, or subsidy, portion of Medicare Part D is the fastest growing Medicare Part D cost as so many prescription drugs now cost thousands of dollars annually.[106] An indication-specific pricing regime would do nothing to decrease or slow the reinsurance costs. Reforms to Medicare Part D should both slow spending and improve patient access, and an indication-specific pricing regime would accomplish neither.

B. Medicaid

Medicaid is the federal government health insurance program that provides health insurance coverage for low-income people in the United States,[107] covering

products, or for expensive new drugs with few, if any, substitutes, Medicare cannot walk away from the table if it does not like the deal companies are offering.").

104. *See Medicare Part D Brief*, *supra* note 67.

105. *See id.*

106. *Id.*

107. *See About Us*, MEDICAID.GOV, https://www.medicaid.gov/about-us/index.html.

approximately seventy million Americans.[108] It is one of the largest payers for healthcare in the United States.[109] Medicaid is administrated by the states and jointly funded by the states and the federal government.[110]

Medicaid comprises approximately 20 percent of the prescription drug market.[111] Prescription drugs are a small but growing portion of Medicaid spending (6 percent to 9 percent from 2010 to 2015).[112] The growth rate of Medicaid prescription drug spending in 2014 outpaced that of overall prescription drug spending in the United States.[113] While prescription drug coverage is an optional benefit under Medicaid, all states currently cover prescription drug costs for Medicaid beneficiaries.[114] Most states charge copayments for prescription drugs purchased under Medicaid, but these copayments are very low, capped at a few dollars per prescription and less than $30 per month.[115]

The price Medicaid pays for prescription drugs is regulated by the Medicaid Drug Rebate Program and the Medicaid Best Price Rule.[116] Under the Medicaid Drug Rebate Program, prescription drug manufacturers receive Medicaid coverage for essentially all of their prescription drug products in exchange for agreeing with the Department of Health and Human Services to provide rebates to Medicaid, the 340B Drug Discount Program, and the Department of Veterans Affairs.[117] As long as the prescription drug manufacturer participates in the Medicaid Drug Rebate

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108. *See Medicaid*, MEDICAID.GOV, https://www.medicaid.gov/medicaid/index.html (68 million covered as of the October 2017 open enrollment period); *Medicaid State Fact Sheets*, KAISER FAM. FOUND. (June 16, 2017), https://www.kff.org/interactive/medicaid-state-fact-sheets/ ("Medicaid and the Children's Health Insurance Program (CHIP) provide health and long-term care coverage to more than 70 million low-income children, pregnant women, adults, seniors, and people with disabilities in the United States.").

109. *See About Us*, MEDICAID.GOV, *supra* note 107.

110. *See Medicaid*, *supra* note 108.

111. *See Health Policy Brief: Veterans Health Administration*, HEALTH AFF. (Aug. 10, 2017), https://www.healthaffairs.org/do/10.1377/hpb20171008.000174/full/healthpolicybrief_174.pdf [hereinafter *Veterans Health Administration Brief*].

112. *See* David Dranove et al., *A Dose of Managed Care: Controlling Drug Spending in Medicaid* 9 (National Bureau of Economic Research Working Paper 23956, Oct. 2017), http://www.nber.org/papers/w23956.

113. *See* Hefei Wen et al., *Number Of Medicaid Prescriptions Grew, Drug Spending Was Steady In Medicaid Expansion States*, 35 HEALTH AFF. 1604, 1604 (2016) (citing Anne B. Martin et al., *National Health Spending in 2014: Faster Growth driven By Coverage Expansion and Prescription Drug Spending*, 35 HEALTH AFF. 150 (2016)).

114. *See Prescription Drugs*, MEDICAID.GOV, https://www.medicaid.gov/medicaid/prescription-drugs/ (accessed Dec. 31, 2017).

115. *See id.* (presenting the prescription drug payments and copayments under Medicaid in each state).

116. *See Health Policy Brief: Medicaid Best Price*, HEALTH AFF. (Aug. 10, 2017), https://www.healthaffairs.org/do/10.1377/hpb20171008.000173/full/ [hereinafter *Medicaid Best Price Brief*].

117. *See id.*

Program, states must cover all of the manufacturer's prescription drugs approved by the Food and Drug Administration (FDA).[118] Because prescription drug manufacturers who do not participate in the Medicaid Drug Rebate Program are excluded from participating in all federal government health insurance programs (a massive share of the prescription drug market), prescription drug manufacturers are basically required to participate.[119]

The value of the rebates is set by statute.[120] Rebates are collected directly by Medicaid.[121] State Medicaid programs are allowed to negotiate further discounts in addition to these rebates.[122] For the majority of new, high-cost prescription drugs (innovator drugs), Medicaid is entitled to a minimum of a 23.1 percent rebate off the average manufacturer price.[123] The rebate is also subject to the Medicaid Best Price Rule: if the lowest price offered by the prescription drug manufacturer is lower than the price Medicaid would pay for the drug after the guaranteed rebate, then Medicaid is entitled to pay for the lower price – the "best price."[124] Certain programs are excluded from the Medicaid Best Price Rule, including Medicare Part D,[125] Medicare Advantage plans,[126] the 340B Drug Discount Program,[127] and the Veterans Health Administration.[128] This means that these programs can receive lower prices than those paid by Medicaid without triggering the Medicaid Best Price Rule.

Medicaid raises significant legal and regulatory challenges to implementing

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118. 42 U.S.C. 1396r–8. *See* Manatt Phelps & Phillips LLP, *Efforts to Cut Drug Prices in Medicaid*, LEXOLOGY (Feb. 27, 2018), https://www.lexology.com/library/detail.aspx?g=9f8fef25-d178-40f6-9c0b-9ee511c018e9.

119. *See Medicaid Best Price Brief*, *supra* note 116.

120. *See Drug Rebate Program*, MEDICAID.GOV, https://www.medicaid.gov/medicaid/prescription-drugs/medicaid-drug-rebate-program/index.html.

121. *See Medicaid Best Price Brief*, *supra* note 116.

122. *See* David Blumenthal & David Squires, *Drug Price Control: How Some Government Programs Do It*, COMMONWEALTH FUND (May 10, 2016), http://www.commonwealthfund.org/publications/blog/2016/may/drug-price-control-how-some-government-programs-do-it.

123. *See Medicaid Best Price Brief*, *supra* note 116; Sachs et al., *supra* note 14, at 7. Some other products are subject to different minimum rebates: blood clotting factors and drugs approved by the FDA for exclusively pediatric indications are subject to a minimum rebate of 17.1 percent off the average manufacturer price, non-innovator drugs are subject to a minimum rebate of 13 percent of the average manufacturer price per unit. *See Drug Rebate Program*, *supra* note 120.

124. *See* Sachs et al., *supra* note 14, at 7; *Medicaid Best Price Brief*, *supra* note 116. *See also* 42 U.S.C. § 1396r-8 (Medicaid Drug Rebate Program and Best Price Rule statute).

125. *See* Sachs et al., *supra* note 14, at 7.

126. *See id.*

127. *See Health Policy Brief: The 340B Drug Discount Program*, HEALTH AFF., (Sept. 14, 2017), https://www.healthaffairs.org/do/10.1377/hpb20171409.000175/listitem/healthpolicybrief_175.pdf [hereinafter *340B Brief*].

128. *See Veterans Health Administration Brief*, *supra* note 111.

an indication-specific pricing model.[129] First, the Medicaid Best Price Rule applies to the lowest price of each prescription drug, not each indication for a prescription drug.[130] Implementing an indication-specific pricing regime without any modification or guidance with respect to the Medicaid Best Price Rule would require prescription drug manufacturers to accept the lowest price for any indication of a product, thereby providing the prescription drug for high-value indications at the cost for its lowest-value indications.[131] With a threat of the price assigned to a lower value indication applying across the board to all indications of the product, prescription drug manufacturers may be less likely, even disincentivized, to research or seek approval for these lower value indications.

Additionally, as these Medicaid rebates are calculated based on the average manufacturer price of a prescription drug, not the average manufacturer price of a specific indication of a prescription drug,[132] modifications to how Medicaid calculates prescription drug prices would be necessary if implementing a pure indication-specific pricing regime. Several potential solutions to this problem have been recommended, including adopting a partial indication-specific pricing regime (an average weighted price incorporating indication-specific prices), product differentiation (seeking FDA approval for each indication as a different drug product), and CMS redefining a drug as "a chemical compound approved for a particular indication."[133]

Despite the guaranteed rebates and the Medicaid Best Price Rule limiting prescription drug prices, Medicaid spending on prescription drugs would likely increase under an indication-specific pricing regime. As Medicaid prices are based on the average sales price to other insurers, who would also have indication-specific prices and likely pay high prices for high-value indications, even the lower price paid by Medicaid would likely increase. This is further aggravated by the law under the Medicaid Drug Rebate Program requiring Medicaid and other federal health insurance programs to cover all FDA-approved drugs by participating prescription drug manufacturers. Even though state Medicaid programs can negotiate additional discounts beyond the mandated Medicaid price, because Medicaid programs cannot decline to cover most prescription drugs, their bargaining power is significantly weakened. This lack of leverage and inability to walk away, like the situation seen with Medicare Part D plans, prevents Medicaid from negotiating true value-based, indication-specific prices. Medicaid reforms to

129. For an in-depth analysis of the Medicaid Best Price Rule as a barrier to implementing value-based payment models, including indication-specific pricing, s*ee generally* Sachs et al., *supra* note 14.

130. *See* Sachs et al., *supra* note 14, at 8.

131. *See id.*

132. *See Medicaid Best Price Brief*, *supra* note 116; Sachs et al., *supra* note 14, at 8.

133. *See* Sachs et al., *supra* note 14, at 8-9.

prescription drug pricing would need to consider the strengths and weaknesses of the Medicaid Drug Rebate Program and the Medicaid Best Price Rule, and indication-specific pricing would worsen the problems of the current Medicaid prescription drug pricing model.

C. 340B Drug Discount Program

The 340B Drug Discount Program mandates the sale of outpatient prescription drugs to covered entities at reduced prices.[134] Covered entities include federally qualified health centers, certain disease specific programs, and publicly owned hospitals with a disproportionate share hospital percentage[135] of at least 11.75 percent.[136] There were approximately 35,000 individual covered entity sites registered by the Health Resources and Services Administration in 2016,[137] encompassing approximately 45 percent of hospitals.[138] Covered entities are able to purchase outpatient prescription drugs at significant discounts, approximately 20 to 50 percent off of the average manufacturer price.[139] This price can be no higher than the net price paid by Medicaid after rebates.[140] Prescription drug manufacturers are allowed to sell outpatient prescription drugs to 340B-eligible purchasers without triggering the Medicaid Best Price Rule, allowing and even incentivizing further reductions.[141] Purchases by covered entities totaled approximately $12 billion in 2015, with savings estimated at $6 billion.[142]

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134. *See 340B Brief*, *supra* note 127; MARK RILEY, WHITE PAPER: MAKING SENSE OF THE 340B DRUG PROGRAM 1 (July 2012).

135. Disproportionate share hospitals are hospitals which serve a disproportionately large number of low income and uninsured patients and are thus entitled to additional payments from the Centers for Medicare and Medicaid Services. *See Disproportionate Share Hospitals*, HEALTH RES. & SERVS. ADMIN. (May 2018), https://www.hrsa.gov/opa/eligibility-and-registration/hospitals/disproportionate-share-hospitals/index.html. The disproportionate share percentage is calculated by statute and described by the Centers for Medicare and Medicaid Services here: *Disproportionate Share Hospital*, CTRS. MEDICARE & MEDICAID SERVS. (last modified Oct. 4, 2018), https://www.cms.gov/medicare/medicare-fee-for-service-payment/acuteinpatientpps/dsh.html. The requirements for a disproportionate share hospital qualifying for the 340B program are codified in 42 U.S.C. § 256b(a)(4)(L).

136. *See 340B Brief*, *supra* note 127.

137. *See id.*

138. *See* Blumenthal & Squires, *supra* note 122. A separate study reports that the 340B hospitals constitute 51 percent of all hospital beds in 2016. *See* Peter B. Bach & Rachel E. Sachs, *Expansion of the Medicare 340B Payment Program: Hospital Participation, Prescribing Patterns and Reimbursement, and Legal Challenges*, J. AM. MED. ASS'N (2018) (citing Centers for Medicare and Medicaid Services. Cost reports, fiscal-year 2017, https://www.cms.gov/Research-Statistics-Data-and-Systems/Downloadable-Public-Use-Files/Cost-Reports.).

139. *See 340B Brief*, *supra* note 127.

140. *See id.*

141. *See id.*

142. *See id.* Other studies have estimated the difference in the purchase and reimbursement for 340B hospitals in 2017 provided $19.3 billion in profit. *See* Bach & Sachs, *supra* note 138 (citing

Eligibility to participate in the 340B Drug Discount Program depends on the facility, not the individual patient.[143] When an insured patient comes to a 340B covered entity and receives a prescription for an outpatient prescription drug from a physician associated with the 340B program, the pharmacy is allowed to dispense the prescription drug purchased through the 340B program but receive reimbursement through Medicare or commercial insurance at their rates.[144] This allows the covered entity to make a profit on the outpatient prescription drugs purchased under the 340B Drug Discount Program; this is permitted because of their status as a provider serving a large uninsured population.[145]

The 340B Drug Discount Program, like Medicaid, calculates the discounted price of prescription drugs based on the average manufacturer price of a prescription drug,[146] not the average manufacturer price of a specific indication of a prescription drug. In order to implement an indication-specific pricing model, the 340B Drug Discount Program would need to modify the way it calculates the cost of prescription drugs. There has also been criticism of the 340B Drug Discount Program continuing to receive mandatory drug discounts in an indication-specific pricing scheme, with people opposing imposing additional discounts when a prescription drug is already being sold at a value-based price.[147] If an indication-specific pricing regime were implemented, it is possible that these discounts would be modified or repealed, undermining the efforts of the program and increasing prescription drug spending.

The high drug discounts in the 340B Drug Discount Program may incentivize inappropriate care or overuse of prescription drugs.[148] This is a result of the revenue 340B-eligible providers receive from the reimbursement for prescription drugs.[149] Some hospitals participating in the 340B Drug Discount Program are abusing the system, gaining immense profits from their prescription drug sales,

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The 340B program reached $19.3 billion in 2017—as hospitals' charity care has dropped, DRUG CHANNELS INST. (May 7, 2018), https://www.drugchannels.net/2018/05/exclusive-340b-program-reached-193.html). Because the program is structured such that the covered entity receives the discount directly upon purchase, the program does not cost the taxpayers and the savings directly help the covered entities to offset losses caused by their disproportionate coverage of uninsured patients and focus on local healthcare priorities, including clinics and transportation in rural and low-income areas. *See* Jim Martin, *We can help rural seniors and veterans by keeping the 340B drug pricing program*, THE HILL (Nov. 4, 2017), http://thehill.com/opinion/healthcare/358771-we-can-help-rural-seniors-and-veterans-by-keeping-the-340b-drug-pricing.

143. *See 340B Brief*, *supra* note 127.

144. *See id.*

145. *See id.*

146. *See id.*

147. *See* Bach & Pearson, *supra* note 8, at 2504.

148. *340B Brief*, *supra* note 127.

149. *See id.*

resulting in the system receiving increased public scrutiny.[150] These profits and incentives for abuse could aggravated by an indication-specific pricing regime. This is true of any fee-for-service program but would be even more likely in a system that already incentivizes inappropriate prescribing.[151]

While incentivizing prescribing high-value indications, indication-specific pricing would also incentivize overuse of drugs for high-value indications and increase overall drug spending. This could be especially prominent in certain contexts, such as cancer care. Because 340B-eligible hospitals can purchase high-price cancer drugs at deep discounts, there has already been a decrease in cancer care by community oncologists and an increase in cancer care in hospital outpatient departments, including 340B-eligible facilities.[152] If these discounts continue and cancer care continues to be more affordable at 340B-eligible facilities, indication-specific pricing could further exacerbate the increase in cancer care at 340B-eligible facilities. Physicians may also be incentivized to try several different prescription drugs to treat cancer at once, whether necessary or not. Overuse and improper use would magnify an increase in drug spending from indication-specific pricing. These challenges would need to be addressed for an indication-specific pricing model to decrease, not increase, prescription drug prices and spending under the 340B Drug Discount Program.

D. Veterans Health Administration

The Department of Veterans Affairs operates its own integrated healthcare system called the Veterans Health Administration (VA), providing healthcare services to qualified members of the military after they leave active duty.[153] The VA directly provides services, including prescription drugs, through its network of medical centers, clinics, and pharmacies.[154]

Prescription drug manufacturers are required to provide the VA and the

150. *See* Andrew Pollack, *Dispute Develops Over Drug Discount Program*, N.Y. TIMES (Feb. 12, 203), http://www.nytimes.com/2013/02/13/business/dispute-develops-over-340b-discount-drug-program.html; Ellen Weaver & Lindsay Boyd, *States tell Congress: stop hospital abuse of federal drug discount program*, THE HILL (June 15, 2016), http://thehill.com/blogs/congress-blog/healthcare/283491-states-tell-congress-stop-hospital-abuse-of-federal-drug.

151. *See* Weaver & Boyd, *supra* note 150 ("The Berkeley findings come on top of previous research that revealed that most 340B hospitals don't actually serve large at-risk populations. One study found that fewer than a third provide charity care exceeding the national average. And last summer, the Government Accountability Office issued a report noting that the program creates an incentive for hospitals to maximize profits by prescribing more—or more expensive—drugs. GAO then tasked Congress with removing these perverse incentives.").

152. *See 340B Brief*, *supra* note 127.

153. *See Veterans Health Administration Brief*, *supra* note 111.

154. *See id.*

Department of Defense a 24 percent discount[155] on the non-federal average manufacturer price.[156] Similar to the Medicaid Best Price Rule, if the prescription drug manufacturer sells their product to another non-federal buyer for less than that amount, they are required to sell to the VA for the lowest price.[157]

The VA operates its prescription drug coverage as a national formulary, a list of medicines covered by the VA.[158] The VA provides low or no cost sharing for its beneficiaries and low costs overall.[159] The buying power of the VA allows it to negotiate additional discounts for many of the drugs on the national formulary, especially those drugs with significant competitors.[160] Further, unlike Medicare and Medicaid, which are required to cover all FDA-approved prescription drugs, the VA is not required to cover all FDA-approved prescription drugs; the ability of the VA to decline to include a drug on its national formulary gives it significantly more bargaining power than other federal payers.[161] If prescription drug manufacturers do not comply with the mandated discounts to the VA, they are excluded from participating in most federal government health insurance programs.[162] As federal government health insurers compose such a large portion of the pharmaceutical market, prescription drug manufacturers generally comply.[163]

The VA would face barriers to indication-specific pricing of prescription drugs similar to those faced by other federal health insurance programs. Like the other federal programs, the VA calculates its prescription drug prices based on the average manufacturer price of the prescription drug.[164] The average manufacturer price does not differentiate based on the indication for which the prescription drug is prescribed. In order to implement an indication-specific pricing regime, the VA would have to change the way it calculates the price of prescription drugs. However, it may be easier in this context to track and collect the necessary data for charging an indication-specific pricing, as the VA is one integrated system instead

155. *See* Blumenthal & Squires, *supra* note 122.

156. The non-federal average manufacturer price is defined by statute as "the weighted average price of a single form and dosage unit of the drug that is paid by wholesalers in the United States to the manufacturer, taking into account any cash discounts or similar price reductions during that period, but not taking into account (A) any prices paid by the Federal Government; or (B) any prices found by the Secretary to be merely nominal in amount." *Veterans Health Administration Brief*, *supra* note 111(quoting 38 U.S.C. § 8126).

157. *See* Blumenthal & Squires, *supra* note 122.

158. *See Veterans Health Administration Brief*, *supra* note 111.

159. *See id.*

160. *See id.*

161. *See id.*

162. *See Veterans Health Administration Brief*, *supra* note 111.

163. *See id.*

164. *See id.* (quoting 38 U.S.C. § 8126).

of independent healthcare providers under Medicare.[165] It may be possible to implement an indication-specific pricing system in the VA prescription drug program, but there are still several barriers to indication-specific pricing lowering prescription drug spending in the United States healthcare system.

III. POLICY ARGUMENTS AGAINST INDICATION-SPECIFIC PRICING

The legal and regulatory barriers to implementing an indication-specific pricing scheme in federal government insurance programs are significant and worthy of consideration, but they are not insurmountable.[166] If accomplished, implementing indication-specific pricing in government health insurance programs would have a significant impact on and face additional barriers with the FDA approval system and incentives for physicians, patients, and manufacturers. Section A discusses the barriers presented by the FDA approval system. Section B explains the risks of liability for off-label promotion. Section C presents the arguments regarding whether indication-specific pricing would decrease prescription drug spending, concluding that an indication-specific pricing model would likely not decrease prices or improve consumers' access to prescription drugs. Section D raises ethical arguments against indication-specific pricing and other value-based pricing models.

A. The FDA Approval System

The current FDA approval system poses significant barriers to an effective indication-specific pricing regime. Each FDA-approved drug receives a unique National Drug Code (NDC).[167] This NDC is used when tracking and calculating the reimbursement price for prescription drugs. The FDA approves prescription drugs for specific indications, not general use.[168] This is because the safety, effectiveness, and risk-benefit analysis may differ for a prescription drug based on indications.[169] For example, a side effect that is harmless for one indication in one patient may be a significant risk for another indication in a different patient. Thus, when a prescription drug has more than one indication, manufacturers must consider how to gain approval for the new use.

Manufacturers have several options to gain FDA approval for new indications. One possibility is to have the new indication approved as a separate product. This

165. *See id.*

166. *See* Bach, *supra* note 18, at 1630 ("Adopting indication-[specific] pricing is thus technically feasible. Political challenges may be more substantial.").

167. *See National Drug Code Directory*, *supra* note 78.

168. Ryan Sila, Note, *Incentivizing Pharmaceutical Testing in an Age of Off-Label Promotion*, 93 N.Y.U. L. REV. 941, 946 (2018).

169. *Id.* at 946-48.

could be done by submitting an Investigational New Drug Application[170] to gain FDA approval to research the new indications and then conducting full clinical trials (the traditional process for FDA approval).[171] The newly approved indication for the prescription drug would be approved as a unique product.[172] It would receive a unique NDC from the FDA, and it would be billed as a separate product by insurers. Another more common option is for the prescription drug manufacturer to file a supplemental New Drug Application[173] to update the label and gain approval for this new indication. This results in adding an indication to an already approved prescription drug. Therefore, the product has the same NDC code and must be billed and priced the same under the existing FDA regulatory scheme.

In order to implement an indication-specific pricing model, the FDA and CMS would need to develop a new or modified coding system incorporating the separate indications with approvals and reimbursements. While New Drug Applications would benefit the healthcare system by providing detailed support on the effectiveness of the new indication, there is no incentive for pharmaceutical companies to follow this route. It is time-intensive, labor-intensive, and expensive. Pharmaceutical companies are more likely to file supplemental New Drug Applications, which are quicker and require less support and expenditure. However, this results in a new indication with the same NDC as the existing product. The FDA and CMS would need to develop a system to track the different indications of individual NDC codes for reimbursement purposes. Further, physicians can prescribe these medications without the additional approvals.[174]

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170. *See* 21 C.F.R. § 312; *Investigational New Drug (IND) Application*, U.S. FOOD AND DRUG ADMIN. (Oct. 5, 2017), https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm.

171. *Id.* If the product is a breakthrough therapy, a cancer drug with no comparable treatment, or certain other types of treatments, the manufacturer may be eligible to gain approval by submitting an application through an Accelerated Approval pathway. *See* 21 U.S.C. § 356(a) (breakthrough therapies); 21 U.S.C. § 356(b) (fast-track products); 21 CFR 314.510; *Accelerated Approval*, U.S. FOOD AND DRUG ADMIN. (Sept. 15, 2014), https://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm.

172. *Id.*

173. *See* 21 CFR § 314; *New Drug Application (NDA)*, U.S. FOOD AND DRUG ADMIN. (Mar. 29, 2016), https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm; *Off-Label Drug Promotion: Health Policy Brief* HEALTH AFF. (June 30, 2016), https://www.healthaffairs.org/do/10.1377/hpb20160630.920075/full/healthpolicybrief_159.pdf [hereinafter *Off-Label Drug Promotion Brief*] ("Currently, a manufacturer can expand a drug's approved indications through a supplemental New Drug Application, but performing the required clinical trials is a costly and time- consuming process, and manufacturers have little incentive to do this for drugs that are al- ready used widely off label.").

174. *See* III.B., *infra.*

These challenges are further described in the next Section.

B. Off-Label Prescribing

Not all indications for which prescription drugs are used are approved by the FDA.[175] While some prescription drugs are approved for multiple indications, many prescription drugs are only approved for one indication, even if they are commonly used for other indications.[176] Using prescription drugs for uses other than their approved indications is called off-label use.[177] Both off-label prescribing and off-label use are permitted.[178] However, off-label promotion of prescription drugs by prescription drug manufacturers is prohibited.[179] Drug company promotion of a prescription drug for a non-approved use is in contradiction with the approved labeling and qualifies as "misbranding" under the Food, Drug and Cosmetic Act.[180]

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175. *See Off-Label Drug Promotion Brief, supra* note 173, ("A drug is used off label any time it is administered in a way that has not been approved by the FDA . . . Providers might choose to prescribe off label for many reasons.").

176. *See* Sachs et al., supra note 14, at 9-10 ("There are many drugs like Colcrys, with multiple FDA-approved indications. But there are also many drugs whose secondary uses are not FDA approved, with large off-label markets.").

177. *Off-Label Drug Promotion Brief: Health Policy Brief, supra* note 173 ("A drug is used off label any time it is administered in a way that has not been approved by the FDA.").

178. *See* Aaron S. Kesselheim & Michelle M. Mello, *Prospects For Regulation Of Off-Label Drug Promotion In An Era Of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 1539, 1546 (2014) ("Once a drug is approved, physicians have autonomy to prescribe it for any indication and patient population and at any dose, including those not described in the official labeling materials—so-called 'off-label' uses. Off-label uses are often medically appropriate, especially for patients with no other therapeutic alternatives where the drug's effectiveness is biologically plausible." (footnote omitted)).

179. *See id.* at 1544 ("The FDCA does not explicitly proscribe off-label drug promotion. Rather, it prohibits introducing any new drug or biological product that has not been approved by the FDA or is misbranded. (citing, *id* at 1544 n.22, "21 U.S.C. § 331(d) (2012); *id.* § 355(a) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective . . . ."); *id.* § 331(a) (forbidding the introduction of adulterated or misbranded food or drugs into commerce); *id.* § 352(a) (defining false or misleading labels as misbranded drugs or devices); *id.* § 352(f) (discussing directions for use and warnings on labels).").

180. *See* Kesselheim & Mello, *supra* note 178, at 1547 ("A manufacturer who promotes off-label uses risks criminal liability under the FDCA if its drug is found to be 'misbranded.' Drugs can be misbranded for false or misleading labeling information or labeling that does not bear 'adequate directions for use.' Since the only legitimate source of information about directions for use is the FDA-approved labeling information, directions provided by the manufacturer for using the drug in an off-label context are not permitted. The combination of the requirements for approval and the misbranding provision provide two avenues for restrictions on off-label promotion: a drug promoted for unapproved uses may be considered to be an "unapproved drug" for that use, or it may be deemed 'misbranded.' Under either statutory provision, in the FDA's view, it can be illegal for a drug's labeling to discuss uses of the drug that the FDA has not validated as being supported by substantial evidence." (quoting 21 U.S.C. § 352 (2012); *id.* § 352(f)(1))).

While manufacturers are allowed to make certain statements about non-approved uses (for example in response to a request by a healthcare professional[181]), manufacturers can only negotiate reimbursement for FDA-approved indications.[182] Even so, insurers in the United States, including Medicare, will generally reimburse providers for prescription drugs even when they are prescribed off-label; however, this could be because insurers cannot tell when drugs are prescribed off-label.[183] Medicare Part B is required to reimburse for off-label use of oncology drugs when there is specific published evidence supporting their use.[184]

Off-label prescribing is relatively common, accounting for approximately 20 percent of all prescriptions in the United States.[185] In some cases, off-label prescribing is beneficial and necessary: some subpopulations (including children and pregnant women) often require off-label prescribing as they are generally not included as subjects in clinical trials, and thus are not included in the FDA approval.[186] Some specialties with few treatments for specific indications, such as oncology, result in off-label uses of prescription drugs becoming the standard of care.[187] Despite the benefits, there is little scientific evidence supporting the effectiveness of over 70 percent of off-label uses of prescription drugs.[188] Permitting drug companies to promote these uses, even allowing them to negotiate reimbursement for their use, may pose great public health risks. Off-label uses lack evidence supporting their safety and effectiveness for treating the non-indicated disease. As off-label prescribing is common absent promotion by manufacturers, permitting such promotion may result in more widespread use of drugs for off-label indications. This would lead to patients gaining access to prescription drugs

181. *See Off-Label Drug Promotion Brief: Health Policy Brief*, *supra* note 173 ("Manufacturers can communicate about off-label uses of their drugs in a number of ways. Companies are permitted to respond to unsolicited requests from health care professionals about unapproved uses and might also support independent continuing medical education activities at which off-label uses are discussed. Since the passage of the Food and Drug Administration Modernization Act (FDAMA) of 1997, companies are also permit- ted to distribute peer-reviewed journals and reference books that discuss off-label uses, although this practice is subject to certain limitations. In 2014 the FDA expanded this authority to include non-peer-reviewed clinical practice guidelines.").

182. *See* Stephen D. Pearson, et al., *Indication-specific pricing of pharmaceuticals in the US healthcare system*, 6 J. COMPARATIVE EFFECTIVENESS RESEARCH 397, 399-400 (2017).

183. *See Off-Label Drug Promotion Brief: Health Policy Brief*, *supra* note 173 ("Payers in the United States, including Medicare, generally reimburse medications used off-label . . . in 2009, 75 percent of U.S. payers reimbursed some off-label uses of prescription drugs.").

184. *See id.* ("Medicare Part B is required to cover anti-cancer drugs used o -label when published compendia—privately owned pharmaceutical reference guides—support their use.").

185. THE PEW CHARITABLE TRUSTS, *supra* note 9, at 20.

186. *See* Patricia J. Zettler, *The Indirect Consequences of Expanded Off-Label Promotion*, 78 OHIO STATE L. J. 1053, 1078 (2017).

187. *See id.*

188. *See id.*

much faster than if manufacturers sought FDA approval through clinical trials or a supplemental New Drug Application. However, as there is a lack of evidence over the safety and effectiveness of the drug for the off-label use and off-label uses are associated with "significantly higher rates of adverse events than on-label uses,"[189] increased off-label use could lead to adverse events and negative health outcomes.[190]

Linking the price of a prescription drug to its FDA-approved indications would be possible. However, while the 21st Century Cures Act expanded the ability of prescription drug manufacturers to share information on off-label uses, the FDA has only provided draft guidance, and sharing this information would likely still qualify as prohibited off-label promotion.[191] Companies may be able to find ways to promote their prescription drugs notwithstanding the off-label promotion prohibitions. Recently, several companies have succeeded on challenging these restrictions on First Amendment grounds, asserting that this is protected truthful commercial speech.[192] Companies could be extend these First Amendment challenges to the payment context, arguing that pharmaceutical companies should be allowed to negotiate with government health insurance programs using scientific evidence supporting the effectiveness of non-approved indications. The development of commercial speech doctrine does not indicate that this is likely, as courts have not yet extended First Amendment protection to unapproved indications.[193]

Without requiring or incentivizing FDA approval for the additional indications, indication-specific pricing may not be a practical solution. However, if prescription drug manufacturers were incentivized to seek FDA approval for new indications, this would cause a deluge of Investigational New Drug Applications[194] to gain FDA approval to research the new indications; supplemental New Drug

189. *Id.* at 1079.

190. *See id.* at 1078-79.

191. *See* Hayes, *supra* note 19.

192. *See* Zettler, *supra* note 186, at 1057 ("Notwithstanding these concerns, courts, increasingly, have seemed willing to find that the First Amendment protects a broader range of off-label promotion than FDA policies have typically permitted."); Sila, *supra* note 168, at 950 ("[the Second Circuit" it held that the effective prohibition of off-label marketing did not directly advance those interests and in any event was substantially more restrictive than the First Amendment permits."); Amarin Pharma, Inc. v. U.S. F.D.A. 119 F.Supp.3d 196 (S.D.N.Y. 2015); United States v. Caronia, 703 F.3d 149 (2d Cir. 2012). *See generally* Sorrell v. IMS Health Inc., 564 U.S. 552 (2011) (explaining that the First Amendment protects companies' rights to engage in truthful commercial speech).

193. *See* Zettler, *supra* note 186, at 1071 ("none of the decisions following *Caronia*—in the Second Circuit or elsewhere—have extended *Caronia* to unapproved products.").

194. *See* 21 C.F.R. § 312; *Investigational New Drug (IND) Application*, U.S. FOOD AND DRUG ADMIN. (Oct. 5, 2017), https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm .

Applications[195] to gain FDA approval for the indication; and applications through Accelerated Approval pathways for breakthrough therapies and prescription drugs that treat cancers with no comparable treatment.[196] Seeking approval for these additional indications as new indications for an existing product would make indication-specific pricing a more real possibility.[197] These additional studies and approvals may provide additional data on the safety and effectiveness of certain prescription drugs, especially as data on off-label uses of prescription drugs are often inadequate.[198] Despite the benefits of the additional research that comes with approval, FDA approval is unnecessary for patients to access these medicines and may not improve affordability. Research time and a lengthy approval process greatly delay patient access and undermine the goal of improving affordability and accessibility of prescription drugs.

Indication-specific pricing would face several regulatory and practical barriers in the FDA approval system and with the risk of liability for off-label promotion. Reforms in these two areas would be necessary in order to make indication-specific pricing feasible. Even so, these reforms may not address the end goal of prescription drug reform: decreasing prescription drug prices and spending. The possible economic effects of indication-specific pricing are discussed further in the next Section.

C. Price Effects of Indication-Specific Pricing

Experts disagree on whether an indication-specific pricing regime would decrease prescription drug spending. In general, supporters argue that indication-

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195. *See* 21 CFR § 314; *New Drug Application (NDA)*, U.S. FOOD AND DRUG ADMIN. (Mar. 29, 2016), https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm; *Off-Label Drug Promotion Brief*, *supra* note 173 ("Currently, a manufacturer can expand a drug's approved indications through a supplemental New Drug Application, but performing the required clinical trials is a costly and time-consuming process, and manufacturers have little incentive to do this for drugs that are al- ready used widely off label.").

196. *See* 21 U.S.C. § 356(a) (breakthrough therapies); 21 U.S.C. § 356(b) (fast-track products); 21 CFR 314.510; *Accelerated Approval*, U.S. FOOD AND DRUG ADMIN. (Sept. 15, 2014), https://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm.

197. *See* Sachs et al., *supra* note 14, at 6.

198. *See id.;* Sila, *supra* note 168, at 951 ("critics argue that the prohibition powerfully incentivizes manufacturers to conduct clinical testing of and seek approval for more than just a single indication.") (citing Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 370 (2007) (explaining that because the FDA requires that "firms conduct rigorous clinical trials before bringing their products to market and before making promotional claims . . . the FDA plays an important structural role in promoting a valuable form of biomedical R&D [research and development] that private firms are undermotivated to perform . . . while internalizing the costs of this R&D to the firms").

specific pricing would "reduce prices for low-value indications but that prices for high-value indications will not increase."[199] Many studies do not support this assertion, however. Evidence suggests that an indication-specific pricing model would not result in the desired policy incentives and effects – rational use of prescription drugs, more affordable prices for prescription drugs, and lower overall prescription drug spending. The core goal of indication-specific pricing of prescription drugs, like other value-based pricing regimes, is to make prescription drug prices better represent the value received by the patient.[200] While maximizing value is important, it does not solve the problem of high prescription drug prices and spending.

Peter Bach, a physician and researcher at Memorial Sloan Kettering Cancer Center and a prominent supporter of indication-specific pricing in oncology care, argues that indication-specific pricing would likely decrease prescription drug spending.[201] Dr. Bach has recommended anchoring the prices of a prescription drug to its highest value indication or setting the price based on a preset value per year of life gained.[202] He has calculated the changes in prices of multi-indication cancer drugs based both on setting the price of the highest-value indication to the current price and by monthly price based on a cost of $150,000 per year of life gained.[203] The large variations in value by indication, he argues, demonstrate that indication-specific pricing is necessary to make prescription drug prices rationally related to value.[204] However, his methodology presupposes that indication-specific pricing would decrease prescription drug prices, and therefore Dr. Bach's analysis does not provide support for this conclusion.[205]

In fact, indication-specific pricing would likely increase prescription drug spending. Amitabh Chandra from the Harvard Kennedy School of Government and Craig Garthwaite from Northwestern University's Kellogg School of

199. Chandra & Garthwaite, *supra* note 21, at 103 (citing Bach, *supra* note 18, at 1629-30).

200. *But see* Bach, *supra* note 18, at 1629-30 ("The primary reason to pursue this enhancement to the system [implementing indication-specific pricing] is to make it possible to rationalize drug pricing.").

201. *See* Flume, et al., *supra* note 46 ("Frequent pricing critic Peter Bach recently suggested that paying by indication could save money in cancer using the example of cetuximab, which is much less effective in advanced head and neck cancer (estimated value-based price: $470) compared with colorectal cancer (estimated value-based price: $10,320)." (citing Bach, *supra* note 18)).

202. *See* Bach, *supra* note 18, at 1629.

203. *See id.* at 1630.

204. *See id.* at 1629 ("However, the relative findings of large differences in value across indications, and large potential shifts in pricing if the drugs were linked to value, illustrate that a change to indication-based pricing may be a necessary step to- ward paying rational prices for expensive drugs used to treat cancer and some other conditions, for which efficacy varies across indications.").

205. *See id.* at 1630 (noting the methodology "Assumes the price of the drug in its most effective setting is the appropriate reference price.").

Management have argued that indication-specific pricing would not decrease the price of prescription drugs and would therefore not decrease prescription drug spending.[206] Instead, they argue that more effective, and supposedly higher value, indications would increase in price, making prescription drugs even more unaffordable (particularly to those who need them most). Their analysis demonstrates that "relative to uniform pricing, indication-[specific] pricing results in higher prices for patients who benefit the most, higher utilization by patients who benefit least, higher overall spending, and higher manufacturer profits."[207] They assert that "setting a price that more closely matches the product's value to each customer," is a well understood economic concept called price discrimination.[208] Price discrimination, while resulting in a value-based price, can result in manufacturers setting the highest price that each segment of the market is willing to pay.[209] Calculating their own indication-specific prices for cancer drugs, Professors Chandra and Garthwaite conclude that prices for high-value indications, both for prescription drugs that are currently expensive and those that are generally affordable, would drastically increase, significantly reducing patient access.[210]

No pure indication-specific pricing regime has yet been implemented, so there is no real-world data to support pricing outcomes in practice. All outcomes are hypothetical and presumptive. The available evidence and incentives support that indication-specific pricing would likely increase prescription drug prices and spending. High-cost prescription drugs may be cost-effective at their current high prices: one study found that Sovaldi was cost-effective at $84,000 per treatment.[211] Relatedly, high-value prescription drugs that are currently priced low enough to be generally available would likely see drastic price increases.[212] Indication-specific

206. *See generally* Chandra & Garthwaite, *supra* note 21.

207. *Id.* at 103-04.

208. *Id.* at 104.

209. *See id.* at 104 ("What would happen if the manufacturer used indication-[specific] pricing—setting a price that more closely matches the product's value to each customer? This is a practice that economists call price discrimination, and its effects are well understood. In the most extreme version, the manufacturer extracts the most money each patient is willing to pay, leaving no consumer surplus.").

210. *See id.* at 105 ("Absent indication-based pricing, the manufacturer could not set such a high price without having payers reduce access for patients with low-value indications—the trade-off would not be worth the lost profits. So what would indication- based pricing accomplish? For drugs currently priced so high that they're unavailable for some indications, it expands access. Drug manufacturers would now be willing to set low prices for low-value indications, since it wouldn't jeopardize their profits on high-value indications. But the same access-expanding pricing flexibility also allows manufacturers to increase prices for high- value indications. Currently, some treatments are priced low enough to be accessible for a wide range of indications, and it is there that we should expect the biggest price increases.").

211. Kesselheim et al., *supra* note 12, at 859 (citing Mehdi Najafzadeh et al., *Cost-effectiveness of novel regimens for the treatment of hepatitis C virus*, 162 ANN. INTERN. MED. 407 (2015)).

212. *See id.*

pricing in many cases, especially for diseases with few alternative treatments, may not result in decreased prices and may perpetuate the prohibitively high prices leaving these drugs out of reach to many patients. Even so, some expensive prescription drugs may become more available; this would be the case for prescription drugs that are overpriced beyond their cost-effectiveness.[213] The low-value indications would be more available and more utilized, as their prices are lowered to match their comparative value making them more affordable to patients.[214] This increased access may have counterintuitive results in terms of healthcare outcomes; while increased access to effective treatments would lead to better healthcare outcomes, increased access to low-value indications (which are perhaps not the standard of care or not adequately effective in treating the secondary indication) would likely lead to poorer healthcare outcomes.

Without an experimental implementation of indication-specific pricing of prescription drugs, it is uncertain whether indication-specific pricing would in fact increase or decrease overall prescription drug spending and individual prescription drug prices. However, the incentives are clear. Indication-specific pricing sets higher prices for higher-value indications. Depending on an individual's prescription drug coverage, these higher prices for high-value indications are likely less affordable and less accessible as a result. Conversely, indication-specific pricing sets lower prices for lower-value indications, resulting in them being more affordable, more accessible, and used more by patient populations who receive a comparatively lesser benefit from them.[215] This could lead to an inefficient allocation of prescription drugs and healthcare resources, overall worse healthcare outcomes, and increased healthcare spending.

D. Ethical Issues of Indication-Specific Pricing

Indication-specific pricing raises several ethical concerns. First and foremost is the ethical distribution of medicines. Indication-specific pricing models suggest that indication-specific pricing in federal government health insurance programs would result in higher prices for more-effective treatments. This regime may demonstrate the value of the medication and incentivize the development of more effective treatments for diseases. In this system, when a patient seeks to buy a more effective medication to treat their disease, it would cost them significantly more money. While the intent of pricing based on value per indication may be to better allocate resources at the health system level, there are challenges to this working at the patient level. What if an individual cannot afford the most effective treatment? There could be prohibitively high out of pocket costs preventing them

213. *See* Chandra & Garthwaite, *supra* note 21, at 105.
214. *See id.*
215. *See* Chandra & Garthwaite, *supra* note 21, at 103-04.

from affording the medication that would best treat, or potentially cure, them. Either this individual will go without treatment and get sicker, later costing the healthcare system more money and having a significantly decreased quality of life, or the individual chooses a less expensive, less effective treatment, which may have poorer outcomes for the patient and result in expensive future healthcare to improve their condition. The purpose of decreasing prescription drug prices is not to justify high prices or to make them more rational; the point is that prescription drug prices are too high for patients, and thus reforms need to both rationalize prices but also make prescription drugs more affordable and accessible. Indication-specific pricing may provide ethical and optimal prescriber-side incentives (rewarding physicians for choosing the most effective, most valuable treatment) but it punishes patients who cannot afford effective prescription drugs. This is unethical and unjust.

The inverse pricing scheme has been suggested for the indication-specific model: making the most effective treatment for an indication the most affordable and therefore most accessible to patients. On the patient-side, this is ideal, assuming this low price for a high-value indication is low enough that anyone and everyone who needs it can afford it. But the physician and system incentives are less clear, and potentially against the best interests of patients and the health system as a whole. If the current physician reimbursement schemes continue, particularly in Medicare Part B, this inverse indication-specific pricing model would not incentivize physicians to provide the best course of treatment. In fact, they might be incentivized to provide less effective treatments. Patients may receive a lower standard of care from their physicians because it financially benefits their provider, and as a result the healthcare system will produce poorer outcomes and higher spending. Pharmaceutical companies would also have questionable incentives under this model. Lower prices for effective drugs disincentivizes the development of cures and effective treatments. When pharmaceutical companies identify treatments that may not be more effective than existing treatments or have little benefit to patients, the company would be incentivized to continue research and development and seek approval for several indications. From an innovation and research perspective, this is a positive: decreased off-label prescribing and additional data on prescription drugs prior to approval. However, this incentivizes companies to direct resources away from breakthrough cures and towards less effective, more profitable treatments. Innovation incentives should not support increases in pharmaceutical profits absent improvements in patient care.

The determination of value for indication-specific pricing, or any value-based pricing, also raises ethical issues. What is value? Should determinations of value be based on survival time, improved quality of life, or other outcomes benchmarks? When comparing value determinations, and therefore price determinations, across indications, there are further concerns. Is treating certain

indications considered inherently more valuable than others such that the prices are higher for effective treatments? For example, should all cancer treatments be considered more valuable and therefore inherently more expensive than a treatment for chronic back pain? Taken a step further, should a cancer treatment with little to no benefit in most patients cost more than a prescription drug that treats chronic back pain, removing virtually all symptoms, in 99 percent of cases?

While that thought experiment is an extreme (not to mention unsupported and unlikely) example, these are the kinds of determinations made in value assessments.[216] Inevitably, value assessments will incentivize companies to develop treatments for certain diseases more than others. This is one of the reasons that rare diseases (which have small populations and therefore small pharmaceutical markets) receive increased attention from the FDA in terms of accelerated approval pathways and incentives for companies that develop treatments. These may not take into account patient perspectives, particularly in terms of approved quality of life. Disability advocates commonly criticize the use of quality adjusted life years (QALYs) as a healthcare metric and raise the potential for disastrous consequences if it is used broadly and incorrectly.[217] The metric used to determine value in an indication-specific pricing regime would need to be carefully constructed to limit the discriminatory effects. Even with careful consideration, it may be impossible to remove discriminatory effects entirely. It is inevitable that an indication-specific pricing regime will prioritize certain outcome measures while disadvantaging other outcomes – and patients.

IV. ALTERNATIVE REFORMS AND RECOMMENDATIONS FOR LAWMAKERS

The incentive effects of indication-specific pricing of prescription drugs contradict the overall goals of prescription drug reform: decreasing prescription drug spending, decreasing prescription drug prices, and increasing the accessibility and affordability of high-value prescription drugs. It is thus clear that in order to decrease prescription drug spending, other models for prescription drug pricing should be pursued. Section A suggests alternative value-based pricing models that

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216. *See* Peter J. Neumann et al., *Should A Drug's Value Depend On The Disease Or Population It Treats? Insights From ICER's Value Assessments*, HEALTH AFF. BLOG (Nov. 6, 2018), https://www.healthaffairs.org/do/10.1377/hblog20181105.38350/full/ ("A central question facing ICER – and by proxy all of us as health plan enrollees, taxpayers, and patients – is whether a drug's value should depend on not only its "generic benefit" – e.g., as measured by quality adjusted life years (QALYs) gained – but also on which disease or population it treats. For example, should ICER invoke higher (i.e., more lenient) cost-per-QALY gained cost-effectiveness benchmarks in some areas (say, cancer or rare diseases) than others and, if so, on what basis?").

217. Ari Ne'eman, *Formulary Restrictions Devalue And Endanger The Lives of Disabled People*, HEALTH AFF. BLOG (Oct. 29, 2018), https://www.healthaffairs.org/do/10.1377/hblog20181025.42661/full/ (criticizing using QALYs as a cost effectiveness measure in determining which drugs to exclude from formularies).

lawmakers could consider in prescription drug reform instead of indication-specific pricing. Section B introduces alternative policy interventions that lawmakers should explore to decrease prescription drug prices and spending. Section C concludes with recommendations for future legislative action.

A. Other Value-Based Pricing Models for Prescription Drugs

Value should be incorporated in the pricing of prescription drugs. Different value-based pricing models could be explored by lawmakers, but would probably not be more likely to decrease prescription drug spending than indication-specific pricing.

Average weighted pricing for multi-indication prescription drugs could be more feasible to implement than indication-specific pricing but would likely not be more effective.[218] Average weighted pricing assigns the price of a prescription drug based on the weighted average value of the prices of each indication for the prescription drug.[219] Unlike a pure indication-specific pricing regime, average-weighted pricing would not face the difficulties of pricing a drug per indication where the system does not track the indication for which a drug is prescribed or recognize differential reimbursement by indication.

However, it is unlikely that an average weighted price would have a significant impact on prescription drug prices or spending. High-value indications that are largely used would likely dominate the pricing calculation, maintaining the high costs of multi-indication prescription drugs. Thus, while average weighted pricing may avoid many of the legal and regulatory barriers related to indication-specific pricing, it would likely provide no benefits in access or affordability to patients and do little or nothing to reduce prescription drug spending.

Outcome-based payments could be another value-based model worth exploring.[220] Instead of directly increasing the cost of high-value indications, outcome-based payments tie the cost of a prescription drug to the outcomes of an individual patient or patient population either by adjusting the initial price to reflect value or providing a rebate based on an individual patient's outcome.[221] Several prescription drug companies have entered into outcome-based contracts in the

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218. *See* PEARSON ET AL., *supra* note 18, at 19 ("Lastly, using a single weighted-average price is far more feasible in the current environment than trying to track indication-specific use and applying different discounts to each indication. The latter approach, although a more 'pure' form of indication-specific pricing, is more likely to create a price that triggers Medicaid best price provisions; it also presents the greatest potential challenges for sorting out and describing to stakeholders how patients and providers are affected by different prices for different indications.").

219. *See id.* at 11-12.

220. *See* Sachs et al., *supra* note 14, at 6.

221. *See id.* at 10.

private sector,[222] and recently the federal government expressed interest in experimenting with outcome-based payment models for prescription drugs for chronic disease treatment.[223] However, the impact of outcomes-based contracts on prescription drug spending is unclear.[224] One recent outcomes-based contract involving Novartis' Kymriah, a drug used for a type of leukemia, resulted in payment only if the patient received a positive response by the end of the first month of treatment; even so, the value-based, outcome-based payment was $475,000.[225]

This case raises doubt as to whether such contracts in the cancer context would actually save money. If prices are set low enough and very specific outcomes benchmarks are set and tracked, it is possible that these contracts could save money. However, such terms would need to be negotiated with and agreed upon by pharmaceutical companies, which seems unlikely. More research should be done on the broader incentive effects of outcome-based payment models, specifically regarding prescription drug prices, overall prescription drug spending, and patient access to prescription drugs. Outcomes based contracts in practice may incentivize pharmaceutical companies to negotiate extremely low or easy to achieve outcomes benchmarks that do not fully demonstrate effectiveness improved quality of life in a patient. Alternatively, companies may emphasize patient perspectives to seek very subjective and potentially clinically insignificant benchmarks. Such contracts would lead to virtually certain payment to prescription drug companies and may do nothing to lower prices for many drugs if the overall value of the contract is not significantly less than the current price. If these benchmarks are not representative of the value of the drug, these prices would likely increase independent of the effectiveness of the prescription drug. With these assumed incentives, prescription drug prices and overall spending would increase, leading to poorer patient access. Unless aggressive negotiating power is given to federal government insurance programs such that they can overcome these

222. *See id.* at 10-11.

223. *See* Robert Saunders et al., *Medicare Accountable Care Organization Results For 2016: Seeing Improvement, Transformation Takes Time*, HEALTH AFF. BLOG (Nov. 21, 2017), https://www.healthaffairs.org/do/10.1377/hblog20171120.211043/full/ ("effective prescription drug use is essential to effective management of most chronic diseases that have significant population health impacts. . . . As CMMI has recently highlighted, one opportunity is implementing value-based payment reforms for drugs that share overall spending and health outcome accountability with drug manufacturers to advance the movement away from fee-for-service.").

224. *See, e.g.*, ELIZABETH SEELEY & AARON S. KESSELHEIM, OUTCOMES-BASED PHARMACEUTICAL CONTRACTS: AN ANSWER TO HIGH U.S. DRUG SPENDING? 1 (Sept. 2017).

225. *See* Daniel et al., *supra* note 26; *Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah(TM) (CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice*, NOVARTIS (Aug. 30, 2017), https://www.novartis.com/news/media-releases/novartis-receives-first-ever-fda-approval-car-t-cell-therapy-kymriahtm-ctl019.

incentives for prescription drug companies, outcomes-based contracts for prescription drugs would not decrease prescription drug prices and spending.

B. Other Policies to Lower Prescription Drug Prices

Other reforms should be considered instead of, or in conjunction with, value-based pricing models. Value-based pricing models have garnered great support and attention from politicians and healthcare professionals, but they only focus on one type of intervention at one point in the pharmaceutical chain – the link between the payer and the pharmaceutical manufacturer. The following list of proposed interventions is by no means exhaustive but raises a broad range of alternative policies lawmakers should consider in prescription drug reform.

Some recommended interventions would affect the interactions between payers and pharmaceutical manufacturers. One popular political talking point is allowing Medicare to negotiate prices for prescription drugs like it does for other healthcare goods and services.[226] However, the Congressional Budget Office has found that Medicare negotiation would have "a negligible effect on federal spending"[227] because each individual Medicare Part D already negotiates with pharmaceutical companies and because Medicare has limited ability, and thus decreased bargaining power, to exclude prescription drugs from coverage.[228] Without the ability to not cover from certain drugs, Medicare Part D plans often must accept high prescription drug prices from companies.[229] Additionally, Medicare negotiation could have a negative impact on the negotiating power of other federal government programs, particularly the 340B Drug Discount Program and the VA.[230] While the federal government could theoretically expand its mandatory discounts to Medicare, this could still threaten the negotiating power of other federal government programs and could incentivize prescription drug manufacturers to increase prices to make up for lost revenue.

Other proposals focus on accessibility and affordability specifically from the patient perspective. Patients generally make copayments when they receive a prescription drug. Scholars have suggested basing beneficiaries' copayments on the effective price of a prescription drug after rebates instead of the on the list

226. Kesselheim et al., *supra* note 12, at 865.

227. Juliette Cubanski & Tricia Neuman, *Searching for Savings in Medicare Drug Price Negotiations*, KAISER FAM. FOUND. (Jan. 23, 2017), https://www.kff.org/medicare/issue-brief/searching-for-savings-in-medicare-drug-price-negotiations/; Congressional Budget Office, *Letter to Senator Ron Wyden* (April 10, 2007), *available at* https://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/79xx/doc7992/ drugpricenegotiation.pdf.

228. *See* Sachs, *supra* note 69, at 2326.

229. *See id.*

230. *See* Outterson & Kesselheim, *supra* note 90, at w834.

price[231] or reducing copayments by payers or through subsidies.[232] While these approaches may make prescription drugs more affordable at the time of purchase, decreasing patients' out-of-pocket spending, patients' premiums would potentially increase and effect a rise in overall federal government spending on prescription drugs.[233] Consideration of the magnitude of the potential premium increases and federal government spending increase would have to be made in comparison to increased accessibility to patients at point-of-service.

Broader reforms of the pharmaceutical patent and antitrust regimes may have the most promise in decreasing prescription drug spending and prices. Patent exclusivity keeps the price of prescription drugs high and prevents competitors from entering into the market. Proposals have been made to limit the exclusivity period of patents, particularly limiting "secondary patents for trivial changes of a patented molecule," as well as prohibiting anti-competitive practices, including pay-for-delay agreements where patent holders pay generic companies to delay their entry into the market.[234] Some scholars have even recommended using executive authority to mandate compulsory licensure of prescription drugs based on government-funded research, though this would not be a system-wide solution.[235] Especially with the amount of research that is partially funded by the federal government,[236] there is a social expectation that prescription drugs will be made reasonably accessible and affordable to the public.[237]

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231. *See* Rachel Sachs, *Drug Policy: The Year In Review, And The Year Ahead*, HEALTH AFF. (Jan. 4, 2018), https://www.healthaffairs.org/do/10.1377/hblog20180103.276023/full/.

232. Darius N. Lakdawalla et al., *U.S. Pharmaceutical Policy in A Global Marketplace*, HEALTH AFF. w138, w138 (2008).

233. *See* Sachs, *supra* note 231 ("As scholars have noted, patients' out-of-pocket costs may be based on their drugs' list prices, even if a Part D sponsor has negotiated a lower price. CMS has proposed passing some of those rebates on to patients; this would decrease many beneficiaries' point-of-sale costs significantly, but would potentially increase beneficiary premiums—and increase CMS' direct subsidy costs— overall.).

234. Kesselheim et al., *supra* note 12, at 864.

235. *See generally* Hannah Brennan et al., *A Prescription for Excessive Drug Pricing: Leveraging Government Patent Use for Health*, 18 YALE J. L. & TECH. 275 (2016); Rachel Sachs, *March-In Rights Alone Won't Solve Our Drug Pricing Problems*, HARV. BILL OF HEALTH (Jan. 12, 2016), https://perma-archives.org/warc/HE43-R9X5/http://blogs.harvard.edu/billofhealth/2016/01/12/march-in-rights-alone-wont-solve-our-drug-pricing-problems/.

236. *See* Kesselheim et al., *supra* note 12, at 863 ("important innovation that leads to new drug products is often performed in academic institutions and supported by investment from public sources such as the National Institutes of Health. A recent analysis of the most transformative drugs of the last 25 years found that more than half of the 26 products or product classes identified had their origins in publicly funded research in such nonprofit centers.").

237. David Gilman & Nathan Dowden, *Is Value-Based Drug Pricing Compatible with Pharma Innovation?*, NEW ENG. J. MED. CATALYST (Nov. 20, 2017), https://catalyst.nejm.org/is-value-based-drug-pricing-compatible-with-pharma-innovation/ ("This innovation has occurred within the context of an implicit social contract. The U.S. government substantially subsidizes basic research and the

Critics have argued that decreasing the exclusivity periods on patents would stifle innovation, removing a key financial incentive for pharmaceutical companies to develop new prescription drugs. Studies have challenged this assertion, demonstrating that the revenue gained in the exclusivity period far exceed the costs of pharmaceutical research and development and decreasing the exclusivity period would leave adequate incentives for drug companies.[238] The Lancet Commission on Essential Medicines recommended creating an Essential Medicines Patent Pool which would essentially result in voluntary or compulsory licensure for all essential medicines.[239] These reforms may also challenge future innovation: while pharmaceutical companies may have adequate economic incentives to continue their work, removing some current incentives may result in companies pursuing less risky, innovative research.

One final proposal is greater transparency in the comparative effectiveness and cost-effectiveness of prescription drugs. There is little transparency in the actual prices paid for prescription drugs and there seems to be little intent on the part of the pharmaceutical industry or the federal government to increase this transparency.[240] The Patient-Centered Outcomes Research Institute was founded to focus on cost-effectiveness research, but the Affordable Care Act "prohibited the partially government-funded research institution from considering the relative value of drugs and from using [quality-adjusted life years] as a cost-effectiveness measure."[241] The governments of several other countries fund assessments of comparative clinical and economic value.[242] Currently, only non-governmental

provision of health care, and it waives its ability to negotiate directly with manufacturers about prices. In return, the biomedical industry is allowed to attempt to recoup its R&D investments during a limited post- approval period defined by the Drug Price Competition and Patent Term Restoration Act of 1984 (often called the Hatch–Waxman Act), with the expectation that drug prices will be set at a point that ensures a reasonable level of population access.").

238. *See, e.g.*, Brennan et al., *supra* note 235, at 328 (explaining that Gilead recouped recouped its expenditure on Sovaldi and Harvoni in two and a half years, likely earning forty times the development costs in that period).

239. Sabine Vogler, et al., *How Can Pricing and Reimbursement Policies Improve Affordable Access to Medicines? Lessons Learned from European Countries*, 15 J. APPLIED HEALTH ECON. & HEALTH POL'Y 307, 316 (2017).

240. HENRY WAXMAN ET AL., GETTING TO THE ROOT OF HIGH PRESCRIPTION DRUG PRICES: DRIVERS AND POTENTIAL SOLUTIONS 30-31 (July 2017)

241. *See* RALPH MARCELLO ET AL., DELOITTE HEALTH POLICY BRIEF: GETTING TO VALUE: WHAT POLICIES ARE ON THE TABLE TO MANAGE DRUG PRICES? 5 (2016). *See also* Kesselheim, *supra* note 16, at 866 ("The Patient-Centered Outcomes Research Institute had been expected to serve in this role. It was hailed at its inception as a vehicle to promote robust comparative effectiveness research, but Congress precluded it from considering drug costs as a central focus of its work, shifting instead to patient engagement and decision aids. The institute's reauthorization in 2019 will provide another opportunity to revisit its mission.").

242. *See* Kesselheim et al., *supra* note 12, at 866 ("In the United Kingdom, Germany, Australia, Canada, and several other countries, government-funded technology assessment activities provide support for comparative effectiveness studies and evaluate new products in light of comparative cost-

organizations in the United States, including the Institute for Clinical and Economic Review and others, conduct such assessments.[243] Lawmakers should repeal the law forbidding the government from using comparative effectiveness research to determine the relative value of treatments and inform insurance coverage and prescription drug pricing decisions.[244] Advocating for further transparency in prescription drug pricing and the comparative clinical and economic effectiveness will encourage both rational prescription drug pricing and more informed healthcare decision-making. This is true not only for patients (knowing how much they will be paying for prescription drugs) and providers (knowing how much the drugs they prescribed will cost the patient). Greater transparency on comparative effectiveness drug prices, and in particular the discounts on prescription drugs, can aid the government in negotiating prices and improving access to patients.[245]

C. Moving Forward: Recommendations for Lawmakers

Ultimately, some combination of interventions is likely needed to truly control prescription drug spending and make prescription drugs accessible and affordable to all in the United States. High prescription drug prices and spending are complex problems, and reforms at various points in the healthcare delivery system could be effective. Moving forward, lawmakers should look to gain more insight on to how these various pricing regimes and other interventions would affect prescription drug spending and pricing in practice. Specifically, it is necessary to gain a better understanding of the incentive effects of such models.

Both the federal and state government have begun experimenting with alternative prescription drug pricing models. On the federal level, CMS can experiment with different prescription drug payment models, as proposed to do with Medicare Part B in 2015 and again in 2018.[246] This plan includes a test of indication-specific pricing of prescription drugs, outcomes-based pricing, and

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effectiveness analysis. The information thus generated could be used by government and private payers to help them respond to company-set prices, make determinations about formulary rules and exclusions, and educate physicians and patients about the value of medication choices.").

243. *Id.* ("patients, physicians, and payers can turn to non- governmental organizations, such as the Institute for Clinical and Economic Review, *The Medical Letter*, the Independent Drug Information Service, Oregon's Drug Effectiveness Review Project, and *Consumer Reports* Best Buy Drugs, which provide information on value-based choices for select medications . . . . The data generated by these groups can support lower drug prices by helping payers organize their formularies and negotiate appropriate rebates, as well as guide prescribers and patients toward more appropriate drug-use decisions.").

244. *See* MARCELLO ET AL., *supra* note 241, at 4.

245. Vogler, et al., *supra* note 239, at 315.

246. *See Medicare Part B Brief*, *supra* note 64; Schrag, *supra* note 81, at 2101; Sachs, *supra* note 17.

reducing or eliminating patient cost-sharing.[247] CMS should continue to explore interventions and implement an experiment on prescription drug pricing in its programs. The resulting data would be particularly valuable to lawmakers moving forward with reforms.

On the state level, some states are experimenting with value-based pricing models in their government health insurance programs. Massachusetts sought a waiver under Section 1115 of the Social Security Act to experiment with the prescription drug part of its Medicaid program.[248] Its model would result in a closed formulary with at least one prescription drug covered in each therapeutic area.[249] The proposal also included a component focusing on value: it would exclude drugs with "limited or inadequate benefit until incremental clinical value is proven."[250] This waiver could have resulted in Massachusetts choosing not to cover several types of prescription drugs, such as those prescription drugs approved through FDA's Accelerated Approval Pathway.[251] Massachusetts proposed that Medicaid beneficiaries could petition to access non-formulary drugs.[252] The federal government initially showed interest in this and similar proposals, with President Trump's February 2018 budget proposing a study that would allow five states to exclude FDA-approved prescription drugs from their formularies, although it did not include continuing the mandatory rebates by prescription drug manufacturers in these states.[253] Even so, the Trump Administration rejected the Massachusetts proposal, reiterating the requirement that Medicaid programs cover all FDA-approved drugs.[254] Such formularies have received criticism from the public for restricting access to drugs, not taking patient perspectives into account,[255] using discriminatory value metrics, and devaluing the

247. *See CMS proposes to test new Medicare Part B prescription drug models to improve quality of care and deliver better value for Medicare beneficiaries*, CTRS. FOR MEDICARE & MEDICAID SERVS. (Mar. 8, 2016), https://www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2016-Press-releases-items/2016-03-08.html.

248. *See* Kesselheim et al, *supra* note 16.

249. *See id.*

250. *Id.*

251. *See* Manatt Phelps & Phillips LLP, *supra* note 118.

252. *See id.*

253. *See id.*

254. *See* Nicholas Bagley & Rachel E. Sachs, *Limiting State Flexibility in Drug Pricing*, 379 NEW ENG. J. MED. 1002, 1002-03 (2018); MaryBeth Musucemi et al., *Section 1115 Medicaid Demonstration Waivers: The Current Landscape of Approved and Pending Waivers*, KAISER FAM. FOUND. (Sept. 20, 2018), https://www.kff.org/medicaid/issue-brief/section-1115-medicaid-demonstration-waivers-the-current-landscape-of-approved-and-pending-waivers/view/footnotes/#footnote-273141-22.

255. Jason Shafrin & Mark Linthicum, *Patent-Centered Formularies: Steps In The Right Direction, But Challenges Remain*, HEALTH AFF. BLOG (Apr. 11, 2018), https://www.healthaffairs.org/do/10.1377/hblog20180404.510552/full/

lives of people with disabilities.[256] Taking these perspectives of value into account would be needed for states and the federal government to move forward with formularies emphasizing value.

Other states have also explored pricing regulation at the state level without a Section 1115 waiver. More than eighty pharmaceutical pricing bills were proposed in 2017 in over thirty states.[257] New York's bill, for example, passed in April 2017, allows the state to put "limits on prescription drug costs based on their therapeutic benefits."[258] Other states should follow and continue to experiment with various interventions to reform prescription drug spending and pricing. This further research and experimentation with various policy interventions will allow data collection so future lawmakers can make informed choices.

Moving forward, lawmakers should continue to make evidence-based proposals that will make prescription drugs more affordable and accessible to patients while allowing for decreased overall prescription drug spending and continued innovation incentives.

CONCLUSION

The skyrocketing prices of prescription drugs and increasing federal drug spending pose significant threats to affordable healthcare in the United States. An indication-specific pricing regime for prescription drugs in federal health insurance programs would neither decrease overall prescription drug spending nor improve accessibility and affordability of prescription drugs for individual patients. The current legal and regulatory framework in Medicare, Medicaid, the 340B Drug Discount Program, and the Veterans Health Administration pose several challenges to implementing any value-based pricing scheme, especially indication-specific pricing. The FDA approval system and the risk of off-label promotion liability also stand in the way of implementing an indication-specific pricing regime in the United States. Additional policy effects and ethical considerations would also have to be made in reforming the prescription drug pricing system in order to protect patients' access to medicines. The barriers to indication-specific pricing may not be insurmountable, but substantial system modifications would have to be made for it to be a realistic option. Even with these

256. Ne'eman, *supra* note 217.

257. *See* BERMAN ET AL., *supra* note 14, at 1. Particularly innovative bills were passed in Maryland, New York, and Nevada. *See id. See also* Theodore T. Lee et al., *Legal Challenges to State Drug Pricing Laws*, 319 J. AM. MED. ASS'N 865, 865-66 (2018) (discussing legal challenges to state laws to control prescription drug prices); Fran Quigley, *On Drug Pricing, States Step In Where Washington Fails*, N.Y. TIMES (Feb. 27, 2018), https://www.nytimes.com/2018/02/27/opinion/drug-pricing-states.html (discussing state efforts on prescription drug price reform).

258. *See* Thomas J. Hwang et al., *Value-Based Pricing and State Reform of Prescription Drug Costs*, 318 NEW ENG. J. MED. 609, 609 (2017).

modifications, indication-specific pricing would likely not decrease prescription drug prices or overall spending.

As the United States continues to pursue healthcare reform and tackles the problem of unaffordable prescription drug prices, value-based pricing regimes should not be disregarded. Other interventions should be considered to decrease prescription drug prices and spending. Moving forward, lawmakers must explore these potential solutions and focus on affordability and accessibility. The problem of high prescription drug prices and spending is complex and multi-faceted, and any change to the current regime will have impacts on the insurance system, patient access, healthcare system spending, healthcare outcomes, and pharmaceutical innovation.

Any reform to prescription drug pricing and spending must prioritize patient access. Indication-specific pricing may create more problems while failing to increase the accessibility and affordability of drugs. The current system of prescription drug pricing is unethical and unaffordable. Reforms must not perpetuate the problem.

EXHIBIT E

MEDICARE DRUG PRICE NEGOTIATION PROGRAM AGREEMENT
(hereinafter referred to as the "Agreement")

Between

the Centers for Medicare & Medicaid Services (CMS), pursuant to delegated authority of the Secretary of Health and Human Services

And

Novartis Pharms Corp
(hereinafter referred to as the "Manufacturer")

For

Entresto
(hereinafter referred to as the "Selected Drug")

WHEREAS, pursuant to sections 1191 through 1198 of the Social Security Act ("the Act"), as set forth in the Inflation Reduction Act (IRA), Pub. L. 117-169, CMS is responsible for the administration of the Medicare Drug Price Negotiation Program (hereinafter referred to as the "Negotiation Program"), which sets forth a framework under which manufacturers and CMS may negotiate to determine a price (referred to as "maximum fair price" in the Act) for selected drugs in order for manufacturers to provide access to such price to maximum fair price eligible individuals; and

WHEREAS, CMS has designated the Manufacturer as the Primary Manufacturer, as defined in applicable guidance or regulations adopted in accordance with section 1193 of the Act, of the Selected Drug, and CMS has included the Selected Drug on the list of selected drugs published on August 29, 2023; and

WHEREAS, the Manufacturer, if it reaches agreement with CMS, intends to provide access to the determined price pursuant to section 1193 of the Act and in accordance with how the price is computed and applied across different strengths and dosage forms of the Selected Drug as identified by CMS and updated, as applicable, in accordance with sections 1194(f), 1195(b), and 1196(a)(2) of the Act and applicable guidance and regulations, including where the Selected Drug is sold or marketed by any Secondary Manufacturers as defined in applicable guidance or regulations;

NOW THEREFORE, CMS, on behalf of the Department of Health and Human Services, and the Manufacturer, on its own behalf, in accordance with sections 1191 through 1198 of the Act, and all applicable guidance and regulations, hereby agree to the following:

I. Definitions

All terms included in this Agreement shall have the meaning given to them under the provisions of sections 1191 through 1198 of the Act and any applicable guidance and regulations implementing those provisions, except where such terms are expressly defined in this Agreement.

II. CMS and Manufacturer Responsibilities

CMS shall administer the Negotiation Program and the Manufacturer agrees to comply with all applicable requirements and conditions for the Negotiation Program set forth in sections 1191 through 1198 of the Act and all applicable guidance and regulations implementing those provisions and any changes to the Act that affect the Negotiation Program.

Without limiting the foregoing, CMS and the Manufacturer agree:

a) During the negotiation period for the initial price applicability year for the Selected Drug, in accordance with section 1194 of the Act and applicable guidance and regulations CMS and the Manufacturer shall negotiate to determine (and, by not later than the last date of such period, agree to) a maximum fair price for the Selected Drug of the Manufacturer in order for the Manufacturer to provide access to such price—
   i. to maximum fair price eligible individuals who with respect to the Selected Drug are described in subparagraph

(A) of section 1191(c)(2) of the Act and are dispensed the Selected Drug (and to pharmacies, mail order services, and other dispensers, with respect to such maximum fair price eligible individuals who are dispensed the Selected Drug) during, subject to paragraph (b) of this section, the price applicability period; and

ii. to hospitals, physicians, and other providers of services and suppliers with respect to maximum fair price eligible individuals who with respect to the Selected Drug are described in subparagraph (B) of section 1191(c)(2) of the Act and are furnished or administered the Selected Drug during, subject to paragraph (b) of this section, the price applicability period.

b) As applicable, CMS and the Manufacturer shall, in accordance with section 1194 of the Act and applicable guidance and regulations, renegotiate (and, by not later than the last date of the period of renegotiation, agree to) the maximum fair price for the Selected Drug, in order for the Manufacturer to provide access to such maximum fair price (as so renegotiated)—

i. to maximum fair price eligible individuals who with respect to the Selected Drug are described in subparagraph (A) of section 1191(c)(2) of the Act and are dispensed the Selected Drug (and to pharmacies, mail order services, and other dispensers, with respect to such maximum fair price eligible individuals who are dispensed the Selected Drug) during any year during the price applicability period (beginning after such renegotiation) with respect to such Selected Drug; and

ii. to hospitals, physicians, and other providers of services and suppliers with respect to maximum fair price eligible individuals who with respect to the Selected Drug are described in subparagraph (B) of section 1191(c)(2) of the Act and are furnished or administered the Selected Drug during any year during the price applicability period (beginning after such renegotiation) with respect to such Selected Drug.

c) Subject to paragraph (f) of this section and in accordance with applicable guidance and regulations, access to the maximum fair price (including as renegotiated pursuant to paragraph (b) of this section), with respect to such a Selected Drug, shall be provided by the Manufacturer to—

i. maximum fair price eligible individuals, who with respect to the Selected Drug are described in subparagraph (A) of section 1191(c)(2) of the Act, at the pharmacy, mail order service, or other dispenser at the point-of-sale of the Selected 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 the Selected Drug), as described in paragraph (a)(i) or (b)(i) of this section, as applicable; and

ii. hospitals, physicians, and other providers of services and suppliers with respect to maximum fair price eligible individuals who with respect to the Selected Drug are described in subparagraph (B) of section 1191(c)(2) of the Act and are furnished or administered the Selected Drug, as described in paragraph (a)(ii) or (b)(ii) of this section, as applicable.

d) The Manufacturer shall submit to CMS, in a form and manner specified by CMS and in accordance with applicable guidance and regulations, for the negotiation period for the price

applicability period (and, if applicable, before any period of renegotiation pursuant to section 1194(f) of the Act), and for section 1192(f) of the Act, with respect to the Selected Drug—

i. information on the non-Federal average manufacturer price (as defined in section 8126(h)(5) of title 38, United States Code) for the Selected Drug for the applicable year or period;

ii. information that CMS requires to carry out the negotiation (or renegotiation) process under sections 1191 through 1198 of the Act; and

iii. information that CMS requires to carry out section 1192(f) of the Act, including rebates under section 1192(f)(4) of the Act.

e) The Manufacturer shall comply with requirements determined by CMS to be necessary for purposes of administering the Negotiation Program and monitoring compliance with the Negotiation Program, including in accordance with applicable guidance and regulations.

f) Under this Agreement and in accordance with applicable guidance and regulations, the Manufacturer—

i. Shall not be required to provide access to the maximum fair price under paragraph (c), with respect to the Selected Drug and maximum fair price eligible individuals who are eligible to be furnished, administered, or dispensed the Selected Drug at a covered entity described in section 340B(a)(4) of the Public Health Service Act, to such covered entity if the Selected Drug is subject to an agreement described in section 340B(a)(1) of such Act and the ceiling price (defined in section 340B(a)(1) of such Act) is lower than the maximum fair price for such selected drug; and

ii. Shall be required to provide access to the maximum fair price to such covered entity with respect to maximum fair price eligible individuals who are eligible to be furnished, administered, or dispensed the Selected Drug at such entity at such ceiling price in a nonduplicated amount to the ceiling price if such maximum fair price is below the ceiling price for the Selected Drug.

g) In accordance with section 1193(c) of the Act and applicable guidance and regulations, information submitted to CMS

under the Negotiation Program by the Manufacturer that is proprietary information of such Manufacturer, as determined by CMS, shall be used only by CMS or disclosed to and used by the Comptroller General of the United States to carry out such Negotiation Program, unless otherwise required by law.

III. Effective Date, Term and Termination

a) This Agreement shall have an effective date of the date this Agreement is signed by both parties.
b) The term of this Agreement shall be from the effective date until the termination date, which shall be the earlier of the first day that the Selected Drug is no longer a selected drug pursuant to CMS' determination in accordance with section 1192(c) of the Act and applicable guidance and regulations, or the date that the Agreement is terminated by either party in accordance with applicable guidance and regulations.
c) Notwithstanding the termination of this Agreement, certain requirements and obligations shall continue to apply in accordance with applicable guidance and regulations.

IV. General Provisions

a) This Agreement contains the entire agreement of the parties with respect to the subject matter of this Agreement and supersedes all prior oral and written representations, agreements, and understandings of the parties. If CMS and the Manufacturer reach agreement on a price for the Selected Drug pursuant to section II(a) or II(b) of this Agreement, CMS and the Manufacturer shall execute an addendum setting forth the price for the Selected Drug that will apply for purposes of this Agreement.
b) CMS retains authority to amend this Agreement to reflect changes in law, regulation, or guidance. When possible, CMS shall give the Manufacturer at least 60-day notice of any change to the Agreement.
c) Any notice required to be given by either party pursuant to the terms and provisions of this Agreement shall be sent by email. CMS shall provide the appropriate email address for notice in guidance, rulemaking, or other publications. The Manufacturer shall provide the appropriate email address(es) for notice to CMS in a form and manner specified by CMS.
d) Nothing in this Agreement shall prohibit the Manufacturer from transferring the Selected Drug and obligations of this Agreement to another entity in accordance with applicable guidance and regulations.
e) Nothing in this Agreement shall limit the Manufacturer from providing access under the Medicare program to a price lower than the price determined pursuant to this Agreement.
f) In signing this Agreement, the Manufacturer does not make any statement regarding or endorsement of CMS' views, and makes no representation or promise beyond its intention to comply with its obligations under the terms of this Agreement with respect to the Selected Drug. Use of the term "maximum fair price" and other statutory terms throughout this Agreement reflects the parties' intention that such terms be given the meaning specified in the statute and does not reflect any party's views regarding the colloquial meaning of those terms.
g) Nothing in this Agreement shall be construed to require or authorize the commission of any act contrary to law. If any provision of this Agreement is found to be invalid by a court of law with competent jurisdiction, this Agreement will be construed in all respects as if any invalid or unenforceable provisions were eliminated, and without any effect on any other provision.
h) No failure by any party to insist upon the strict performance of any requirement, obligation or condition of this Agreement shall constitute a waiver of any such requirement, obligation or condition.
i) This Agreement shall be construed in accordance with Federal law and any ambiguities shall be interpreted in the manner that best effectuates the statute. Any litigation relating to this Agreement, to the extent that jurisdiction and a cause of action would otherwise be available for such litigation, shall be resolved in Federal court. Actions by the Manufacturer for damages are not permitted pursuant to this Agreement, and the Manufacturer's remedies for any breach are limited to termination of the Agreement or other action consistent with applicable statutes, regulations, or guidance.
j) CMS and the Manufacturer acknowledge and agree that in accordance with section 1197 of the Act and 26 U.S.C. § 5000D, the Manufacturer may be subject to civil monetary penalties and an excise tax, as applicable, for failure to meet the requirements of the Negotiation Program, including violations of this Agreement.
k) Neither party shall be liable for failure to perform its obligations under this Agreement if such failure is occasioned by a contingency beyond such party's reasonable control, including, but not limited to, lockouts, riots, wars, fires, floods or storms (a "Force Majeure Event"). A party claiming a right to excused performance under this section shall promptly notify the other party in writing of the extent of its inability to perform, which notice shall specify the Force Majeure Event that prevents such performance and include a timeline for remediation. The party failing to perform shall use reasonable efforts to avoid or remove the cause of the Force Majeure Event and shall resume performance

under the Agreement promptly upon the cessation of the Force Majeure Event.

V. Signatures

FOR THE MANUFACTURER

A. By signing this Agreement, the Manufacturer agrees to abide by all provisions set forth in this Agreement and acknowledges having received notice of potential penalties for violation of the terms of the Agreement.

B. The undersigned individual hereby attests that he or she is authorized by the Manufacturer to execute this Agreement with regard to the Selected Drug and to legally bind the Manufacturer on whose behalf he or she is executing the Agreement to all terms and conditions specified herein. The undersigned individual further attests that he or she has obtained access in the CMS Health Plan Management System (CMS HPMS) as an authorized representative to be signatory for the Manufacturer and that the individual's CMS HPMS access credentials contain the same information regarding the undersigned individual as the information set forth below.

Date: 09/27/2023

Name: Odalys Caprisecca

Title: VP Finance

P-Number: P1008

Manufacturer Address: One Health Plaza, East Hanover, New Jersey 07936

FOR THE CENTERS FOR MEDICARE & MEDICAID SERVICES

By:

Date: 09/28/2023

Name: Cheri Rice

Title: Deputy Director
Center for Medicare

Signature:

EXHIBIT F

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, Maryland 21244-1850

CENTER FOR MEDICARE

DATE: June 30, 2023

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: Revised Guidance, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026

This memorandum provides interested parties with the revised Medicare Drug Price Negotiation Program guidance for initial price applicability year 2026. It includes four sections:

A. An introduction, which begins on page 1.
B. A summary of changes and clarifications to the initial memorandum released on March 15, 2023, which begins on page 2.
C. A summary of the public comments received in response to the initial memorandum, and the Centers for Medicare & Medicaid Services' (CMS') responses, which begins on page 8.
D. Revised guidance that establishes final policies on the topics discussed for initial price applicability year 2026, which begins on page 92 and for which a table of contents appears on page 94.

CMS may supplement this guidance with further program instruction to explain how these policies will be implemented during initial price applicability year 2026 (e.g., technical instructions for data submissions).

A. Introduction

Sections 11001(c) and 11002(c) of the Inflation Reduction Act (IRA) direct the Secretary to implement the Medicare Drug Price Negotiation Program (hereafter the "Negotiation Program") for 2026, 2027, and 2028 by program instruction or other forms of program guidance. In accordance with the law, on March 15, 2023, CMS issued an initial memorandum for implementation of the Negotiation Program for initial price applicability year 2026. CMS also voluntarily solicited comments on a number of key aspects of the initial memorandum. The 30-day comment period for the initial memorandum began March 15, 2023 and concluded April 14, 2023. CMS received more than 7,500 comment letters in response to the initial memorandum, representing a wide range of views from academic experts and thought leaders, consumer and patient organizations, data vendors/software technology entities, health plans, health care providers, health systems, individuals, labor unions, pharmaceutical and biotechnology

manufacturers, pharmacies, pharmacy benefit managers (PBMs), state governments, trade associations, venture capital firms, and wholesalers.

CMS will make public copies of the timely comment letters that CMS received on the Inflation Reduction Act website at https://www.cms.gov/inflation-reduction-act-and-medicare in July 2023. Comment letters from individuals not representing organizations will have the name, address, and contact information of the individual removed for privacy purposes. Additionally, substantively duplicative letters (e.g., submitted as part of a coordinated advocacy campaign) will be combined into a single document.

After consideration of the comments received, CMS is making certain changes to the policies described in the initial memorandum in this revised guidance for initial price applicability year 2026. These comments also may be considered in development of program guidance for initial price applicability years 2027 or 2028 of the Negotiation Program, for which CMS also intends to solicit comments. CMS will develop its policies for 2029 and all subsequent initial price applicability years of the Negotiation Program through notice-and-comment rulemaking. The public will have an additional opportunity to submit comments as part of that rulemaking process, and comments submitted in response to the initial memorandum may be considered as part of that rulemaking process.

CMS is providing a summary of significant comments that it received in response to the initial memorandum, as well as the agency's response to those significant comments, which begins on page 8. CMS is not responding in this document to all 7,500 comments that it received, but instead is addressing those significant comments that have prompted a revision or a clarification of its policies under the Negotiation Program, or that otherwise raised a significant issue warranting a response that would explain to the public the agency's resolution of that question.

B. Summary of Changes and Clarifications in Revised Medicare Negotiation Guidance

CMS received many constructive, thoughtful, and helpful comments from consumer and patient groups, manufacturers, pharmacies, individuals, and other interested parties on the initial Medicare Drug Price Negotiation Program Guidance that was released on March 15, 2023. This section provides a summary of the key changes and clarifications made to the initial memorandum based on these comments and other feedback. CMS provides responses to the comments received in section C of this revised guidance and has made corresponding changes and clarifications to the policies described in the initial memorandum, as summarized below.

Section 30 – Identification of Selected Drugs for Initial Price Applicability Year 2026: In section 30 of this revised guidance, CMS has made clarifications to policies detailed in section 30 of the initial memorandum, including:

- Bona Fide Marketing of a Generic Drug: CMS has clarified in section 30.1 of this revised guidance the process it will use to determine if bona fide marketing of a generic drug or biosimilar competitor to a potential qualifying single source drug is occurring for the purposes of drug selection. CMS will review both Prescription Drug Event (PDE) data and Average Manufacturer Price (AMP) data reported by manufacturers. The determination whether a generic drug or biosimilar is marketed on a bona fide basis will be based on a totality of the circumstances, including PDE and AMP data.

- Orphan Drug Exclusion: CMS has clarified in section 30.1.1 of this revised guidance that a drug that has designations from the U.S. Food and Drug Administration (FDA) for more than one rare 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) and that CMS will only consider 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. CMS does not have the statutory authority to change the starting date from which qualifying single source drug status is determined, regardless of whether the drug or biological product was previously eligible for the Orphan Drug Exclusion under 1192(e)(3)(A) of the Social Security Act ("the Act").
- Exception for Small Biotech Drugs and Biosimilar Delay: CMS has clarified in sections 30.2.1 and 30.3.1 of this revised guidance the scope of the data that CMS will use to calculate the Small Biotech Drug Exception, which patents and litigation will be considered related to the Biosimilar Delay determination and how CMS will evaluate the manufacturing schedule for the marketing of the Biosimilar, as well as how, for both the Small Biotech Exception and the Biosimilar Delay, CMS will protect information from disclosure and communicate to the public whether there were successful requests.

Section 40 – Requirements for Manufacturers of Selected Drugs for Initial Price Applicability Year 2026: CMS has made the following changes and clarifications to policies detailed in section 40 of the initial memorandum:

- Manufacturer Negotiation Agreement: CMS revised section 40.1 to establish a process for a Primary Manufacturer that is unwilling to enter into an Agreement for the Negotiation Program to expedite its termination from the Medicare Coverage Gap Discount Program and the Manufacturer Discount Program. The revised guidance also specifies that a Primary Manufacturer may terminate its Agreement with CMS at any time, provided the conditions for termination are met, as described in section 40.6 of this revised guidance.
- Data Submission, Confidentiality, and Data Use Provisions: CMS revised section 40.2.2 of the guidance to state that CMS will not publicly discuss ongoing negotiations prior to the release of the explanation of the maximum fair price (MFP) unless a Primary Manufacturer publicly discloses information regarding the negotiation process. Primary Manufacturers may choose to publicly disclose information regarding ongoing negotiations at its discretion. In addition, CMS will treat as proprietary certain data submitted by a Primary Manufacturer of a selected drug in accordance with sections 1194(e)(1) and 1194(e)(2) of the Act, but if a Primary Manufacturer chooses to disclose any material that is made public that CMS has previously deemed to be proprietary information of that Primary Manufacturer, CMS will no longer consider that material proprietary. CMS removed the data destruction requirements under the confidentiality policy pertaining to Primary Manufacturers in section 40.2.2 of this revised guidance. Section 40.2.3 of the revised guidance also provides that CMS will provide the Primary Manufacturer an opportunity for corrective action in the event a submission is incomplete or inaccurate.
- Public Explanation of MFP: CMS will publish a public explanation of the MFP for initial price applicability year 2026 for each selected drug by March 1, 2025 that will include a narrative explanation of the negotiation process, the agreed-upon MFP, and redacted

information regarding the section 1194(e) data received, exchange of offers and counteroffers, and the negotiation meetings, if applicable.

- Use of Medicare Transaction Facilitator (MTF): CMS clarified in section 40.4 of this revised guidance that it intends to engage with an MTF to facilitate the exchange of data between pharmaceutical supply chain entities to help effectuate access to the MFP through a retrospective refund model. CMS is also exploring allowing the use of a standardized refund amount from the manufacturers to the pharmacies under a retrospective refund model and confirms it will require the use of a 14-day prompt pay standard for the refund from manufacturers to pharmacies and other dispensing entities to reimburse dispensing entities for passing through the MFP.
- Suggestion of Error: CMS clarified in section 40.5 of this revised guidance that if a Primary Manufacturer in good faith believes that CMS has made an error in the calculation of the ceiling or the computation of MFP across dosage forms and strengths, the Primary Manufacturer can submit a suggestion of error. CMS will respond to suggested errors within 30 days.
- Manufacturer Ownership Transfer of Selected Drugs: CMS clarified in section 40.7 of this revised guidance the Primary Manufacturer's ongoing responsibilities if the Primary Manufacturer of a selected drug transfers ownership of one or more New Drug Application(s) (NDA) / Biologics License Application(s) (BLA) of the selected drug to another entity, unless and until the Primary Manufacturer transfers all the NDAs / BLAs of the selected drug that it holds to an entity and such acquiring entity assumes responsibility as the new Primary Manufacturer as evidenced by a novation that meets certain criteria.

Section 50 – Negotiation Factors: In the revised guidance, CMS reaffirmed that it will not use evidence from comparative clinical effectiveness research in a manner that treats extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill. CMS also clarified that, for initial price applicability year 2026, it will review cost-effectiveness measures and studies that use such measures to determine whether the measure used may be considered in accordance with section 1194(e)(2) of the Act. However, while such measures may be considered, they will not be used to adjust the initial offer if the measure does not provide relevant information or is not permitted in accordance with section 1194(e)(2) of the Act and section 1182(e) of the Act. CMS has also noted that outcomes such as changes to productivity, independence, and quality of life will be considered when these outcomes correspond with a direct impact on the individuals taking the selected drug or therapeutic alternative(s) and are permitted by section 1194(e)(2) of the Act.

Section 60 – Negotiation Process: CMS has revised the guidance to provide additional detail about how CMS will use the days' supply field in PDE data to calculate a 30-day equivalent supply using the methodology described in 42 C.F.R. § 423.104(d)(2)(iv)(A)(2) when calculating the MFP ceiling (described in section 60.2 of this revised guidance) and using the Wholesale Acquisition Cost (WAC) ratio to apply the MFP across dosage forms and strengths (described in section 60.5 of this revised guidance). As described in section 60.3.2 of this revised guidance, when comparing prices of therapeutic alternatives for purposes of informing a starting price for the initial offer, CMS may use an alternative methodology for calculating a 30-day equivalent

supply when appropriate. In addition, the following revisions were made in this section of the guidance:

- Limitations on Offer Amount: CMS has revised section 60.2 of this revised guidance to use the single ceiling per 30-day equivalent supply across all dosage forms and strengths of the selected drug. CMS has also clarified that the time period for determining whether a selected drug is an extended- or long-monopoly drug runs from NDA approval to the start of the applicable initial price applicability year and clarified that PDE units will be used when averaging non-Federal average manufacturer price ("non-FAMP") across 11-digit National Drug Codes (NDC-11s).
- Unmet Medical Need: In section 60.3.3.1, CMS has revised the definition of unmet medical need to further align with FDA's "Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics."[1]
- Addition of Manufacturer and Patient-Focused Meetings: To facilitate communication with manufacturers, CMS has described in section 60.4 that a CMS-manufacturer meeting will be added to the overall MFP negotiation process that would occur in Fall 2023 after the October 2, 2023 manufacturer data submissions, so that the manufacturer has an opportunity to present the data elements submission and share new information on the section 1194(e)(2) factors, if applicable, with CMS. In addition, CMS will be holding patient-focused listening sessions in Fall 2023 after the October 2, 2023 deadline for patients and other interested parties to share patient-focused input on therapeutic alternatives and other section 1194(e)(2) data regarding selected drugs.
- Negotiation Process: CMS revised section 60.4.3 to clarify that CMS will respond in writing no later than 30 days after receipt of a manufacturer's counteroffer regardless of whether CMS accepts or rejects the counteroffer. CMS has clarified that, to effectuate any MFP agreed upon by CMS and the Primary Manufacturer, both CMS and the Primary Manufacturer must sign and execute an Addendum to the Agreement. CMS also clarified in section 60.4.4 of the revised guidance that if an agreement on an MFP is not reached by the statutory end of the negotiation period, the Primary Manufacturer will enter a period during which an excise tax potentially may be assessed. The Primary Manufacturer can end this period by agreeing to an MFP or sending a notice terminating all of its applicable agreements under the Medicare and Medicaid programs and establishing that none of the Primary Manufacturer's drugs are covered by an agreement under section 1860D-14A or section 1860D-14C of the Act.
- Publication of MFPs for Selected Drugs: CMS clarified in section 60.6 of the revised guidance that CMS will publish the following on the CMS website by September 1, 2024 for all initial price applicability year 2026 selected drugs where an MFP was agreed upon: the selected drug, the initial price applicability year, and the MFP pricing file (which would be updated annually to show the inflation-adjusted MFP for a selected drug). CMS will strive to publish the explanation of the MFP earlier than March 1, 2025, if feasible.
- Manufacturer Delay in Negotiation Process: CMS has clarified in section 60.8 of the revised guidance that, if a Primary Manufacturer is delayed in meeting one or more deadlines related to the negotiation process, CMS will continue to engage in the negotiation process, as described in section 60.4. If delays occur such that the MFP is established after the end of the

[1] FDA Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014. See: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics.

negotiation period, CMS will follow timelines consistent with this revised guidance and take the time to complete the negotiation process as described.

Section 70 – Removal from the Selected Drug List Before or During Negotiation, or After an MFP is in Effect: In accordance with the policy clarification in section 30, CMS clarified that, in addition to monitoring PDE data for a selected drug, CMS will use AMP data reported by manufacturers to determine whether bona fide marketing is occurring when the agency undertakes the process of deselecting a selected drug and monitoring for the continued bona fide marketing of a generic drug or biosimilar. CMS will consider an approved generic drug or licensed biosimilar biological product to be marketed when the totality of the circumstances, including these data, reveals that the manufacturer of the generic drug or biosimilar biological product is engaging in bona fide marketing of that drug or product.

In addition, the revised guidance clarifies that status as a selected drug is unaffected by whether the Primary Manufacturer effectuates or terminates the Agreement to participate in the Negotiation Program or divests of the selected drug.

Section 80 – MFP-Eligible Individuals: CMS clarified in section 80 of this revised guidance that for initial price applicability year 2026, an MFP for a selected drug must be provided to a Medicare beneficiary who uses their Part D plan (including a Medicare Advantage Prescription Drug (MA-PD) plan under Medicare Part C or an Employer Group Waiver Plan) if Part D coverage is provided under such plan for such selected drug. The MFP is not required to be made available to a Medicare beneficiary who uses other sources of prescription drug coverage, such as a plan that receives the Retiree Drug Subsidy, prescription drug discount cards, or cash. For initial price applicability year 2026, CMS does not expect manufacturers to provide access to the MFP of a selected drug to hospitals, physicians, and other providers of services and suppliers with respect to a drug furnished or administered to MFP eligible individuals enrolled under Part B, including an individual who is enrolled in an MA plan.

Section 90 – Manufacturer Compliance and Oversight: CMS made revisions to note that, while the statute clearly requires that the manufacturers of selected drugs are responsible for providing access of the MFP to MFP-eligible individuals and to pharmacies, mail order services, and other dispensers, CMS intends to engage with an MTF to facilitate the exchange of data between supply chain entities to verify eligibility of MFP-eligible individuals such that the MFP can be effectively passed through by the manufacturer to pharmacies, mail order services, and other dispensers. CMS also intends to explore options to facilitate retrospective payment exchange between interested parties to help effectuate access to the MFP.

Consistent with the changes and clarifications noted in sections 30 and 70 of this summary, CMS has also reaffirmed in section 90.4 of this revised guidance that it intends to monitor whether the manufacturer of a generic drug or biosimilar for the selected drug is engaging in "bona fide marketing" of the product by reviewing both PDE data and AMP data. CMS has also clarified that use of these data is not exhaustive, and all data and other information will be reviewed in totality in monitoring if manufacturers of these applicable generic drugs and biosimilars continue to engage in bona fide marketing.

Section 100 – Civil Monetary Penalties (CMPs): In the revised guidance, CMS has provided additional details on the CMP Notification that will be sent to the Primary Manufacturer, an opportunity for corrective action in applicable circumstances, additional details on CMP calculations, and information regarding the payment and appeals processes. CMS will provide an opportunity for corrective action prior to imposing CMPs in some circumstances, providing, for example, a Notice of Potential Noncompliance that includes an opportunity for the Primary Manufacturer to correct or mitigate noncompliance in applicable situations. CMS also revised the guidance to adopt a definition for "knowingly" that is consistent with language used by the Office of the Inspector General in administration of CMPs at 42 C.F.R. § 1003.110 such that "knowingly" means that a person, with respect to an act, has actual knowledge of the act, acts in deliberate ignorance of the act, or acts in reckless disregard of the act, and no proof of specific intent to defraud is required. CMS has also removed the "knowingly" requirement as related to the submission of false information under the Manufacturer Agreement.

Section 110 – Part D Formulary Inclusion of Selected Drugs: The revised guidance has clarified that the statute requires Part D plans to include on their formularies all dosage forms and strengths of the selected drug that constitute a covered Part D drug and for which the MFP is in effect and has established the agency's expectations for how this requirement will be met for initial price applicability year 2026.

Section 120 – Application of Medicare Part B and Part D Prescription Drug Inflation Rebate Programs to Selected Drugs: In the revised guidance, CMS has reaffirmed that selected drugs will also be subject to the Part D drug inflation rebate, but clarified that the MFP for a selected drug is not included in the AMP for the selected drug and thus will not affect the Part D inflation rebate calculation (see section 1927(k)(1)(B)(i)(VI)).

Appendix C – Definitions for Purposes of Collecting Manufacturer-Specific Data: After consideration of the comments on this guidance and the Negotiation Data Elements Information Collection Request (ICR) (CMS-10847 / OMB 0938-NEW), CMS has revised certain definitions in Appendix C. For example, CMS has revised the definition of non-FAMP in Appendix C to clarify that any restatements of the non-FAMP made in any applicable manufacturer non-FAMP submissions to the Department of Veterans Affairs must be reflected in the non-FAMP submitted to CMS as part of the section 1194(e)(1) data submission. CMS has consolidated several research and development (R&D) cost categories in Appendix C and has revised the R&D-related definitions by, for example, requiring reporting of acquisition costs as part of R&D rather than market data and revenue and sales volume data. CMS has also revised Appendix C to clarify that CMS will consider both a Primary Manufacturer's global and U.S. revenue when determining whether to adjust the preliminary price based on manufacturer-submitted data. In addition, CMS has revised the definition related to patents and exclusivities to provide clarification about the types of patents and patent applications that CMS considers to be "related to" the selected drug.

CMS removed certain definitions in Appendix C that are no longer needed due to deletions and revisions to information requested in the 30-day public notice for comment on the Negotiation Data Elements Information Collection Request, including 340B ceiling price, 340B prime vendor program price, manufacturer average net unit price to Part D plans, and quarterly total U.S. unit

volume. CMS revised the definition of unmet medical need and clarified when CMS will consider caregiver perspectives and outcomes such as changes to productivity, independence, and quality of life.

CMS directs interested parties to the 30-day public notice for comment on the Negotiation Data Elements ICR for revisions to ICR instructions and questions that are out of scope for this revised guidance.

C. Summary of Public Comments on the Initial Medicare Drug Price Negotiation Program Memorandum and CMS' Responses

CMS Statutory Authority to Issue Program Instruction and to Issue Section 30 of the Initial Memorandum as Final

Comment: Many commenters stated that CMS should use notice-and-comment rulemaking procedures to implement sections of the IRA. Specifically, a few commenters suggested that by issuing policy through program instruction, CMS violated the Administrative Procedure Act (APA) and the Medicare statute, which require use of notice procedures in certain circumstances and 60 days for comment. Relatedly, a few commenters stated that CMS violated the Due Process Clause of the U.S. Constitution by releasing section 30 of the initial memorandum as final without soliciting comments. Commenters asserted that in relying on the strict statutory deadlines for implementing the Negotiation Program as the rationale for issuing section 30 of the initial memorandum as final, CMS has not shown "good cause" to issue section 30 as final. In addition, a couple of commenters indicated that by issuing section 30 as final, CMS exceeded the scope of what Congress permitted in statute and engaged in *ultra vires* conduct.[2] Some commenters stated that it was improper for CMS to establish substantive obligations without providing notice and opportunity for comment, with one of these commenters further stating that such obligations are invalid and unenforceable because the guidance did not go through rulemaking procedures. A couple of commenters also wrote that the fact that CMS published the initial memorandum seven months after the IRA was enacted does not exempt it from providing opportunities for comment. Several commenters specifically requested that CMS use notice-and-comment rulemaking to codify the negotiation process for initial price applicability years 2027 and beyond. Other commenters recommended that CMS finalize the guidance well in advance of the selected drug publication date for initial price applicability year 2026 to provide interested parties with adequate time to review this revised guidance and conform their actions accordingly.

Response: Sections 11001(c) and 11002(c) of the IRA state that CMS "shall implement" the Negotiation Program "for 2026, 2027, and 2028 by program instruction or other forms of program guidance." Thus, the initial memorandum is not subject to the notice-and-comment requirements of the APA or the Medicare statute. The terms "program instruction" and "program guidance" are terms of art that Congress routinely uses in Medicare statutes to refer to agency pronouncements other than notice-and-comment rulemaking. The statutory directive in sections 11001(c) and 11002(c) thus specifies that CMS shall follow policymaking procedures that differ from the notice-and-comment procedures that would otherwise apply under the APA or the

[2] *Ultra vires* means "beyond the powers," and is used to describe actions taken by governmental bodies that exceed the scope of power given to them by law.

Medicare statute. Congress underscored this directive by placing the Negotiation Program in the newly-enacted Part E of Title XI of the Social Security Act.

Even if the notice-and-comment procedures of the APA and the Medicare statute were applicable, the use of those procedures would be impracticable, unnecessary, and contrary to the public interest, and CMS thus had good cause to depart from those procedures. CMS solicited public comment on many key aspects of the initial memorandum, and also concluded, as stated in the initial memorandum, that in light of the complexity of the actions that must be undertaken in advance of the statutorily-mandated publication of the selected drug list by September 1, 2023, there was good cause to issue parts of the initial memorandum as final, including section 30, without soliciting public comment and without a delayed effective date. CMS reiterates this good-cause justification in this final guidance. CMS also has good cause to issue this revised guidance as final in advance of the statutory September 1, 2023, publication date of the selected drug list for initial price applicability year 2026. CMS agrees with the commenters who encouraged CMS to finalize the guidance well in advance of September 1, 2023 in order to allow interested parties advanced notice of the final policies for the Negotiation Program for initial price applicability year 2026. In particular, manufacturers need to take a number of actions well in advance of September 1, 2023, to prepare for the possibility that a drug that they manufacture will be included on the selected drug list for initial price applicability year 2026. For example, manufacturers may need to engage in internal discussions regarding whether the manufacturers would choose to participate in the Negotiation Program if their drug is included on the selected drug list published on September 1, 2023, review the template Medicare Drug Price Negotiation Program Agreement and guidance to understand Negotiation Program requirements for participating manufacturers in advance of the statutory deadline of October 1, 2023, for entering agreements, and gather information for potential submission to CMS by the statutory deadline of October 2, 2023. In addition, for the reasons explained below, the deadline for a biosimilar manufacturer to submit a delay request under section 1192(f) of the Act was May 22, 2023. CMS could not have proceeded through notice-and-comment rulemaking and still provided interested parties with guidance sufficiently far in advance of these deadlines to allow them adequate time to complete their preparations for potential participation in the Negotiation Program.

Although section 30 was issued as final in the initial memorandum due to these timing constraints, CMS received many comments on section 30. In this guidance, CMS summarizes and responds to those comments, and CMS revised section 30 to help clarify, as needed, the policies it will follow to implement the selection of drugs for initial price applicability year 2026. CMS will continue to consider these comments as it develops guidance and rulemaking for future years of the Negotiation Program.

CMS also disagrees that the use of program guidance to implement the Negotiation Program for initial price applicability year 2026 or the issuance of section 30 as final violates the Due Process Clause of the U.S. Constitution. To the contrary, the reason CMS has undertaken efforts to finalize this guidance well before September 1, 2023, is to ensure that interested parties have advance notice about the procedures CMS will use to implement the Negotiation Program in accordance with the statute. The statute expressly directs CMS to use program guidance rather than notice-and-comment rulemaking to implement the Negotiation Program for 2026, 2027, and 2028, and, even so, through the publication of the initial memorandum, CMS ensured that

interested parties were given notice of and an opportunity to comment on many key aspects of the procedures CMS intends to follow in advance of any selection or negotiation for initial price applicability year 2026. And as explained, although CMS did not solicit comment on section 30, it received many comments on that section and revised to clarify the section in light of those comments.

Further, since enactment of the IRA in August 2022 CMS has engaged with interested parties through various platforms. On January 11, 2023, CMS issued a memorandum outlining how CMS will approach implementation of the Negotiation Program for initial price applicability year 2026, including engagement with the public; program guidance; information collection requests; and a timeline outlining key dates.[3] CMS considered the feedback it received through this engagement in the development of the initial memorandum for the Negotiation Program. Following the issuance of the initial memorandum in March 2023, CMS continues to engage with interested parties, with the intention to engage interested parties throughout implementation of the Negotiation Program.

Between September 2022 and March 2023, CMS accepted 104 meetings with interested parties representing the views of consumer and patient organizations, health care providers, health plans, PBMs, pharmaceutical and biotechnology manufacturers, pharmacies, researchers and academic experts, and wholesalers. In these meetings, CMS leadership and staff received feedback on implementation of the Negotiation Program ranging from policy concerns, questions requiring clarification, and recommendations on policy or operations. CMS also received 129 written materials totaling more than 1,100 pages submitted by pharmaceutical and biotechnology manufacturers and their trade associations, researchers and academic experts, consumer and patient organizations, and health plans and their trade associations, among other interested parties, before publishing the initial memorandum. Based on CMS' tracking of meeting agendas and materials provided, interested parties commonly provided feedback on key Negotiation Program topics including how to identify qualifying single source drugs for negotiation, how to apply the Orphan Drug Exclusion, how to operationalize requests by a biosimilar sponsor to delay selection and negotiation of a biological product that is a reference product for biosimilar market entry, and how to effectuate the MFP. Additionally, CMS leadership participated in 22 speaking engagements on IRA implementation hosted by interested parties. In addition to meetings with interested parties on specific issues of importance to the individual company or organization, CMS has held monthly one-hour calls open to all pharmaceutical and biotechnology manufacturers since December 2022. During these monthly calls, CMS staff provide an overview of recent IRA activities and take questions from manufacturer participants. In addition, in Fall of 2022, CMS established an IRA webpage for all program policies and updates and created an IRA mailbox (IRARebateandNegotiation@cms.hhs.gov) to receive queries from the public related to implementation of the Part B and Part D Inflation Rebate Program and the Negotiation Program. For example, CMS has received queries through the IRA mailbox from interested parties on how to ensure beneficiaries have access to the MFP through their Part D plan.

[3] CMS memorandum *Medicare Drug Price Negotiation Program: Next Steps in Implementation for Initial Price Applicability Year 2026.* Accessible at https://www.cms.gov/files/document/medicare-drug-price-negotiation-program-next-steps-implementation-2026.pdf.

Through external meetings with interested parties, monthly IRA calls with pharmaceutical and biotechnology manufacturers, and the IRA mailbox, interested parties have had multiple touchpoints with CMS. Therefore, CMS disagrees that it has not provided opportunity for interested parties to engage with CMS on policies that may impact their business operations and patients. CMS remains committed to ongoing engagement efforts with interested parties and plans to meet with the Primary Manufacturer of each selected drug as well as hosting patient-focused listening sessions on the selected drugs in Fall 2023, as described in section 60.4 of this revised guidance.

Identification of Qualifying Single Source Drugs for Initial Price Applicability Year 2026 (Section 30.1)

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 the NDA or of a biological product with the same active ingredient and the same holder of the BLA, for the purposes of identifying potential qualifying single source drugs. Some commenters stated that this approach is consistent with the clear statutory instruction to aggregate across dosage forms and strengths. A couple of commenters stated that this policy is critical to prevent gaming. In their view, this reading of the statute will prevent pharmaceutical manufacturers from engaging in "product hopping," attempting to shift use of their products away from those with an MFP to those without an MFP, based solely on modest or minor modifications, a practice which increases revenue for pharmaceutical companies. Other commenters asserted that this approach is not supported by the statute and that the statute defines a qualifying single source drug in reference to a distinct NDA or BLA.

Response: 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 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." The aggregation rules under sections 1192(d)(3)(B) and 1196(a)(2) 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, of an active moiety / active ingredient can 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, 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(e), 1192(d)(3)(B), 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) 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 initial memorandum, 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 shift use of its products away from those with an MFP to those without an MFP, 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 revised guidance, CMS maintains the approach described in the initial memorandum for identifying potential qualifying single source drugs.

Comment: Some commenters raised questions about how CMS will treat products that have different formulations or routes of administration within the same qualifying single source drug, given the policy to define a qualifying single source drug based on active moiety or active ingredient. Some commenters expressed concerns that aggregation will limit pharmaceutical innovation, including innovation for rare diseases and conditions, and commenters urged CMS to consider the patient perspective on whether new formulations demonstrate an improvement to patient care. In contrast, one commenter was concerned that aggregating products with different indications and/or routes of administration into the same qualifying single source drug could be problematic because one product with different indications and/or routes of administration from the other products within a potential qualifying single source drug could have a generic or biosimilar competitor that would disqualify all products from the Negotiation Program.

Response: CMS thanks these commenters for their input. CMS is committed to recognizing the clinical benefit of products, including products with different 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 revised guidance, which details CMS' approach to adjusting the starting point for an initial offer based on clinical benefit.

CMS appreciates the concern raised that a generic or biosimilar competitor for one product within a potential qualifying single source drug will disqualify all products within that potential qualifying single source drug from the Negotiation Program. However, as explained above, the statute directs CMS to aggregate across dosage forms and strengths of the drug, and CMS must apply that requirement faithfully not only for purposes of identifying the qualifying single source drug, but also for purposes of disqualifying products with generic or biosimilar competition that satisfies the relevant statutory criteria.

CMS is committed to ensuring that the statutory criteria are satisfied for any such disqualification, including the requirement that a generic or biosimilar be "marketed." This is particularly important given that a drug or biological product will not be considered a qualifying

single source drug for initial price applicability year 2026 if such competition is determined to exist at the time of drug selection; if such determination occurs after drug selection, it will cause a selected drug (1) to be no longer subject to the negotiation process or (2) to cease to be a selected drug, depending on the timing of such determination. CMS directs readers to section 90.4 of this revised guidance, which details how CMS will monitor whether a generic drug or biosimilar competitor is engaging in bona fide marketing such that a potential qualifying single source drug is disqualified from participation in the Negotiation Program.

Comment: Many commenters asserted that the distinct time periods for when a drug versus 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, at least 11 years must have elapsed since the drug or biological product was approved or licensed, respectively.

Response: 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.[4] 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.[5] CMS is implementing the program in accordance with these statutory requirements.

Comment: A couple of commenters expressed support for CMS' reading of the statute in the initial memorandum 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 qualifying single source drugs. One commenter raised a concern that this reading, while sensible in some cases, creates a gaming opportunity for manufacturers to seek approval of fixed combination drugs with one active moiety / active ingredient in common and market them in a way that could influence volume for each fixed combination drug in an effort to avoid selection. For example, a sponsor might market a fixed combination drug that contains active moiety / active ingredient X and Y and a fixed combination drug that contains active moiety / active ingredient X and Z. The commenter encouraged CMS to aggregate sales for fixed combination drugs with other dosage forms containing the newest active moiety / active ingredient if the products are made by the same manufacturer.

Response: CMS appreciates commenters' support for its understanding of the statutory language and acknowledges the concern outlined by one commenter. CMS believes that a fixed combination drug is distinct in its composition from the individual active moieties / active ingredients and in this revised guidance maintains its approach on fixed combination drugs,

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[4] 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 revised 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.

[5] 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 revised 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.

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.

Orphan Drug Exclusion from Qualifying Single Source Drugs (Section 30.1.1)

Comment: Many commenters asked CMS to clarify that the 7- or 11-year periods prior to eligibility as a qualifying single source drug would begin on the date the Orphan Drug Exclusion ceases to apply to a drug or biological product. That is, a drug or biological product could not become a qualifying single source drug until 7 or 11 years had passed between the date on which the drug or biological product, respectively, loses eligibility for the Orphan Drug Exclusion and the selected drug publication date.

Response: CMS does not have the statutory authority to change the starting date from which qualifying single source drug status is determined. Sections 1192(e)(1)(A)(ii) and (B)(ii) of the Act require CMS to use the date of the approval or licensure of the drug or biological product 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 has added language to section 30.1.1 of this revised guidance to clarify the timing that CMS will use to identify qualifying single source drugs.

Comment: Many commenters asserted that drugs or biological products with multiple orphan designations (for multiple rare diseases or conditions) that are approved only for indications within the scope of a single rare disease or condition should qualify for the Orphan Drug Exclusion. A few commenters remarked that designating a drug under section 526 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for a rare disease is done very early in the drug development process and is important to unlocking Orphan Drug Act incentives. These commenters expressed concern that the current Orphan Drug Exclusion policy in the Negotiation Program will stymie innovation for drugs or biological products and discourage sponsors from seeking designations for more than one rare disease or condition.

Response: CMS thanks these commenters for their feedback. Section 1192(e)(3)(A) of the Act describes a drug that qualifies for the Orphan Drug Exclusion as a "drug 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) is for such disease or condition." CMS therefore does not have the statutory authority to exclude a drug under the Orphan Drug Exclusion that has designations for multiple rare diseases or conditions, even if the drug has been approved only for indication(s) within a single rare disease or condition. CMS has added a clarification about designations for multiple rare diseases or conditions to section 30.1.1 of this revised guidance, which addresses how CMS will implement this exclusion.

Comment: A couple of commenters urged CMS to interpret the term "rare disease or condition" with sufficient breadth to capture designations and approved indications for different mutations or subtypes of one disease. Commenters noted that this interpretation would allow a drug or biological product to seek designations and approvals for sub-conditions within the same rare

disease or condition and remain eligible for the Orphan Drug Exclusion and would preserve incentives for drug development across sub-conditions.

Response: CMS will follow the statutory directive in section 1192(e)(3)(A) of the Act to consider orphan designations and approvals within the scope of the same rare disease or condition. As clarified in section 30.1.1 of this revised guidance, CMS will consult with the FDA as needed to determine whether a drug is designated under section 526 of the FD&C Act for, or has approved indications for, one or more rare diseases or conditions, as part of determining whether a drug meets the requirements in section 1192(e)(3)(A) of the Act to qualify for the Orphan Drug Exclusion.

Comment: Commenters offered contrasting perspectives on whether CMS should consider orphan designations that have been withdrawn when evaluating a drug or biological product for the Orphan Drug Exclusion. Some commenters asserted that CMS should not consider withdrawn designations. In contrast, one commenter recommended that CMS should consider withdrawn designations because a manufacturer could withdraw a designation that is not yet FDA-approved so that a drug or biological product could qualify for the Orphan Drug Exclusion.

Response: CMS appreciates this feedback. CMS understands that a drug or biological product may be designated for a rare disease or condition early in the drug development process, and that designation might not always result in FDA-approved indications that fall within the scope of that designation, and that a manufacturer may choose to withdraw the designation. Similarly, there may be situations where, for example, a manufacturer decides to request that FDA withdraw approval of an indication. In accordance with section 1192(e)(3)(A) of the Act, only designations and approvals active at the time of identifying qualifying single source drugs will be considered for purposes of determining a drug's eligibility for the Orphan Drug Exclusion to best reflect the status of the drug at the time it is evaluated for qualifying single source drug eligibility. As such, CMS has clarified in section 30.1.1 of this revised guidance that it will not consider withdrawn orphan designations or withdrawn approvals when evaluating a drug for the Orphan Drug Exclusion.

Comment: A few commenters raised questions as to whether a potential qualifying single source drug will qualify for the Orphan Drug Exclusion if some but not all dosage forms and strengths of that potential qualifying single source drug meet the Orphan Drug Exclusion criteria. One commenter requested that, when a drug or biological product loses eligibility for the Orphan Drug Exclusion, CMS carve out the original approval(s) that qualified for the Orphan Drug Exclusion from the resulting qualifying single source drug. Another commenter requested that potential qualifying single source drugs that qualify for the Orphan Drug Exclusion must qualify across all dosage forms and strengths. An additional commenter asked whether a fixed combination drug will qualify for the exclusion if only one of the two active moieties / active ingredients qualifies for the Orphan Drug Exclusion.

Response: The initial memorandum states that, in order to qualify for the Orphan Drug Exclusion, "all dosage forms and strengths and different formulations of the qualifying single source drug described in section 30.1 of this memorandum must meet the criteria for exclusion." In this revised guidance, CMS maintains this requirement. Because section 1192(e)(3)(A) of the

Act is an exclusion from the definition of qualifying single source drug under section 1192(e)(1) of the Act, CMS must consider whether the drug, including all products that constitute the potential qualifying single source drug, meets the statutory criteria for the Orphan Drug Exclusion.

Comment: A few commenters expressed concern that the FDA Orphan Drug Product designation database and the FDA approvals database will not allow CMS to identify whether an indication falls within an orphan designation. To alleviate this concern, commenters recommended that CMS consult with FDA and consider written communications between FDA and the manufacturer during the review and approval process. Commenters also suggested that CMS establish a pathway for manufacturers and other interested parties to demonstrate that an indication falls within an orphan drug designation.

Response: CMS appreciates these comments. CMS believes that consulting the FDA Orphan Drug Product designation database and approvals on the FDA website, in addition to consultation with FDA as needed, will allow CMS to successfully implement the Orphan Drug Exclusion. CMS will monitor this approach to ensure that it accurately operationalizes the Orphan Drug Exclusion.

Comment: A few commenters requested that CMS support the development of diagnosis codes for rare diseases and disorders; support early dialogue between payers and rare disease manufacturers; and create new payment and service delivery models with the Center for Medicare and Medicaid Innovation (CMMI) that bolster innovation in the treatment of rare diseases or conditions.

Response: CMS noted in the initial memorandum that CMS is considering whether there are additional actions that CMS might take in its implementation of the Negotiation Program to support orphan drug development, and CMS directs readers to the discussion in section 60.3.3 of how it will consider unmet medical need and the impact of a selected drug on specific populations when developing the initial offer. CMS notes, however, that these specific requests related to CMMI, diagnosis code development, and other payers' interactions with manufacturers are outside the scope of this revised guidance.

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

Comment: A few commenters provided feedback on CMS' description of how it will calculate the Low-Spend Medicare Drug Exclusion. One commenter supported the approach that CMS detailed in the initial memorandum. Another commenter recommended that CMS include rebates in the calculation of Total Expenditures under Part B and Part D for purposes of the Low-Spend Medicare Drug Exclusion. One commenter recommended that CMS exclude beneficiary cost sharing under Part B and net out Direct and Indirect Remuneration (DIR) under Part D when calculating total Part B and Part D expenditures for purposes of this exclusion.

Response: 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) of the Act). The term "gross covered prescription

drug costs" is also defined in the Part D regulations at 42 C.F.R. § 423.308. In the initial memorandum, CMS indicated that it had proposed to update this regulatory definition of gross covered prescription drug costs to eliminate any potential ambiguity in the regulation text and help to ensure there is a consistent understanding of the term for purposes of both the Part D program and the IRA. Since the initial memorandum was issued, CMS has issued a final rule adopting the proposed revisions to 42 C.F.R. § 423.308 (see Contract Year 2024 Policy and Technical Changes to the Medicare Advantage and Medicare Prescription Drug Benefit Programs Final Rule (0938-AU96), 88 Fed. Reg. 22,120, 22,259 (Apr. 12, 2023)).[6] CMS has updated this revised guidance to reflect the issuance of the final rule.

Using PDE data combined with Part B claims data, inclusive of beneficiary cost sharing, to calculate combined Total Expenditures under Part D and Part B will allow CMS to implement the Low-Spend Medicare Drug Exclusion in a manner that aligns with the statute and regulatory policy. CMS will use Part B claims data that are inclusive of beneficiary cost sharing to determine Part B Total Expenditures to maintain consistency with the approach to determining "gross covered prescription drug costs" under Part D, which are defined in the statute and regulations as inclusive of Part D beneficiary cost sharing. CMS has clarified in section 30.1.2 of this revised guidance that, in accordance with section 1191(c)(5) of the Act, expenditures for a drug or biological product that are bundled or packaged into the payment for another service are excluded from the calculation of total allowed charges under Part B for purposes of determining Total Expenditures under Part B.

Comment: One commenter asked CMS to clarify that the 30-day additional period from June 1, 2023 to June 30, 2023 for Part D plan sponsors and Part B providers and suppliers to submit PDE and Part B claims data is a grace period.

Response: As described in section 30.1.2 of this revised guidance, the 30-day period from June 1, 2023 to June 30, 2023 provides time for data to be submitted. In identifying low-spend Medicare drugs for initial price applicability year 2026, CMS will only consider PDE data and Part B claims with dates of service that occur during the 12-month period beginning June 1, 2022, and ending May 31, 2023.

Plasma-Derived Product Exclusion from Qualifying Single Source Drugs (Section 30.1.3)

Comment: Some commenters asked CMS to provide further clarification on which products will be considered plasma-derived for the purpose of the Plasma-Derived Product Exclusion. A couple of commenters asserted that cellular or gene therapies should not be subject to the exclusion. A couple of commenters requested a more holistic approach to identifying plasma-derived products, such as through consultation with FDA and other interested parties.

Response: CMS continues to believe that referring to product information available on the FDA Approved Blood Products website[7] and the FDA Online Label Repository[8] is the best way to

[6] Accessible at: https://www.federalregister.gov/documents/2023/04/12/2023-07115/medicare-program-contract-year-2024-policy-and-technical-changes-to-the-medicare-advantage-program.
[7] See: https://www.fda.gov/vaccines-blood-biologics/blood-blood-products/approved-blood-products.
[8] See: https://labels.fda.gov/.

identify plasma-derived products for the purpose of implementing the Plasma-Derived Product Exclusion in a consistent manner. CMS agrees that there may be specific products where additional insights from FDA would be beneficial, and as noted in section 30.1.3, CMS will also consult with FDA as needed to implement this exclusion.

CMS confirms that cellular and gene therapies are not categorically ineligible for the Plasma-Derived Product Exclusion described in section 1192(e)(3)(C) of the Act, which applies the exclusion to biological products derived from human whole blood or plasma. As described by FDA, cellular therapy products include cellular immunotherapies, cancer vaccines, and other types of both autologous and allogeneic cells for certain therapeutic indications. As further described by FDA, human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.[9] Cellular and gene therapies will be assessed using the same standards as other biological products to determine whether they qualify for the Plasma-Derived Product Exclusion.

Identification of Negotiation-Eligible Drugs for Initial Price Applicability Year 2026 (Section 30.2)

Comment: One commenter asked CMS to clarify whether rebates will be incorporated into the calculations used to rank the 50 negotiation-eligible drugs.

Response: In identifying and ranking the negotiation-eligible drugs for initial price applicability year 2026, CMS will use Total Expenditures under Part D, which are defined at section 1191(c)(5) of the Act as "total gross covered prescription drug costs," as defined in section 1860D-15(b)(3). Section 1860D–15(b)(3) of the Act defines "gross covered prescription drug costs" in relevant part as "the costs incurred under the plan, not including administrative costs, but including costs directly related to the dispensing of covered part D drugs during the year and costs relating to the deductible." The term is also defined in the Part D regulations at 42 C.F.R. § 423.308. As discussed in the Contract Year 2024 Final Rule (see 88 Fed. Reg. 22,120, 22,259 (Apr. 12, 2023)), costs directly related to the dispensing of covered Part D drugs are most logically calculated as the accumulated total of the negotiated prices that are used for purposes of determining payment to the pharmacy or other dispensing entity for covered Part D drugs. Consistent with this policy, CMS will calculate Total Expenditures under Part D for purposes of the Negotiation Program using PDE data and will not consider any rebates or other price concessions not reflected in the negotiated price of the drug on the PDE to identify and rank negotiation-eligible drugs.

[9] See: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products.

Exception for Small Biotech Drugs (Section 30.2.1)[10, 11]

Comment: A couple of commenters requested that CMS create a dispute resolution process so that a manufacturer that disagrees with CMS' determination of its eligibility for the Small Biotech Exception can dispute this determination. One commenter requested that CMS allow small biotech companies to provide additional data after the deadline to support their application for the exception before CMS makes a final determination.

Response: CMS thanks these commenters for their recommendations. CMS requests all information necessary to determine eligibility for the Small Biotech Exception in the Small Biotech Exception ICR Form. Additionally, because of the ambitious statutory deadlines for the Negotiation Program for initial price applicability year 2026, CMS will not accept incomplete or late requests for the Small Biotech Exception for initial price applicability year 2026, including additional data submitted by companies to support their application after the deadline, but before CMS makes a final determination. CMS also declines to create a dispute resolution process for the Small Biotech Exception.

Comment: A couple of commenters requested further detail on the Small Biotech Exception for initial price applicability years 2027 and 2028. Commenters recommended that CMS introduce a streamlined application for manufacturers that had previously received the exception, wherein such manufacturers would only have to attest that they have not been acquired by another entity in order to receive the exception again. One commenter requested clarity on whether manufacturers only have one chance to apply for the Small Biotech Exception or if a manufacturer may submit each year.

Response: This revised guidance establishes the policies CMS will use to implement the Negotiation Program for initial price applicability year 2026. A determination by CMS that a given qualifying single source drug qualifies for the Small Biotech Exception for initial price applicability year 2026 does not mean that this drug will continue to qualify for the Small Biotech Exception for future initial price applicability years. CMS will share the submission process for the Small Biotech Exception for initial price applicability years 2027 and 2028 in future guidance and appreciates the feedback received from commenters.

Comment: One commenter asserted that, for the purpose of identifying drugs that qualify for the Small Biotech Exception for initial price applicability year 2026, CMS must consider whether

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[10] On January 24, 2023, CMS released the Small Biotech Exception ICR (CMS-10844 / OMB 0938-1443) to detail the specific data that CMS is requesting for purposes of implementing this exception. The comment period for the 60-day notice closed on March 27, 2023, and the comment period for the 30-day notice closed on May 24, 2023. Section 30.2.1 of this revised guidance reflects revisions that CMS made in response to feedback from interested parties on the Small Biotech ICR and section 30.2.1 of the initial memorandum. Here, CMS responds to comments on the discussion of the Small Biotech Exception in the initial memorandum that raised inquiries or recommendations not already addressed by revisions to the Small Biotech ICR. To view the Small Biotech ICR Form, a summary of changes made to the Small Biotech ICR in response to comments received during the 60-day and 30-day notice periods, as well as comments received on the Small Biotech ICR and CMS' responses to those comments, please see https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202304-0938-016.

[11] On June 2, 2023, CMS released the Small Biotech Exception functionality in CMS HPMS. To request the Small Biotech Exception for a qualifying single source drug for initial price applicability year 2026, manufacturers must submit a Small Biotech Exception request via HPMS by 11:59 p.m. PDT on July 3, 2023.

Total Expenditures for a qualifying single source drug meet the expenditure requirements under either Part B or Part D. If the qualifying single source drug meets the requirements with respect to either Part B or Part D Total Expenditures, then that qualifying single source drug would qualify for the Small Biotech Exception.

Response: CMS appreciates this recommendation but, for initial price applicability year 2026, sections 1191(a) and 1192(d) of the Act require CMS to evaluate whether a qualifying single source drug meets the criteria to be considered a negotiation-eligible drug, including with respect to the Small Biotech Exception, based on Total Expenditures under Part D only.

Comment: One commenter requested that CMS make the Small Biotech Exception permanent rather than exclude small biotech drug products for only the first three years of the Negotiation Program.

Response: The Small Biotech Exception, as required by section 1192(d)(2)(A) of the Act, applies only with respect to initial price applicability years 2026, 2027, and 2028. CMS does not have the authority to make the Small Biotech Exception permanent.

Although the Small Biotech Exception is limited to initial price applicability years 2026, 2027, and 2028, CMS notes that the temporary floor for small biotech drugs described in section 1194(d) applies to qualifying single source drugs described in section 1192(d)(2) with respect to initial price applicability years 2029 and 2030.

Comment: One commenter requested that CMS clarify which 2021 Total Expenditure data it will use to determine eligibility for the Small Biotech Exception.

Response: As described in section 30.2.1 of this revised guidance, CMS will use PDE data for dates of service during the 12-month period beginning January 1, 2021 and ending December 31, 2021 to determine eligibility for the Small Biotech Exception.

Selection of Drugs for Negotiation for Initial Price Applicability Year 2026 (Section 30.3)

Comment: A few commenters requested greater transparency into the process of selecting drugs for negotiation. A couple of commenters requested that CMS notify the manufacturer of a drug that will be selected for negotiation at least 30 days in advance of the selected drug list publication date. One commenter asked that CMS publish the calculations used to determine the list of selected drugs and establish a process for manufacturers to identify concerns in advance of the selected drug publication date. A couple of commenters suggested that CMS establish a pathway for interested parties to provide input into which negotiation-eligible drugs are included on the selected drug list.

Response: For initial price applicability year 2026, the statute requires that CMS publish the selected drug list no later than September 1, 2023. CMS believes that disclosing to manufacturers whether their drug is a selected drug before this date is operationally infeasible due to the time constraints required to meet statutory deadlines and the complexity of the preparation that must be undertaken in advance of the publication of the selected drug list by September 1, 2023 for

initial price applicability year 2026. For example, sections 1191(d)(3)(B) and 1192(d)(1)(A) of the Act require that CMS identify negotiation-eligible drugs for initial price applicability year 2026 using Total Expenditure data during the period beginning on June 1, 2022, and ending on May 31, 2023. As discussed in section 30 of this revised guidance, Total Expenditures under Part D will be calculated using PDE data for dates of service between June 1, 2022 and May 31, 2023. To allow a reasonable time for Part D plan sponsors to submit PDE data, CMS will use PDE data for the dates of service during this 12-month period that have been submitted to CMS by June 30, 2023. The complexity of the data analyses and quality checks that must then be performed on the data prior to September 1, 2023 forecloses the possibility of disclosing to manufacturers whether their drug is a selected drug prior to the statutory selected drug list publication date for initial price applicability year 2026.

Although CMS appreciates the request for a pathway for interested parties to provide input into the selected drug list for initial price applicability year 2026, section 1192(b)(1)(B) of the Act requires that CMS select the highest ranked drugs from the list of negotiation-eligible drugs using Total Expenditures under Part D. CMS is committed to engaging with interested parties throughout the implementation of the Negotiation Program. As detailed earlier in this guidance, CMS solicited input from interested parties throughout the development of the initial memorandum and this revised guidance. Further, CMS refers readers to sections 50.2 and 60.3.3 of this revised guidance, which detail CMS' approach to adjusting the starting point for the initial offer using evidence submitted by the public on therapeutic alternatives to the selected drug, in accordance with section 1194(e)(2) of the Act. CMS also refers readers to section 60.4 of this guidance, which describes how, in response to comments from interested parties, CMS is providing for additional engagement opportunities for interested parties—specifically, meetings with manufacturers and patient-focused listening sessions—after the October 2, 2023 deadline for submission of section 1194(e) data.

Delay in the Selection and Negotiation of Certain Biologics with High Likelihood of Biosimilar Market Entry) (Section 30.3.1)

Comment: One commenter expressed support for a stringent process for assuring that a Biosimilar Manufacturer and Reference Manufacturer cannot have entered into agreements that require or induce the Biosimilar Manufacturer to limit market share, as well as the process for assuring that there is a high likelihood that the Biosimilar will be marketed before September 1, 2025. The commenter urged CMS to apply similar levels of scrutiny to all areas of implementation where proof of competition is required, including the definition of a qualifying single source drug.

Response: CMS appreciates this commenter's perspective. Section 1192(f)(2)(D)(iv) of the Act excludes certain Biosimilar Manufacturers from the Biosimilar Delay if CMS determines that the Biosimilar Manufacturer is the same as the Reference Manufacturer, or that the Biosimilar Manufacturer has entered into any agreement with the Reference Manufacturer that requires or incentivizes the Biosimilar Manufacturer to submit an Initial Delay Request, or that restricts the quantity (either directly or indirectly) of the Biosimilar that may be sold in the United States over a specified period of time. As described in section 90.4 of this revised guidance, CMS plans to monitor whether the manufacturer of a generic or biosimilar competitor of a potential qualifying

single source drug or selected drug is engaging in bona fide marketing when identifying qualifying single source drugs and selected drugs.

Comment: One commenter expressed concern that a Reference Manufacturer will not have transparency into whether a Reference Drug will be a selected drug because the Reference Manufacturer will not know whether a Biosimilar Manufacturer has submitted an Initial Delay Request to delay the inclusion of that Reference Manufacturer's Reference Drug on the selected drug list. The commenter recommended that CMS publish a list of Biosimilar Manufacturers submitting an Initial Delay Request and make CMS' determinations known publicly.

Response: CMS thanks this commenter for raising this issue. The submission of an Initial Delay Request does not guarantee that a Reference Drug would be a selected drug absent the Initial Delay Request, nor does it guarantee that the Initial Delay Request will be granted even if the Reference Drug would be a selected drug absent the Biosimilar Delay. CMS, therefore, will not publish a list of Biosimilar Manufacturers submitting an Initial Delay Request or CMS' determinations. However, as described in section 30.3.1.4 of this revised guidance, CMS will notify each Biosimilar Manufacturer that submits an Initial Delay Request of CMS' determination regarding such request on or after September 1, 2023, but not later than September 30, 2023. CMS will also notify each Reference Manufacturer named in a successful Initial Delay Request and will identify the Reference Drug that would have been a selected drug, absent the successful Initial Delay Request. In recognition that the public has an interest in understanding the impact of the Biosimilar Delay, CMS is clarifying in this revised guidance that it will publish the number of Reference Drugs that would have been selected drugs for initial price applicability year 2026, absent successful Initial Delay Requests, as part of publishing the selected drug list by September 1, 2023.

Comment: Some commenters asserted that the information required from a Biosimilar Manufacturer to demonstrate a high likelihood that the Biosimilar will be licensed and marketed before September 1, 2025 is too narrow. A couple of commenters contended that section 1192(f)(1)(B)(ii)(I)(aa) of the Act directs CMS to consider all documents that a Biosimilar Manufacturer believes support a high likelihood determination. One commenter stated that the Act does not specify that the scenarios described in sections 1192(f)(3)(A) and (B) are the only scenarios under which a high likelihood determination can be made. The commenter noted that other documentation should therefore suffice to demonstrate a high likelihood that the Biosimilar will be licensed and marketed before September 1, 2025.

Response: CMS thanks these commenters for their feedback related to the high likelihood determination. Section 30.3.1.2 of this revised guidance aligns with the statutory language, which requires CMS to identify whether a Biosimilar has a high likelihood of being licensed and marketed within two years after the publication of the selected drug list. CMS believes the information detailed in section 30.3.1.2 will allow CMS to implement the high likelihood provision of the Biosimilar Delay in a manner that benefits the Medicare program by minimizing the likelihood of CMS approving a delay request for a Biosimilar that is not highly likely to become licensed and marketed within two years after the publication of the selected drug list. Further, CMS believes this approach will support robust biosimilar competition.

Comment: One commenter stated that the metrics proposed to assess the operational readiness of a Biosimilar Manufacturer are generally sensible, but filings with the Securities and Exchange Commission (SEC) on future revenues are often subject to significant caveats about uncertainty and changing market conditions. The commenter recommended that CMS consider a more concrete indicator of operational readiness but did not provide any examples.

Response: CMS believes that section 30.3.1.2 of the guidance aligns with the statutory language and that SEC filings, despite any potential uncertainties, represent a meaningful source of information about a manufacturer's plans to manufacture and market a drug. CMS also notes that, in determining whether a Biosimilar Manufacturer will be operationally ready to market the Biosimilar before September 1, 2025, CMS will also consider supporting documentation provided to CMS as part of the Initial Delay Request, such as the copy of the manufacturing schedule submitted to FDA, which as CMS has clarified in section 30.3.1.2 of this revised guidance, must be consistent with public-facing statements and demonstrative of readiness to meet revenue expectations. Further, operational readiness is only one component of the high likelihood determination. To meet the high likelihood threshold, the Initial Delay Request must also demonstrate that an application for licensure under section 351(k) of the Public Health Service Act ("PHS Act") for the Biosimilar has been accepted for review or approved by FDA, and that patents related to the Reference Drug are unlikely to prevent the Biosimilar from being marketed before September 1, 2025.

Comment: One commenter explained that, upon review of a BLA, FDA may issue a Complete Response letter identifying the deficiencies that preclude approval. The applicant will generally work to address the deficiencies and resubmit the section 351(k) BLA, and FDA will generally act on a resubmitted section 351(k) BLA within six months of receipt. The commenter recommended that CMS make clear that a section 351(k) BLA in Complete Response status remains eligible for the Special Rule Delay.

Response: CMS thanks this commenter for the recommended clarification. CMS has clarified in section 30.3.1.2 of the guidance that CMS will consider a section 351(k) application for licensure that has been accepted for review and has received a Complete Response letter to meet the section 1192(f)(3)(A) requirement that a section 351(k) BLA for the biosimilar biological product has been accepted for review by FDA.

Comment: One commenter recommended that CMS collaborate with FDA to identify key milestones that would indicate a high likelihood that a Biosimilar will be licensed and marketed before September 1, 2025.

Response: Both the initial memorandum and revised guidance incorporate technical assistance from FDA along with other federal agencies. To demonstrate there is a high likelihood that a Biosimilar will be licensed and marketed before September 1, 2025, an Initial Delay Request must demonstrate that the Biosimilar meets the high likelihood threshold described in section 30.3.1.2 of the revised guidance. This threshold requires that, for Initial Delay Requests submitted with respect to initial price applicability year 2026, the Biosimilar's application for licensure must be approved or accepted for review by FDA no later than August 15, 2023, and that the Initial Delay Request demonstrate clear and convincing evidence that the Biosimilar will

be marketed before September 1, 2025. The clear and convincing evidence criteria will be satisfied if the Initial Delay Request demonstrates both (1) that patents related to the Reference Drug are unlikely to prevent the Biosimilar from being marketed and (2) that the Biosimilar Manufacturer will be operationally ready to market the Biosimilar. CMS will continue to consult with FDA as needed on its policies for implementing the Biosimilar Delay.

Comment: One commenter stated that the purpose of the manufacturing schedule submitted to FDA during FDA's review of a section 351(k) BLA – and to CMS under section 1192(f)(1)(B)(ii)(III)(aa) of the Act – is to facilitate an FDA inspection of the establishment that is manufacturing the biological product to confirm the establishment is in operation and manufacturing the proposed product. This manufacturing schedule, therefore, does not reflect any post-approval manufacturing dates. The commenter advised CMS to omit the reference to "consistent with the public-facing statements and any revenue expectations" in the revised guidance.

Response: CMS thanks this commenter for offering their perspective on the uses of the manufacturing schedule submitted to FDA during FDA's review of a section 351(k) BLA. CMS has included a clarification in section 30.3.1.2 of this revised guidance that the manufacturing schedule must be consistent with the manufacturer's public-facing statements and demonstrate readiness to meet revenue expectations, in recognition that the schedule does not reflect post-approval manufacturing dates.

Comment: A few commenters remarked that ongoing patent litigation may be irrelevant to a Biosimilar launch. A Biosimilar Manufacturer can carve out indications with active patents from the Biosimilar's labeling, or a Biosimilar can launch at risk. The commenters asserted that active litigation should, therefore, not prevent manufacturers from meeting the high likelihood threshold.

Response: CMS has clarified that an Initial Delay Request for initial price applicability year 2026 only has to meet one of the following criteria to satisfy the patent-related component of the high likelihood determination: (1) there are no unexpired patents relating to the reference product included in the Reference Drug that are applicable to the Biosimilar; (2) one or more court decisions establish the invalidity, unenforceability, or non-infringement of any potentially applicable unexpired patent relating to the reference product included in the Reference Drug that the patent holder asserted was applicable to the Biosimilar; or (3) the Biosimilar Manufacturer has a signed legal agreement with the Reference Manufacturer that permits the Biosimilar Manufacturer to market the Biosimilar before September 1, 2025, without imposing improper constraints on the Biosimilar Manufacturer. For example, if a Biosimilar Manufacturer has carved out a patent-protected indication or method of use from the Biosimilar's labeling, then such patents would not be considered to be "applicable to the Biosimilar." CMS reiterates that the above criteria reflect how CMS will determine if the Initial Delay Request clearly demonstrates that patents related to the Reference Drug are unlikely to prevent the Biosimilar from being marketed before September 1, 2025.

Comment: A few commenters requested that CMS clarify the specific circumstances under which CMS will find that an agreement between a Biosimilar Manufacturer and a Reference

Manufacturer would disqualify a Biosimilar Manufacturer from making an Initial Delay Request. The commenters noted that a signed legal agreement between the Reference Manufacturer and the Biosimilar Manufacturer permitting the Biosimilar Manufacturer to market the Biosimilar may serve as evidence that patents related to the Reference Drug are unlikely to prevent the Biosimilar from being marketed. At the same time, however, for a Biosimilar Manufacturer to meet the requirements for CMS to grant an Initial Delay Request, the Biosimilar Manufacturer and the Reference Manufacturer must not have entered into an agreement that requires or incentivizes the Biosimilar Manufacturer to submit an Initial Delay Request, or that directly or indirectly restricts the quantity of the Biosimilar that may be sold in the United States over a specified period of time.

Response: CMS does not believe that the two agreement types that the commenters raise conflict since it is possible to have an agreement that permits commercialization without either directly or indirectly restricting volume or incentivizing the Biosimilar Manufacturer to submit an Initial Delay Request. CMS reiterates that, consistent with section 1192(f)(2)(D)(iv)(II) of the Act, the Biosimilar Manufacturer and the Reference Manufacturer must not have entered into an agreement that either requires or incentivizes the Biosimilar Manufacturer to submit an Initial Delay Request, or that directly or indirectly restricts the quantity of the Biosimilar that may be sold in the United States over a specified period of time.

Comment: A few commenters expressed concern that the timeline for submitting Initial Delay Requests is unreasonably accelerated and will jeopardize the accuracy of the requests and create a barrier to biosimilar competition, as the timeline effectively eliminates the additional runway for a Biosimilar competitor to come to market between the deadline on May 22, 2023 for a Biosimilar Manufacturer to submit the documentation for its Initial Delay Request and the selected drug list publication date on September 1, 2023. A few commenters also expressed concern that CMS will not permit the Biosimilar Manufacturer to supplement its Initial Delay Request, except if CMS requests follow-up information or if the Biosimilar Manufacturer would like to update CMS on the status of the Biosimilar application for licensure before 11:59pm PT on August 15, 2023. Commenters requested that CMS set the Initial Delay Request submission deadline as close as reasonably possible to the selected drug list publication date and permit broad supplementation of a timely request with late-breaking information.

Response: CMS thanks these commenters for their feedback and reiterates that the statute is clear that an Initial Delay Request submitted with respect to initial price applicability year 2026 must demonstrate that there is a high likelihood that the Biosimilar will be licensed and marketed before September 1, 2025. The Initial Delay Request timeline therefore does not preclude a Biosimilar from coming to market between the deadline on May 22, 2023 for a Biosimilar Manufacturer to submit the documentation for its Initial Delay Request and the selected drug list publication date on September 1, 2023 (though CMS notes that if the Biosimilar launches between May 22, 2023 and September 1, 2023, then CMS may determine the Reference Drug is not a qualifying single source drug based on the process described in section 30.1 of this revised guidance). Further, the Initial Delay Request deadline has already been set as close to the selected drug publication date as is administratively feasible. CMS adopted this timeline under the authority granted to it in section 1192(f)(1)(B)(ii) of the Act to set the time, form, and manner of Biosimilar Delay requests, and has exercised this authority to establish a timeline

(which is described in section 30.3.1.4 of the revised guidance) that allows CMS to carefully review the Initial Delay Request documentation and, if applicable, to request follow-up information from the Biosimilar Manufacturer on its Initial Delay Request. The timeline ensures that CMS will have adequate time to review follow-up data and make a well-informed determination. Regarding commenters' requests that CMS permit broad supplementation of a timely request, CMS believes that the timeline described in section 30.3.1.4 allows Biosimilar Manufacturers sufficient opportunity to provide CMS with information during the Initial Delay Request process. CMS is not able to accommodate broad supplementation of an Initial Delay Request given the ambitious statutory deadlines for implementing the Negotiation Program for initial price applicability year 2026. CMS will consider adjusting the Initial Delay Request timeline for initial price applicability year 2027 in future guidance, if feasible.

Comment: A few commenters requested that CMS create a way for a Biosimilar Manufacturer to ascertain, before the Initial Delay Request deadline, whether a Reference Drug is likely to be selected for negotiation. One commenter recommended that CMS enable a Biosimilar Manufacturer to inquire with CMS in advance of the Initial Delay Request deadline. A couple of commenters requested that CMS update the Part D Drug Spending Dashboard more frequently or direct manufacturers to other sources of publicly available information to inform assessments of the likelihood that a Reference Drug will be selected for negotiation.

Response: CMS thanks these commenters for their feedback. CMS must complete all steps of the drug selection process with fidelity, including the identification of negotiation-eligible drugs using PDE data with dates of service during the 12-month period beginning June 1, 2022, and ending May 31, 2023. As described in section 30.2 of this revised guidance, 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 service during this 12-month period that Part D plans have submitted to CMS no later than 30 days after May 31, 2023, i.e., by June 30, 2023. Further, to ensure that a potential qualifying single source drug does not have generic or biosimilar competition, CMS will review PDE data for the 12-month period beginning August 16, 2022 and ending August 15, 2023, using PDE data available on August 16, 2023, as well as AMP data for the 12-month period beginning August 1, 2022 and ending July 31, 2023, using the AMP data available on August 16, 2023 for a given generic drug or biosimilar biological product for which a potential qualifying single source drug is the listed drug or reference product. CMS is, therefore, unable to disclose information regarding the selected drug list in advance of the selected drug publication date due to the ambitious statutory deadline for identifying selected drugs and publishing the selected drug list.

CMS appreciates feedback received on the Part D Drug Spending Dashboard. This dashboard allows for a longer claims runout to provide time for claims to be submitted, processed, and finalized than is possible for the data that CMS is statutorily required to use to identify and rank negotiation-eligible drugs. CMS recently announced that it plans to continue its annual updates to the Drug Spending Dashboards to provide the public with comprehensive data on trends related to drug spending for Medicare and Medicaid.[12]

[12] See: https://www.cms.gov/blog/cms-drug-spending-dashboards-and-inflation-reduction-act.

Comment: A couple of commenters asked that CMS notify each Biosimilar Manufacturer that submits an Initial Delay Request of the results of such request in advance of the selected drug publication date. These commenters requested that CMS establish a mechanism by which manufacturers can dispute CMS' determination.

Response: Ambitious statutory deadlines prevent CMS from providing each Biosimilar Manufacturer that submits an Initial Delay Request for initial price applicability year 2026 with advance notice of CMS' determination regarding its request prior to the selected drug list publication date. However, CMS will notify each Biosimilar Manufacturer of CMS' determination on or after September 1, 2023, but not later than September 30, 2023. CMS does not intend to establish a dispute resolution process for Initial Delay Requests.

Comment: One commenter was uncertain whether Appendix B of the initial memorandum includes conflicting information on whether CMS will accept Initial Delay Requests that are incomplete or not timely.

Response: CMS appreciates this request for clarity and confirms that CMS will not accept Initial Delay Requests that are incomplete or not timely. CMS directs readers to section 30.3.1.4 of this revised guidance, which includes a table providing a summary of key dates related to implementation of the Biosimilar Delay for initial price applicability year 2026 as specified in section 30.3.1 of this revised guidance. The deadline for a Biosimilar Manufacturer to email CMS regarding its intent to submit an Initial Delay Request for initial price applicability year 2026 was 11:59 p.m. PT on May 10, 2023.

Comment: One commenter inquired about Question 10 of Appendix B: Template for the Initial Delay Request Form. The commenter remarked that a Biosimilar may qualify for an Initial Delay Request if its section 351(k) BLA is accepted for filing by August 15, 2023. Given FDA's 60-day filing review, the section 351(k) BLA must be submitted no later than June 16, 2023. A Biosimilar Manufacturer that has not yet submitted its section 351(k) BLA by May 22, 2023, but intends to do so by June 16, 2023, must select option (D) on the form detailed in Appendix B of the initial memorandum. The commenter requested that, to guard against any inadvertent disqualification of such Initial Delay Requests, CMS should make clear that selecting this option does not preclude eligibility for the Initial Delay Request.

Response: Selecting option (D) on the form detailed in Appendix B of this guidance does not preclude eligibility for the Initial Delay Request. Biosimilar Manufacturers have until 11:59 p.m. PT on August 15, 2023, to update CMS on the status of the Biosimilar's application for licensure.

Comment: A couple of commenters urged CMS to favor policies that support a robust biosimilars market that drives down prices for patients but did not reference any specific policies. These commenters stated that CMS should consider how to mitigate potential unintended consequences that may disincentivize the development of biosimilars and hinder a robust biosimilars market.

Response: CMS firmly supports a robust biosimilars market and believes that the policies for implementing the special rule to delay selection and negotiation of biologics for biosimilar

market entry will help support biosimilar entry and price competition in the biosimilars market. CMS welcomes input on specific approaches to monitor for potential unintended consequences of these policies and may consider modifications if necessary to mitigate any unintended impact.

Medicare Drug Price Negotiation Program Agreement (Sections 40, 40.1, and 40.6)

Comment: One commenter commented that the statute defines manufacturer by reference to section 1847A(c)(6)(A) of the Act and requested that CMS clarify the definition of Primary Manufacturer as it pertains to the very broad statutory definition.

Response: CMS thanks this commenter for the recommendation. Section 1193(a)(1) of the Act instructs CMS to negotiate with "the manufacturer" to arrive at the MFP for a given selected drug, and the phrase "the manufacturer" appears repeatedly throughout the statutory provisions establishing the Negotiation Program. The best statutory interpretation is to interpret the term "manufacturer" as a single entity for the negotiation process, responsible for negotiating the maximum fair price for a given selected drug. As described in section 40 of this revised guidance and pursuant to section 1191(c)(1) of the Act, to the extent that more than one entity meets the statutory definition of manufacturer for a selected drug for purposes of initial price applicability year 2026, CMS will designate the entity that holds the NDA(s) / BLA(s) for the selected drug to be "the manufacturer" (referred to in this revised guidance as the Primary Manufacturer) of the selected drug.

Comment: Some commenters requested that CMS remove requirements related to Secondary Manufacturers because they view such requirements as inconsistent with CMS' past interpretation of the definition of "manufacturer" in Section 1927(k)(5) of the Act.

Response: CMS appreciates commenters' feedback. In previous interpretations of other provisions of the Act, CMS has expressed concern with burdening manufacturers with no relationship to the holder of an NDA / BLA. In this revised guidance, CMS reiterates its position to exclusively limit any requirements with respect to the terms of the Agreement to manufacturers listed on the NDA / BLA, or manufacturers that market the selected drug pursuant to an agreement with the Primary Manufacturer. Any requirements placed on the Primary Manufacturer by the Negotiation Program to address Secondary Manufacturer actions are solely related to its voluntarily assumed relationship.

CMS also notes that, under the Negotiation Program, Primary Manufacturers enter into an agreement to negotiate an MFP with CMS and to provide access to that MFP for the selected drug, including sales of the selected drug by Secondary Manufacturers. Harm to competition from Primary Manufacturers ensuring MFP availability in sales by Secondary Manufacturers is unlikely because the requirement to provide access to the MFP is mandated by the Negotiation Program and not imposed by the Primary Manufacturer, and because accepting that approach is a requirement of the Negotiation Program. Moreover, the Negotiation Program offers operational flexibility to manufacturers and would not restrict the Primary Manufacturer or Secondary Manufacturer(s) from offering the selected drug at a price lower than the MFP. For these reasons, applying the MFP to sales by Secondary Manufacturers is unlikely to create a situation inconsistent with the antitrust laws.

Comment: In connection with their feedback on the Secondary Manufacturer policies, a few commenters cited the provisions of a 2007 Medicaid Drug Rebate Program (MDRP) rule relating to the treatment of authorized generic drugs. A few commenters also cited a provision from a 2016 MDRP rule relating to the treatment of line extensions.

Response: CMS thanks these commenters for their input. This revised guidance echoes the relationship between manufacturers in the 2007 and 2016 MDRP rules. This revised guidance defines a Secondary Manufacturer as either listed as a manufacturer in the NDA or BLA or marketing the selected drug pursuant to an agreement with the Primary Manufacturer. As it relates to the comments regarding the 2016 MDRP rule, in which the primary concern expressed by commenters involves unrelated manufacturers, CMS notes that the initial memorandum focuses on Secondary Manufacturers with agreements with the Primary Manufacturer thereby limiting the applicability of those concerns. More generally, the 2007 and 2016 MDRP rules suggest that CMS has previously interpreted the statutory definition of "manufacturer" at section 1927(k)(5) of the Act to apply to situations involving multiple manufacturers in a manner that is consistent with the IRA initial memorandum policy of imposing obligations on a Primary Manufacturer with regard to Secondary Manufacturers. Where differences remain under which the Negotiation Program imposes more substantial obligations on the Primary Manufacturer for commercial practices and data of Secondary Manufacturers, these differences are supported by the text, scope, and purpose of the IRA.

Comment: One commenter questioned whether CMS' definition of Secondary Manufacturer could include firms that do not meet the statutory definition of manufacturer with respect to the selected drug but have a marketing agreement in place with the Primary Manufacturer.

Response: CMS thanks this commenter for their input. As described in section 40 of this revised guidance, for initial price applicability year 2026, CMS will refer to any entity other than the Primary Manufacturer that meets the statutory definition of manufacturer, under section 1191(c)(1) of the Act, for a drug product included in the selected drug, and that either (1) is listed as a manufacturer in an NDA or BLA for the selected drug or (2) markets the selected drug pursuant to an agreement with the Primary Manufacturer, as a Secondary Manufacturer. Secondary Manufacturers will include any manufacturer of any authorized generics and any repackager or relabeler of the selected drug that meets these criteria, including those entities that have a marketing agreement with the Primary Manufacturer. A firm that does not meet the statutory definition of a manufacturer under section 1191(c)(1) of the Act does not meet CMS' definition of a Secondary Manufacturer.

Comment: Several commenters requested that CMS provide a comment period for the Medicare Drug Price Negotiation Program Agreement (herein referred to as the "Agreement") to allow manufacturers and the public the opportunity to review and comment on the Agreement. A few commenters expressed concern that lack of advance notice could result in a manufacturer's inability to establish appropriate processes prior to the Agreement's effective date, resulting in possible noncompliance. A couple of commenters also stated that there are only three options for manufacturers within the Negotiation Program under the IRA: sign the Agreement, pay the excise tax, or leave Medicare and Medicaid. Manufacturers expressed concern with the lack of options available to a manufacturer that chooses not to sign the Agreement.

Response: In section 40 of the initial memorandum, CMS included descriptions of and solicited comments on the Agreement requirements to provide interested parties an opportunity to comment on these requirements. Given the thoughtful and extensive comments CMS received on these requirements, CMS determined to set forth the parameters of the manufacturer's obligations under the Negotiation Program in this revised guidance, while reserving for the Agreement certain general provisions and term and termination provisions. The decision to not separately repeat the program requirements in the Agreement means that the program requirements applicable to a manufacturer of a selected drug that enters into an Agreement for initial price applicability year 2026 are preserved and presented in this revised guidance for which there has been public notice and comment. In light of the complexity of the actions the agency must undertake in advance of the Agreement being signed by the statutory deadline of October 1, 2023, CMS will not provide a comment period on the Agreement. However, CMS will make reasonable efforts to make the final text of the Agreement available to the public before the selected drug list is published for initial price applicability year 2026. Please see the responses to comments below for a discussion of the options available to manufacturers who choose not to participate in the Negotiation Program.

Comment: One commenter asked that CMS provide manufacturers with information on how CMS plans to monitor compliance with the Agreement and allow for manufacturers to provide feedback on this information.

Response: The initial memorandum and subsequent revised guidance provide information on how CMS plans to monitor compliance with the Agreement, including the requirements within this revised guidance. As described in section 90.1 of this revised guidance, CMS will provide information about the negotiation process to the Primary Manufacturer of each selected drug. CMS anticipates this information will include operational and statutory timelines, procedural requirements, system instructions, IRA resources, and contact information. During the negotiation period, CMS plans to track and monitor progress during all steps of the process and engage in direct communications with each Primary Manufacturer, including as it relates to compliance. CMS is committed to supporting compliance with program requirements and will provide written reminders and warnings of potential noncompliance (described in section 90.1 of this revised guidance). Following the conclusion of negotiations, CMS plans to monitor compliance related to the Primary Manufacturer's obligations to provide access to the MFP, as described in section 40.4 and section 90.2 of this revised guidance.

As described in section 40.5 of this revised guidance, in monitoring compliance, CMS may engage in auditing processes to verify the accuracy and completeness of any information provided by the Primary Manufacturer, as well as any data related to the Primary Manufacturer providing access to the MFP, including where the selected drug is provided by any Secondary Manufacturer(s).

Comment: A few commenters stated that CMS should not require Primary Manufacturers to submit points of contact for the Agreement within five calendar days of publishing selected drugs, as this process is not included in statute. Commenters noted that CMS should state its

authority in developing this timeline and clarify implications of noncompliance with this timeline.

Response: CMS thanks these commenters for their feedback. CMS revised its policy in section 40.1 of this revised guidance regarding providing points of contact. CMS recommends but does not require this action be taken within five days following publication by CMS on September 1, 2023 of the list of selected drugs and prior to the Agreement being signed to facilitate communication between CMS and the Primary Manufacturer and support efficient effectuation of the Agreement. Primary Manufacturers must provide points of contact by October 1, 2023 at the time that the Agreement is signed.

Comment: A few commenters suggested that CMS consider different ways to designate a Primary Manufacturer other than the holder of the NDA / BLA, given scenarios like split licensures and acquisitions. Commenters recommended CMS consider using the FDA product labeler ID to determine the manufacturer for purposes of negotiating the MFP.

Response: When an application to market a new drug or biological product for human use is submitted to the FDA, the NDA / BLA that is submitted lists only one sponsor. The policy for identifying the Primary Manufacturer with responsibility for the selected drug based on the holder of the NDA / BLA for the selected drug under the Negotiation Program is consistent with the FDA regulatory framework under which the single sponsor of the NDA / BLA in its application describes the manufacturing process and lists the facilities that will produce the sponsor's product. In section 1191(c)(1) of the Act, the statute adopts the definition of "manufacturer" established in section 1847A(c)(6)(A) of the Act. CMS understands that the holder of an NDA or BLA can enter into agreements regarding the sale of drugs approved under a particular NDA or BLA with other entities that may also meet this statutory definition of "manufacturer." CMS must find a mechanism to identify the appropriate manufacturer for purposes of negotiation and ensure other aspects of the Negotiation Program apply to the selected drug. In addition, section 1193(a)(1) of the Act instructs CMS to negotiate with "the manufacturer" to arrive at the MFP for a given selected drug and the term "the manufacturer" appears repeatedly throughout the statutory provisions establishing the Negotiation Program. The best statutory interpretation is to interpret the term "manufacturer" as a single entity for the negotiation process, responsible for negotiating the maximum fair price for a given selected drug. Thus, the most effective way to determine the "manufacturer" described in section 40 of this revised guidance, and the signatory of the Agreement, is to identify the NDA / BLA holder as the Primary Manufacturer.

Comment: Many commenters made recommendations pertaining to the Agreement and how it applies to Secondary Manufacturers. Commenters recommended CMS require all Secondary Manufacturers to sign the same Agreement that applies between Primary Manufacturers and CMS. A few commenters suggested that Secondary Manufacturers sign a unique Agreement with CMS in addition to the Agreement between Primary Manufacturers and CMS. A few commenters were supportive of CMS' policy to enter into an Agreement with only the Primary Manufacturer.

Response: Given that section 1193(a)(1) of the Act instructs CMS to negotiate with "the manufacturer" to arrive at the MFP for a given selected drug to which "the manufacturer" would provide access in accordance with the statute, and given that the term "the manufacturer" appears repeatedly throughout the statutory provisions establishing the Negotiation Program, the best statutory interpretation is to interpret the term "manufacturer" as a single entity for the negotiation process, responsible for negotiating a single maximum fair price for a given selected drug. Thus, in accordance with section 1193(a)(1) of the Act and other statutory references to "the manufacturer," CMS will enter into an Agreement with "the manufacturer" of a selected drug, where "the manufacturer" is the NDA / BLA holder as described in section 40 of this revised guidance. CMS has adopted the designations of "Primary Manufacturer" and "Secondary Manufacturer," respectively, to establish a process to negotiate the maximum fair price with "the manufacturer" to align with the meaning of the statutory language and establish responsibilities and requirements of the Primary Manufacturer related to data collection and submission and MFP availability for the selected drug sold by the Secondary Manufacturer(s).

Comment: One commenter asked CMS to clarify whether a Primary Manufacturer is only responsible for data submission and MFP availability for sales of the selected drug by a Secondary Manufacturer when there is a contractual agreement between the two parties.

Response: CMS thanks this commenter for their question. For initial price applicability year 2026, a Primary Manufacturer will be responsible for data submission and MFP availability for sales of the selected drug by a separate manufacturer of the selected drug if that separate manufacturer is a Secondary Manufacturer as described in section 40 of this revised guidance. An entity is a Secondary Manufacturer if it meets the statutory definition of a manufacturer for the selected drug and either (1) is listed as a manufacturer in an NDA or BLA for the selected drug or (2) markets the selected drug pursuant to an agreement with the Primary Manufacturer. Specifically, any manufacturer that qualifies as a Secondary Manufacturer for initial price applicability year 2026 will have an existing relationship with a Primary Manufacturer. A Secondary Manufacturer will include any manufacturer of any authorized generics and any repackager or relabeler of the selected drug.

Comment: A few commenters stated that CMS should allow each Secondary Manufacturer to participate in all negotiation activities, including negotiation meetings, and have access to all written correspondence between the Primary Manufacturer and CMS. If CMS chooses not to allow this, the Primary Manufacturer should be allowed to share any and all documentation with the Secondary Manufacturer.

Response: The best statutory interpretation is to interpret the term "the manufacturer" as a single entity for the negotiation process responsible for negotiating a single maximum fair price for a given selected drug. In addition, section 1193(a)(1) of the Act instructs CMS to negotiate with "the manufacturer" to arrive at the MFP for a given selected drug, and the phrase "the manufacturer" appears repeatedly throughout the statutory provisions establishing the Negotiation Program. Congress's use of the singular definite article demonstrates that, for any one selected drug, the "manufacturer" with which CMS negotiates is a single entity. Thus, CMS believes that the most effective way to determine the "manufacturer" described in section 40 of the guidance and the signatory of the Agreement, is to identify the NDA / BLA holder as the

Primary Manufacturer. CMS has adopted the designations of "Primary Manufacturer" and "Secondary Manufacturer," respectively, to establish a process to negotiate an MFP with a single manufacturer to align with the meaning of the statutory language "the manufacturer," and establish responsibilities and requirements of the Primary Manufacturer related to data collection and submission and ensuring MFP availability for selected drug sold by the Secondary Manufacturer(s).

As described in section 40.2.2 and 60.6.1 of this revised guidance, CMS does not intend to publicly discuss the negotiation process prior to the public explanation of the MFP being released, unless a Primary Manufacturer discloses information that is made public. If a Primary Manufacturer discloses information that is made public regarding any aspect of the negotiation process prior to the explanation of the MFP being released by CMS, CMS reserves the right to publicly discuss the specifics of the negotiation process regarding that Primary Manufacturer. Primary Manufacturers engaged in negotiating an MFP with CMS are reminded that statements to or discussions with other Primary Manufacturers also engaged in the MFP negotiation process with CMS could negatively impact the competitive process for each independent MFP negotiation. Primary Manufacturers should consider the antitrust implications of any such actions. CMS will protect the confidentiality of any proprietary information from Primary Manufacturers or Secondary Manufacturers (described in section 40.2.1) as required under section 1193(c) of the Act and other applicable law. If a Primary Manufacturer chooses to disclose any material that is made public that CMS has previously deemed to be proprietary information of that Primary Manufacturer, CMS will no longer consider that material proprietary consistent with section 40.2.1 of this revised guidance. Neither the IRA nor this revised guidance prevents Primary Manufacturers from disclosing any information to Secondary Manufacturers.

Comment: One commenter stated that CMS should revise the National Drug Rebate Agreement and the Coverage Gap Discount Program Agreement, and work with the Health Resources and Services Administration (HRSA) to revise the Pharmaceutical Pricing Agreement, to permit immediate termination from all applicable federal programs in the event that an agreement on an MFP cannot be reached or a manufacturer is dissatisfied with the MFP.

Response: CMS thanks this commenter for their recommendation. CMS has clarified in section 40.6 of the revised guidance that a Primary Manufacturer that decides not to participate in the Negotiation Program may voluntarily terminate the Medicare Drug Price Negotiation Program Agreement if it also ceases participation in the Medicaid Drug Rebate Program, the Medicare Coverage Gap Discount Program, and the Manufacturer Discount Program through the end of the price applicability period for the selected drug. CMS has also clarified in section 40.1 of the revised guidance that a Primary Manufacturer that elects not to participate in the Medicare Drug Price Negotiation Program may take similar measures to cease its participation in the Medicaid Drug Rebate Program, the Medicare Coverage Gap Discount Program, and the Manufacturer Discount Program. Sections 40.1 and 40.6, as revised, set forth the procedures for the Primary Manufacturer to initiate termination processes under the Medicare and Medicaid programs and the steps CMS will take to facilitate an expeditious termination of the Primary Manufacturer's agreements under the Medicare Coverage Gap Discount Program and the Manufacturer Discount Program, as applicable. As a result of these procedures, any manufacturer that declines to enter an Agreement for the Negotiation Program may avoid incurring excise tax liability by submitting

the notice and termination requests described herein 30 days in advance of the date that excise tax liability otherwise may begin to accrue. Moreover, any manufacturer that has entered into an Agreement will retain the ability to promptly withdraw from the program prior to the imposition of civil monetary penalties or excise tax liability.

Manufacturer Data Submission, Proprietary Information, and Confidentiality (Section 40.2)

Comment: Several commenters requested that CMS not publish any proprietary information in the MFP public explanation and continue to provide strong protections to proprietary data otherwise collected under Part D. Several commenters also stated that CMS should give manufacturers the opportunity to review, raise concerns, and designate any information therein that is confidential and proprietary in advance of the publication of the public explanation of the MFP. A few commenters stated that CMS should clarify that any proprietary information shall be disclosed or exclusively used by CMS or the Comptroller General of the United States only for IRA-related purposes, and not used or disclosed for any other reason, regardless of whether the requirements of the Freedom of Information Act (FOIA) are satisfied.

Response: Section 1193(c) of the Act requires that information submitted to CMS by the manufacturer of a selected drug that is proprietary information, as determined by CMS, shall be used only by CMS or disclosed to and used by the Comptroller General of the United States for purposes of carrying out the Negotiation Program. CMS is committed to protecting confidential and proprietary information obtained from manufacturers throughout the negotiation process. In addition, CMS is also committed to protecting information that is obtained from Prescription Drug Plans (PDPs) and MA-PD plans that will inform the negotiation process. For initial price applicability year 2026, as described in section 40.2.1 of this revised guidance, CMS will treat information on non-FAMP as proprietary, as well as treat certain data elements submitted by a Primary Manufacturer of a selected drug in accordance with sections 1194(e)(1) and 1194(e)(2) of the Act as proprietary, if the information constitutes confidential commercial or financial information of the Primary Manufacturer or a Secondary Manufacturer that meets the requirements set forth under Exemptions 3 and/or 4 of FOIA (5 U.S.C. § 552(b)(3), (4)). In addition to the protections under the FOIA for trade secrets and commercial or financial information obtained from a person that is privileged or confidential, the Trade Secrets Act at 18 U.S.C. § 1905 requires executive branch employees to protect such information. CMS understands commenters' concerns pertaining to the confidentiality of proprietary information and will protect confidential and proprietary information as required by applicable law. However, if a Primary Manufacturer chooses to disclose any material that is made public that CMS has previously deemed to be proprietary information of that Primary Manufacturer, CMS will no longer consider that material proprietary consistent with section 40.2.1 of this guidance.

Comment: Some commenters stated that CMS should remove, or at least modify, the data destruction requirements within the confidentiality policy for manufacturers following the deselection of a selected drug. One commenter stated that CMS should consider removing the 30-day timeline for data destruction, or let manufacturers petition for an extension. Other commenters stated that CMS should impose parallel data destruction requirements or revise the policy to align with other federal programs.

Response: After reviewing these comments and further consideration of the issue, CMS has removed the data destruction requirements under the confidentiality policy described in section 40.2.2 of this revised guidance pertaining to Primary Manufacturers.

Comment: Many commenters requested that CMS clarify whether specific data elements submitted by Primary Manufacturers (including, where applicable, Secondary Manufacturer data submitted by the Primary Manufacturer) will be released publicly. Commenters asked that CMS aggregate and release information about prior Federal financial support, approved patents, exclusivities, approvals, aggregate estimates or deidentified research and development costs, historic sales, volume of sales, revenue, and market data of selected drugs. Commenters requested that CMS clarify that information that is publicly available will not be deemed proprietary.

Response: CMS thanks these commenters for their input. As stated in section 40.2.2 of the revised guidance, CMS revised the confidentiality policy for the negotiation process in response to comments received and further consideration of the issue. In the interest of balancing transparency and confidentiality, CMS has made revisions in the guidance pertaining to what information CMS will keep confidential and for how long. As described in section 40.2.2 and 60.6.1 of this revised guidance, as a part of the public explanation of the MFP published in March 2025, CMS will make public a narrative explanation of the negotiation process and the agreed-upon MFP and share redacted information regarding the section 1194(e) data received, exchange of offers and counteroffers, and the negotiation meetings. CMS maintains that any information submitted by manufacturers that constitutes confidential commercial or financial information of the Primary Manufacturer or a Secondary Manufacturer will be considered proprietary and will be redacted.

A Primary Manufacturer may choose to publicly disclose information regarding any aspect of the negotiation process at any time, including prior to the public explanation of the MFP being released by CMS. Of note, while CMS generally plans to wait to release information about the negotiation process until CMS publishes the public explanation of the MFP, if the Primary Manufacturer chooses to disclose information prior to the publication of the public explanation of the MFP, CMS may decide to make early disclosures about the negotiation process as well.

Comment: One commenter stated that CMS should clarify what elements of the Biosimilar Initial Delay Request will be exempt from any FOIA requests or disclosures.

Response: CMS revised section 30.3.1 of this revised guidance to clarify that information in an Initial Delay Request and in a Small Biotech Exception ICR Form that is a trade secret or confidential commercial or financial information will be protected from disclosure if the proprietary information meets the requirements set forth under Exemptions 3 and/or 4 of FOIA (5 U.S.C. § 552(b)(3), (4)).

Comment: One commenter stated that CMS should clarify that the existence and status of a pending NDA or BLA, in addition to information contained in a pending NDA or BLA, will be treated as proprietary information.

Response: As stated in the initial memorandum, for initial price applicability year 2026, CMS will treat certain data elements submitted by a Primary Manufacturer of a selected drug in accordance with section 1194(e)(1) of the Act as proprietary if the information constitutes confidential commercial or financial information of the Primary Manufacturer or a Secondary Manufacturer. It is CMS' presumption that a pending NDA or BLA would qualify as proprietary under this standard.

Comment: One commenter asked CMS to release the full negotiation records five to ten years after the patents for a selected drug expire.

Response: As stated in section 40.2.2 of this revised guidance, CMS revised the confidentiality policy for the negotiation process in response to comments received and after further consideration of the issue. In the interest of balancing transparency and confidentiality, CMS has made revisions in the guidance pertaining to what information CMS will keep confidential and for how long. As described in sections 40.2.2 and 60.6.1 of this revised guidance, as a part of the public explanation of the MFP published in March 2025, CMS will make public a narrative explanation of the negotiation process and the agreed-upon MFP and share redacted information regarding the section 1194(e) data received, exchange of offers and counteroffers, and the negotiation meetings.

At this time, CMS is issuing guidance for implementation of initial price applicability year 2026 and does not foresee that CMS would subsequently provide additional disclosure in the manner the commenter is suggesting. CMS will continue to consider whether such additional disclosure is appropriate in the future.

Comment: One commenter asked CMS to clarify the consequences for violating the requirements of confidentiality for both manufacturers and CMS.

Response: CMS thanks this commenter for their input. In the interest of balancing transparency and confidentiality, CMS revised the confidentiality policy for the negotiation process in response to comments received and further consideration of the issue. CMS does not intend to publicly discuss the negotiation process prior to the public explanation of the MFP being released, unless a Primary Manufacturer chooses to discuss the negotiation publicly. If a Primary Manufacturer discloses information that is made public regarding any aspect of the negotiation process prior to the explanation of the MFP being released by CMS, CMS reserves the right to publicly discuss the specifics of the negotiation process regarding that Primary Manufacturer. Primary Manufacturers engaged in negotiating an MFP with CMS are reminded that statements to or discussions with other Primary Manufacturers also engaged in the MFP negotiation process with CMS could negatively impact the competitive process for each independent MFP negotiation. Primary Manufacturers should consider the antitrust implications of any such actions.

The Trade Secrets Act at 18 U.S.C. § 1905 requires executive branch employees to protect proprietary information. If a Primary Manufacturer chooses to disclose any material that is made public that CMS has previously deemed to be proprietary information of that Primary

Manufacturer, CMS will no longer consider that material proprietary consistent with section 40.2.1 of this revised guidance.

Comment: One commenter asked how CMS will enforce the confidentiality requirements for individuals who no longer work at a manufacturer of a selected drug or at CMS.

Response: CMS thanks this commenter for their question. In the interest of balancing transparency and confidentiality, CMS revised the confidentiality policy for the negotiation process in response to comments received and further consideration of the issue. Primary Manufacturers have the authority to determine how former employees may use or discuss its proprietary information as it pertains to the Negotiation Program. CMS employees that leave CMS are informed prior to their departure that they are not permitted to disclose nonpublic information obtained as a result of CMS employment that has not been released to the public.

Comment: Many commenters stated that the confidentiality policy as described in the initial memorandum violates the First Amendment rights of manufacturers, is not supported by statute, or is not necessary to administer or monitor compliance with the Negotiation Program. One commenter asked that CMS align the confidentiality policy so manufacturers and CMS are bound by the same confidentiality standards. Many commenters raised concerns that the confidentiality policy would prevent manufacturers from disclosing to their board and investors pertinent information related to the negotiation process. One commenter asked CMS to make all offers and counteroffers public. A few commenters were supportive of CMS' confidentiality policy as it is consistent with private sector negotiation processes.

Response: CMS thanks these commenters for their input. As stated in section 40.2.2 of the revised guidance, CMS revised the confidentiality policy for the negotiation process in response to comments received and upon further consideration of the issue. In the interest of balancing transparency and confidentiality, CMS has made revisions pertaining to which information CMS will keep confidential and for how long in the revised guidance. As described in sections 40.2.2 and 60.6.1 of the revised guidance, as a part of the public explanation of the MFP published in March 2025, CMS will make public a narrative explanation of the negotiation process and the agreed-upon MFP and share redacted information regarding the section 1194(e) data received, exchange of offers and counteroffers, and the negotiation meetings. CMS maintains that any information submitted by manufacturers that constitutes confidential commercial or financial information of the Primary Manufacturer or a Secondary Manufacturer will be considered proprietary and will be redacted.

A Primary Manufacturer may choose to publicly disclose information regarding any aspect of the negotiation process at any time, including prior to the explanation of the MFP being released by CMS. Of note, while CMS generally plans to wait to release information about the negotiation process until CMS publishes the explanation of the MFP, if the Primary Manufacturer chooses to disclose information about the negotiation process prior to the publication of the public explanation of the MFP, CMS may decide to make early disclosures about the negotiation process as well. If a Primary Manufacturer chooses to disclose any material that is made public that CMS has previously deemed to be proprietary information of that Primary Manufacturer,

CMS will no longer consider that material proprietary consistent with section 40.2.1 of this revised guidance.

Comment: One commenter stated that CMS should allow manufacturers to negotiate the scope and terms of any confidentiality policies, including whether manufacturers may publicly discuss the Negotiation Program, as a part of the broader negotiation process.

Response: CMS thanks this commenter for their input. In the interest of balancing transparency and confidentiality, CMS made revisions in the guidance to clarify that a Primary Manufacturer may publicly disclose information regarding the Negotiation Program, as described in section 40.2.2 of this revised guidance. In section 40.2 of this revised guidance, CMS describes a confidentiality policy that applies to all Primary Manufacturers of selected drugs who choose to sign an Agreement. Adopting a standard confidentiality policy allows CMS to focus the negotiations on the statutory goal of negotiating to achieve agreement on the lowest MFP and creates uniform protection of information determined to be proprietary as well as transparency upon the release of the explanation of the MFP.

Comment: One commenter asked CMS to consider revising the policies for classification and handling of proprietary data in the coming years and re-evaluate whether this approach should be applied to a narrower set of data elements.

Response: CMS thanks this commenter for their input and will take the comment under advisement as CMS considers policies for future years of the Negotiation Program.

Comment: A few commenters asked how CMS plans to secure manufacturer-submitted data. Commenters asked CMS to outline a cybersecurity policy regarding how CMS plans to implement safeguards to protect manufacturer-submitted data, how such data will be stored, and a process for alerting manufacturers of any breach or erroneous use.

Response: CMS thanks these commenters for their comments on safeguarding data submitted by manufacturers. Primary Manufacturers will submit the information to CMS via the Health Plan Management System ("CMS HPMS"). The CMS HPMS adheres to all applicable policies, procedures, controls, and standards required by the Department of Health and Human Services (HHS)/CMS information security and privacy programs to ensure the confidentiality, integrity, and availability of manufacturer information and government information systems. The CMS HPMS system is the primary CMS system for exchange of information between CMS and Medicare Advantage and Medicare Prescription Drug Plans, and as such is designed to receive and keep confidential proprietary and commercially sensitive information.

As required by CMS, the CMS HPMS integrates security into every aspect of the system development life cycle. The CMS HPMS is subject to the agency's Security Assessment and Authorization (SA&A) process, a rigorous methodology during which the system must demonstrate a sound and comprehensive information security posture. In order to achieve and maintain an Authority to Operate (ATO), the CMS HPMS routinely undergoes system penetration testing as well as a Security Control Assessment (SCA), where independent auditors

perform a detailed assessment to ensure that the system's security controls meet the CMS Acceptable Risk Safeguards (ARS).

An individual must apply for and obtain a CMS-issued user account and password in order to access the CMS HPMS. In addition to the CMS-issued user ID and password, internal CMS staff must use an HHS identification badge (referred to as a PIV card) when accessing the website on the CMS network, while all users accessing the system from outside of the CMS network must use multi-factor authentication. The CMS HPMS further employs role-based access, ensuring that each user is granted access only to those functions required by their position.

The CMS HPMS is hosted at a CMS approved cloud service provider. The system is protected by a suite of firewall and intrusion detection services, including Akamai Content Delivery Network (CDN), which serves as an additional web application firewall that offers robust distributed denial of services protection and access control. The CMS HPMS utilizes a multi-zone architecture comprised of a presentation zone, an application zone, and a data zone, designed to provide further defense against security attacks. CMS will employ encryption at rest in the database for sensitive manufacturer data (e.g., proprietary information, including trade secrets and confidential commercial or financial information) in addition to encryption in transit.

The CMS HPMS adheres to the CMS Information Security Incident Handling Procedures, which are supplemented by the CMS HPMS Security Incident Handling Procedures. These documents outline the procedures for managing known or suspected security or privacy incidents, including, but not limited to, roles and responsibilities, escalation procedures, and guidelines for notifying impacted individuals or organizations.

Negotiation and Agreement to an MFP and Renegotiation in Later Years (Section 40.3)

Comment: One commenter noted that CMS has not outlined the specific conditions under which a renegotiation will occur in subsequent years.

Response: CMS thanks this commenter for the comment. This guidance includes details regarding the Negotiation Program for initial price applicability year 2026. CMS will provide additional information in the future for initial price applicability years 2027 and beyond, including renegotiation, which will be implemented for initial price applicability year 2028 and subsequent years, in accordance with the statute.

Access to the MFP (Sections 40.4 and 90.2)

Comment: One commenter expressed concern that the MFP would be adopted as a reference price by non-Medicare payers. For example, commercial plans and PBMs might use a selected drug's MFP to inform negotiations or to establish payment and reimbursement amounts for the selected drug outside of the Medicare program.

Response: The IRA directs CMS to negotiate an MFP for each selected drug for the Medicare program and requires the manufacturers of such drugs to make the MFP available to MFP-eligible individuals. As discussed in section 80 of this revised guidance, for initial price

applicability year 2026, Primary Manufacturers of selected drugs must provide access to the MFP for a selected drug to Medicare beneficiaries who use their Part D plan (including an MA-PD plan under Medicare Part C or an Employer Group Waiver Plan, but not a plan that receives the Retiree Drug Subsidy) if Part D coverage is provided under such plan for such selected drug. The Negotiation Program does not regulate payment rates by payers outside of the Medicare program (e.g., in the commercial markets). CMS will publish the MFP for each selected drug, as required by law. The MFP for each selected drug could be published by pharmaceutical pricing database companies and could be used by other payers for reimbursement and other purposes. Payers will continue to have discretion to consider Medicare payment rates among other considerations in establishing their own payment policies. CMS notes that Medicare already establishes and publishes payment rates for drugs under Part B using the Average Sales Price (ASP) methodology that may be used by other payers (such as state Medicaid programs), and Medicaid also publishes various pharmaceutical pricing benchmarks, such as the National Average Drug Acquisition Cost (NADAC) file and Federal Upper Limits (FULs) for multiple source drugs, that may be used by other payers.

Comment: Many commenters provided perspectives and recommendations regarding CMS' policies in the initial memorandum to monitor access to the MFP. Many commenters recommended CMS require manufacturers to use a retrospective MFP refund approach to adjust reimbursement to pharmacies, mail order services, and other dispensing entities for dispensing a selected drug to an MFP-eligible individual. Many commenters recommended CMS help effectuate a retrospective refund model by contracting with a third-party administrator (TPA) or clearinghouse to facilitate data and/or payment exchange between entities in the supply chain so pharmacies, mail order services, and other dispensing entities receive retrospective refunds in a timely manner. Many commenters recommended that, in contracting with a TPA, CMS include processes to allow manufacturers to avoid providing the 340B price and an MFP refund for the same unit(s) of a selected drug dispensed to an MFP-eligible individual.

Response: CMS thanks these commenters for the recommendations. CMS intends to engage with a Medicare Transaction Facilitator (MTF) to facilitate the exchange of data between supply chain entities to verify eligibility of MFP-eligible individuals. CMS appreciates the value of the role an MTF could play in supporting the identification of selected drugs dispensed to MFP-eligible individuals to facilitate appropriate retrospective reimbursement by manufacturers. CMS is also exploring options to facilitate retrospective payment exchange between interested parties to help effectuate access to the MFP. CMS is committed to the goal of ensuring prompt payment to dispensers for pass through of the MFP, consistent with other prompt pay rules in Part D.[13] Pursuant to section 40.4 of this revised guidance, CMS requires that the MFP be passed through to dispensers within 14 days of the manufacturer receiving sufficient information to verify that an individual is eligible for access to the MFP. With respect to the establishment of a process to allow manufacturers to avoid providing a 340B price and an MFP for the same unit of drug, CMS understands the value of the identification of 340B units for the Negotiation Program and the Part D Drug Inflation Rebate Program. CMS intends to examine options with respect to identification of 340B units and intends to work with HRSA accordingly. CMS has revised sections 40.4 and 90.2 of this revised guidance to include further detail regarding access

[13] See 42 C.F.R. § 423.520, Prompt Payment by Part D Sponsors, which requires Part D sponsor payment to pharmacies within 14 days after receiving a Part D claim and determining that the Part D claim is a clean claim.

to the MFP and will provide more information in advance of initial price applicability year 2026.

Comment: Some commenters recommended that CMS define the amount of the MFP refund that is due from the manufacturers to the pharmacies. Some advocated for a retrospective "true up" payment from the manufacturer to the dispensing entity, using a standardized amount, such as the difference between a publicly reported pricing metric (such as WAC) and the MFP, rather than a dispensing entity's actual acquisition cost for the selected drug. One commenter recommended CMS use the annual non-FAMP as the standardized metric.

Response: CMS thanks these commenters for their recommendation. The majority of the comments received from supply chain entities on this topic, including manufacturers and pharmacies, supported the use of a standardized, published pricing metric to calculate the refund due from the manufacturer to the pharmacy or other dispenser for the pass through of the MFP. After reviewing the comments and further consideration of the topic, CMS is exploring the option of allowing manufacturers to use a standardized refund amount, such as the WAC of the selected drug minus the MFP (WAC-MFP). CMS plans to provide further information regarding this topic in technical guidance before initial price applicability year 2026.

Comment: Some commenters recommended CMS regularly monitor whether Primary or Secondary Manufacturers are compliant with the requirements of the Negotiation Program, including providing access to the MFP. One commenter recommended CMS create an online option and phone options for reporting violations related to access to the MFP with respect to MFP-eligible individuals. One commenter recommended CMS set a time limit to respond to individuals reporting violations, report the number of complaints CMS receives, and create an ombudsman to serve as a point of contact for individuals submitting complaints.

Response: CMS thanks these commenters for their recommendations, including those relating to the importance of having multiple avenues for reporting violations and timely resolution of investigating such complaints. As further described in sections 40.4 and 90.2 of this revised guidance, CMS will closely monitor the Primary Manufacturers' compliance with the terms of the Agreement and other aspects of the Negotiation Program, including whether the Primary Manufacturer is ensuring that the MFP is available for the selected drug sold by Secondary Manufacturers, where applicable. CMS will establish procedures by which individuals, as well as pharmacies, mail order services, and other dispensing entities, will be able to report instances to CMS in which the MFP should have been made available but was not. CMS will respond to reports of violations in a timely manner, and plans to issue more information on reporting procedures in advance of initial price applicability year 2026.

Comment: A few commenters recommended that CMS establish a financially viable model for pharmacy reimbursement when a pharmacy dispenses a selected drug to an MFP-eligible individual, including by requiring a dispensing fee that covers a pharmacy's business operation costs to dispense a selected drug. A couple of commenters recommended that CMS clarify that claims paid for a selected drug must be excluded from pharmacy DIR or other fees imposed by entities in the supply chain. A couple of commenters recommended CMS prohibit PBMs, Part D plan sponsors, or other entities in the supply chain from charging administrative fees to

manufacturers or pharmacies for providing access to a selected drug. One commenter recommended CMS require higher dispensing fees for entities dispensing a selected drug.

Response: CMS thanks these commenters for their recommendations. Under section 1860D-2(d)(1)(D) of the Act, as amended by section 11001(b) of the IRA, the negotiated prices used in payment by each Part D plan sponsor for each selected drug must not exceed the applicable MFP plus any dispensing fees for such drug. CMS intends to allow manufacturers to use either a prospective upfront discount model or a retrospective refund model to make the MFP available. After reviewing the comments and further consideration of the topic, CMS is working with interested parties to explore developing a standard retrospective rebate model process that would allow for the pass through of the MFP for a selected drug by manufacturers to dispensing entities for dispensing a selected drug to an MFP-eligible individual. As noted above, CMS intends to engage with an MTF to facilitate the exchange of data between pharmaceutical supply chain entities to verify eligibility of MFP-eligible individuals under a retrospective rebate model. As described in section 40.4 of this revised guidance, neither Primary Manufacturers nor their contracted entities shall charge any transaction fee to dispensing entities for the pass through of the MFP to the dispenser.

Provided that Part D plans comply with all applicable requirements, plan sponsors retain flexibility in determining the fees paid or charged to pharmacies, including dispensing fees. However, CMS is committed to the goal of assuring prompt payment to pharmacies and other dispensers for passing through the MFP, consistent with other prompt pay rules in Part D, and is requiring manufacturers to pass through the MFP within 14 days of confirming an individual is eligible for the MFP. Please refer to sections 40.4 and 90.2 of this revised guidance for more information.

Comment: Some commenters recommended CMS collaborate with interested parties to implement a single process for manufacturers to provide access to the MFP that works for entities across the pharmaceutical supply chain. A few commenters recommended CMS work with interested parties in the pharmaceutical supply chain to develop standards for facilitating the transaction of the MFP refund.

Response: CMS thanks these commenters for their recommendations. Consistent with section 40.4 of this revised guidance, Primary Manufacturers must provide access to the MFP by either (1) ensuring that the price paid by the dispensing entity when acquiring the drug is no greater than the MFP, or (2) providing retrospective reimbursement for the difference between the dispensing entity's acquisition cost and the MFP. However, CMS notes that the majority of the commenters support the retrospective rebate or refund approach. CMS intends to engage with an MTF that could assist with data facilitation in a retrospective rebate model. CMS has been working with, and plans to continue working with, interested parties to explore processes for facilitating data exchange while minimizing burden.

Comment: A few commenters supported the options CMS outlined in the initial memorandum for providing access to the MFP. One commenter recommended CMS incentivize manufacturers to prospectively effectuate access to the MFP by making the MFP available to dispensing entities at the point of acquisition of a selected drug. One commenter recommended CMS require

manufacturers to create secondary NDCs for selected drugs and make secondary NDCs available to wholesalers at the MFP.

Response: CMS thanks these commenters for their recommendations. The majority of commenters supported a retrospective refund or rebate approach to making pharmacies, mail order services, and other dispensers whole with respect to the pass through of the MFP. CMS intends to engage with an MTF to help facilitate data exchange to confirm MFP-eligibility to provide access to the MFP using a retrospective approach for pharmacies, mail order services, and other dispensers. CMS is not requiring manufacturers to create secondary NDCs for selected drugs and the assignment of labeler codes is the responsibility of the FDA. Moreover, the NDCs for the dosage forms and strengths of a selected drug will be published on the CMS website, and CMS expects that pharmaceutical drug pricing compendia will also publish them.

Comment: Some commenters recommended CMS share detailed Part D claims data with manufacturers to verify that an individual is eligible to receive a selected drug at the MFP. One commenter recommended CMS minimize the data shared with manufacturers and other entities in the supply chain while facilitating access to the MFP.

Response: CMS thanks these commenters for their recommendations. CMS agrees that a Primary Manufacturer should be able to verify that a selected drug was dispensed to an MFP-eligible individual. As further described in sections 40.4 and 90.2 of this revised guidance, after consideration of the comments, CMS plans to release more information in advance of initial price applicability year 2026 regarding how CMS might support and facilitate data exchange between pharmaceutical chain entities.

Comment: A couple of commenters recommended that CMS require Primary Manufacturers to report the MFP of a selected drug and the effective date for the MFP in standard drug pricing compendia.

Response: CMS thanks these commenters for their recommendation. CMS will publish the MFP at the per-unit level for the dosage forms and strengths for a selected drug and keep this list up-to-date over time on the CMS IRA website. CMS anticipates that various drug pricing compendia will decide to include the MFP in their pricing files.

Comment: Some commenters recommended CMS remove or lengthen the requirement for retrospective payment to dispensing entities be made within 14 days, due to operational complexities. Some commenters recommended CMS clarify that the 14-day reimbursement requirement begins when the claim is verified for an MFP-eligible individual. One commenter recommended that CMS clarify that the 14-day reimbursement period begins when the Primary Manufacturer receives the request for reimbursement.

Response: CMS thanks these commenters for their recommendations. CMS will apply the standards set forth in current Part D prompt pay reimbursement regulations regarding payment by plan sponsors to pharmacies to manufacturers for their pass through of the MFP for selected drugs. That is, CMS will require that a Primary Manufacturer ensure that pharmacies, mail order services, and other dispensers are reimbursed timely for the pass through of the MFP within 14

days of verifying eligibility of an MFP-eligible individual. This will ensure that pharmacies are paid for the claim for the selected drug in the same timeframe as if the entire claim would have been filled through the regular Part D process. Please see sections 40.4 and 90.2 of this revised guidance for more information.

Comment: Many commenters made recommendations regarding CMS policy relating to non-duplication of the MFP and the 340B ceiling price. One commenter recommended CMS clarify that the same unit(s) of a drug dispensed to an MFP-eligible individual is not eligible for a duplicate 340B discount. A few commenters wrote that it is burdensome for pharmacies and dispensing entities to identify 340B units proactively or retroactively to avoid duplication of the MFP and 340B ceiling price. Some commenters recommended CMS contract with a TPA to identify 340B units at the point of sale or during retrospective reimbursement. A few commenters recommended CMS condition claims payment for units of selected drugs on including an accurate 340B or non-340B claim modifier. A few commenters recommended CMS work with HRSA to ensure the MFP for a selected drug is not applied to a drug that was acquired at the 340B ceiling price. Some commenters recommended CMS implement an oversight system to audit selected drug units dispensed at the MFP and identify if the same units of a selected drug were acquired at the 340B ceiling price.

Response: CMS thanks these commenters for their recommendations. CMS reiterates, as described in section 40.4.1 of the initial memorandum, that a manufacturer that provides an MFP for a unit of a selected drug is not also required to provide a 340B discount on that same drug if the MFP is lower than the 340B ceiling price (and vice versa, that the MFP does not need to be made available if the 340B ceiling price is lower). That is, these price concessions are not cumulative.

Further, CMS understands the interest in ensuring compliance with the statutory requirement to avoid duplication of the MFP and the 340B ceiling price for a selected drug. CMS also notes the interest in requiring that all Part D claims be marked as either 340B or non-340B to ensure that there is no duplication of 340B prices with the pass through of the MFP. At this time, CMS is examining options with respect to identification of 340B units in consultation with HRSA and interested parties. In addition to any policies or procedures that CMS may adopt in this regard, CMS will also work with HRSA to ensure the MFP is made available where appropriate in a nonduplicated amount to the 340B ceiling price.

Comment: A few commenters recommended CMS create accessible materials that list the MFP for a selected drug and the date the MFP applies for Medicare beneficiaries to reference to understand access to the MFP. A few commenters recommended CMS incorporate information about the MFP of a selected drug into various beneficiary outreach materials.

Response: CMS thanks these commenters for their recommendations. CMS is committed to helping Medicare beneficiaries understand access to a negotiated MFP for a selected drug during the price applicability period. CMS will publish on its website the MFP at the per unit (e.g., tablet) level for each NDC-11 associated with the selected drug. CMS will also develop accessible materials to educate Medicare beneficiaries, as well as the health care providers and other organizations that serve them, on benefits related to the Negotiation Program.

Comment: One commenter recommended CMS reduce the need for Primary Manufacturers to retain any records relating to sales of the selected drug to entities that dispense the selected drug to MFP-eligible individuals, including pharmacies, mail order services, and other dispensers for units of selected drug. The commenter recommended CMS reduce the timeframe from ten years to six years from the date of sale due to the burden and costs associated with retaining these records.

Response: CMS thanks this commenter for the recommendation. CMS believes ten years is a reasonable requirement for record retention for these sales to align with the statute of limitations period under the False Claims Act.[14]

Suggestion of Error and Corrective Actions and Compliance (Sections 40.2.3 and 40.5)

Comment: Some commenters asked CMS to consider a dispute resolution process for any disputes on claims-level data, including 340B claims. A few commenters suggested that CMS delay reimbursement during any dispute resolution process. A few commenters suggested that if CMS does not create a dispute resolution process, that CMS develop stewardship principles within the Negotiation Program, including for facilitating access to the MFP.

Response: CMS thanks these commenters for their recommendations. CMS notes that it intends to engage with an MTF to facilitate the exchange of data between pharmaceutical supply chain entities to support the verification of dispensing of a selected drug to an MFP-eligible individual. CMS believes that engaging with an MTF to facilitate data transfer for eligibility purposes could minimize the potential for claims-level disputes. With respect to the Primary Manufacturer's obligation to provide access to the MFP, requirements are described in sections 40.4 and 90.2 of this revised guidance. CMS is also providing Primary Manufacturers with a corrective action process, detailed in section 40.2.3 of this revised guidance.

Comment: A few commenters asked that CMS establish a dispute resolution process that would apply to various aspects of the Negotiation Program. One commenter asked that the dispute resolution process be established prior to the September 1, 2023, deadline for publication of selected drugs.

Response: CMS thanks these commenters for their recommendations. Section 1198 of the Act prohibits administrative or judicial review of CMS' determinations of drug selection, unit determination, and the determination of MFP. CMS recognizes that Primary Manufacturers, at times, may disagree with CMS regarding certain calculations during the negotiation process. Therefore, if a Primary Manufacturer in good faith believes that CMS has made an error in the calculation of the ceiling for the selected drug or the computation of MFP across dosage forms and strengths, section 40.5 of this revised guidance notes that the Primary Manufacturer can submit a suggestion of error. Additionally, sections 40.2.3 and 100.2 of this revised guidance have been revised to provide an opportunity for corrective action in certain circumstances in which a violation of a requirement could result in a CMP being issued.

[14] 31 U.S.C. § 3731(b).

Comment: A commenter asked that CMS allow for broader stakeholder input in any dispute resolution process that is created.

Response: CMS thanks the commenter for their recommendations. After considering feedback from multiple interested parties for initial price applicability year 2026, CMS updated section 40.5 of this revised guidance to allow Primary Manufacturers the opportunity to suggest potential errors to CMS in the event that the Primary Manufacturer has a good faith belief that CMS has made an incorrect calculation. Further, CMS updated section 100.2 of this revised guidance to describe how Primary Manufacturers will have an opportunity to correct identified incompleteness or inaccuracies in certain manufacturer-submitted information in instances in which a violation of a data submission requirement could result in the imposition of a CMP. CMS will continue to evaluate those processes for future years.

Other Provisions in the Agreement (Section 40.7)

CMS solicited comment on this section, but did not receive any comments that are not otherwise addressed elsewhere (see the Medicare Drug Price Negotiation Program Agreement (Sections 40, 40.1, and 40.6) section above).

Negotiation Factors (Section 50)

Comment: Many commenters supported the use of certain cost-effectiveness measures to gain insight into the relationship between cost and effectiveness for a selected drug and its therapeutic alternative(s). Cost-effectiveness measures mentioned by commenters included Equal Value of Life-Years Gained (evLYG), Equal Value Life-Year (evLY), and Health Years in Total (HYT) and alternative methods recommended for assessing cost-effectiveness included Generalized Risk-Adjusted Cost-Effectiveness (GRACE) and Generalized Cost-Effectiveness Analysis (GCEA). Some commenters recommended convening experts to advise CMS on whether such metrics or methods are appropriate for assessing clinical benefit within the context of negotiation. Some commenters requested CMS clarify that the use of such measures is permitted when evaluating clinical benefit.

Response: CMS appreciates these commenters' responses and suggestions. CMS indicates in section 50.2 of this revised guidance that CMS will review cost-effectiveness measures and studies that use such measures for initial price applicability year 2026 to determine if such measures are permitted under section 1194(e) of the Act. CMS may use content in a study that uses a cost-effectiveness measure if it determines that the cost-effectiveness measure used is permitted in accordance with the law. A measure will not be used to adjust the initial offer if the measure does not provide information related to the negotiation factors described in section 1194(e) of the Act or is used in a manner that treats extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than the life of an individual who is younger, nondisabled, or not terminally ill, in accordance with section 1194(e)(2) and section 1182(e) of Title XI of the Act. CMS clarifies in this revised guidance that it will not use Quality-Adjusted Life Years (QALYs) to determine any offer.

Comment: Many commenters interpreted the initial memorandum as stating a CMS decision not to use QALYs when assessing clinical benefit of a selected drug and its therapeutic alternative(s) and supported such a decision.

Response: CMS appreciates these commenters' feedback and reaffirms that QALYs will not be used in the Negotiation Program. CMS will consider studies that use QALYs only when they contain other content that is relevant and permitted under section 1194(e)(2) of the Act and section 1182(e) of Title XI of the Act.

Comment: Some commenters urged CMS not to use any metrics of cost-effectiveness or clinical effectiveness because the metric and/or the underlying data or assumptions used to develop the metric may be discriminatory. Some commenters stated that CMS should adopt a full prohibition on the use of QALYs and/or "similar measure[s]" under the relevant prohibition in the Patient Protection and Affordable Care Act.

Response: CMS reaffirms that QALYs will not be used in the Negotiation Program to adjust CMS offers. In response to feedback received on whether any measures may be permissible under section 1194(e)(2) and section 1182(e) of Title XI of the Act, CMS revised section 50.2 of this revised guidance to indicate CMS will review and consider cost-effectiveness measures and studies that use such measures for initial price applicability year 2026. However, while such measures may be reviewed, they will not be used to adjust the initial offer if the measures do not provide information related to the negotiation factors described in section 1194(e) of the Act or are prohibited under section 1194(e)(2) of the Act, or under section 1182(e) of the Act.

Comment: Regarding CMS' intent to use data that can be separated from the use of QALYs within a given study, a couple of commenters requested clarification on how CMS would separate such evidence from QALYs. A few commenters requested that CMS not consider any study referencing QALYs in determining the initial offer.

Response: Per section 1194(e)(2) of the Act, comparative clinical effectiveness research may not be used "in a manner that treats extending the life of an elderly, disabled, or terminally ill individual as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill." CMS will not, per section 1182(e) of Title XI of the Act, use QALYs but may review the underlying data, results, or other content in studies that employ QALYs. By doing so CMS may glean important insights into the outcomes associated with the drug under consideration. For example, a study using QALYs to examine the cost-effectiveness (i.e., reviewing the cost per outcome) of drug A compared to drug B for the treatment of cardiovascular disease will describe the population of interest and quantify the outcomes. Factors in the study that do not treat extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or terminally ill, such as demographic information, blood pressure, cardiovascular events, and mortality before and after starting drug A versus starting drug B may provide important data to CMS about the clinical benefit of drug A when compared to drug B. Reviewing demographic information and outcomes, such as in this example, does not require CMS to review the results of the QALY calculation but may still provide important clinical information.

This approach aligns with CMS' decision to not use QALYs in the Negotiation Program while also enabling CMS to review and consider relevant information.

Comment: Many commenters requested that CMS simplify the process by which the public, including patients and caregivers, can submit information on the negotiation factors described in section 1194(e)(2) of the Act and the Negotiation Data Elements ICR (CMS-10847 / OMB 0938-NEW). Commenters requested additional time for submissions and clarity on the format in which information should be submitted to ensure usability for the submission of factors related to sections 1194(e)(1) and 1194(e)(2) of the Act.

Response: CMS appreciates commenters' feedback. Due to the statutory timeline of the negotiation period, including the requirement under sections 1191(d)(5)(B) and 1194(b)(2)(B) of the Act for CMS to issue an initial offer by February 1, 2024, it is not feasible to extend the timeframe for the submission of information under section 1194(e)(2) of the Act. However, as described in section 60.4 of this revised guidance, CMS will host patient-focused listening sessions that will be open to the public, including patients, beneficiaries, caregivers, consumer and patient organizations, and other interested parties, to share patient-focused input on the therapeutic alternative(s) and other section 1194(e)(2) information regarding selected drugs. These patient-focused listening sessions will occur in Fall 2023 after the section 1194(e) data submission, which will give patients and other interested parties additional time to prepare their feedback. Regarding the standardization of submissions, CMS expects a wide range of data to be appropriately submitted as part of the process and does not seek to limit the types of data submitted based on format. CMS will review submissions in alignment with sections 50 and 60 of this revised guidance.

Comment: Some commenters supported CMS' decision to open the submission of section 1194(e)(2) factors to the public. Some commenters suggested evaluating bias in information submitted or requiring a conflict of interest disclosure.

Response: CMS appreciates commenters' feedback. As described in section 50.2 of this revised guidance, CMS will consider, among other factors, the source of information, whether the study has been through peer review, as well as risk of bias during review. CMS also requires that declarative statements submitted via the Negotiations Data Elements ICR be supported by cited evidence unless the submission is a description of personal experience. This approach focuses on the merit of the information provided.

Comment: One commenter suggested requiring an executive summary of manufacturer-submitted data and another suggested requiring manufacturers to report rebates at the drug level.

Response: CMS appreciates commenters' suggestions. The comment suggesting that CMS require an executive summary of manufacturer-submitted data is out of scope for the Negotiation Program guidance and will be considered for the revised Negotiation Data Elements ICR. Regarding the comment suggesting manufacturers be required to report rebates at the drug level, CMS consulted with subject matter experts and representatives of the pharmaceutical and biotechnology industry in developing the definitions described in Appendix C of this guidance to align with statutory data collection requirements and other federal programs.

Comment: A few commenters suggested that CMS validate manufacturer data using independent data sources or suggested a third-party entity validate manufacturer data instead of CMS. One commenter recommended that CMS specify that submissions may be audited to ensure accuracy.

Response: CMS will validate manufacturer-submitted data to the extent possible, including via audit as deemed appropriate, pursuant to compliance monitoring activities under section 1196(b) of the Act.

Comment: Some commenters stated that the Negotiation Data Elements ICR included unclear expectations or data formatting inconsistent with current manufacturer approaches to tracking such data. A few commenters stated this could generate risk for the manufacturer and that a standard data format should be clarified. One commenter requested that CMS clarify that only the Primary Manufacturer is responsible for submitting data on factors described in section 1194(e)(1) of the Act.

Response: The Primary Manufacturer is responsible for providing manufacturer-submitted data described in section 1194(e)(1) of the Act and section 50.1 of this revised guidance. More information on what must be reported can be found in Appendix C of this revised guidance. Comments on formatting are out of scope for the Negotiation Program guidance and will be considered in the revised Negotiation Data Elements ICR.

Comment: A couple of commenters requested that CMS accept any information provided by a manufacturer of a selected drug even if such information is not tied to a specific statutory factor.

Response: CMS will accept information as outlined in this revised guidance and the Negotiation Data Elements ICR in accordance with statutory requirements.

Comment: One commenter requested manufacturer data submissions be provided to CMS on a rolling basis to permit adequate time to compile accurate and complete data given the relationship between inadequate submissions and CMPs. Another commenter requested sufficient time for manufacturers to evaluate requests for information and price offers from CMS before a manufacturer is determined to be noncompliant and/or enforcement actions are taken. This commenter suggested that CMS has flexibility to establish the timeframe between publication of the selected drug list (September 1, 2023 for initial price applicability year 2026) and submission of data required under section 1194(e) of the Act (stated in the initial memorandum as October 2, 2023), particularly given the resulting tax liability for failure to submit data.

Response: CMS appreciates commenters' concerns regarding deadlines. Pursuant to sections 1191(d)(5)(A) and 1194(b)(2)(A) of the Act, Primary Manufacturers must submit the manufacturer-specific data described in sections 1193(a)(4)(A) and 1194(e) of the Act to CMS by October 2, 2023 for initial price applicability year 2026. CMS will use data submitted by the Primary Manufacturer and other interested parties when developing the initial offer for a selected

drug along with CMS analyses and assessments of evidence as described in section 50.2 of this guidance. CMS is abiding by the statutory deadlines in this revised guidance.

Comment: One commenter requested that CMS clarify that consideration of manufacturer average net unit price will not trigger a future renegotiation of MFP.

Response: Renegotiation is out of scope for this revised guidance for initial price applicability year 2026 and will be addressed in future guidance or rulemaking, as appropriate.

Establishment of a Single MFP for Negotiation Purposes (Section 60.1)

Comment: Some commenters expressed concern with CMS' proposal to use a 30-day equivalent supply to apply the MFP across dosage forms and strengths, particularly for drugs with irregular intervals, topicals, and drugs taken for acute symptoms. Some commenters requested that CMS provide alternative options, consult with manufacturers on the methodology to be used for a selected drug, and/or work with interested parties to better understand how 30-day equivalent supplies are calculated for those medicines that have irregular or varied dosing schedules.

Response: CMS appreciates commenters' feedback and requests for clarity. This revised guidance provides additional detail about how CMS will use the days' supply field in PDE data to calculate 30-day equivalent supply using the methodology described in 42 C.F.R. § 423.104(d)(2)(iv)(A)(2) when calculating the MFP ceiling (described in section 60.2 of this revised guidance) and using the WAC ratio for initial price applicability year 2026 to apply the MFP across dosage forms and strengths (described in section 60.5 of this revised guidance). For purposes of weighting across dosage forms and strengths, CMS believes that calculating a 30-day equivalent supply, using the days' supply field, is feasible for the high-expenditure, single source Part D drugs that might be subject to negotiation for initial price applicability year 2026. As described in section 60.3.2 of this revised guidance, when comparing prices of the therapeutic alternative(s) for purposes of informing a starting price for the initial offer, CMS may use an alternative methodology for calculating a 30-day equivalent supply when appropriate.

Limitations on Offer Amount (Section 60.2)

Comment: A few commenters opposed the approach described in the initial memorandum, which these commenters asserted would result in the ceiling being applied twice. One commenter agreed with CMS that an MFP should be calculated specific to dosage forms and strengths and account for the variation in prices "specific to each dosage form and strength of the selected drug," but proposed negotiating multiple MFPs per drug by calculating the ceiling for the lowest unit of measure of a selected drug and establishing a metric from which CMS may negotiate a percent of the MFP ceiling to arrive at the published MFP per lowest unit of measure.

Response: CMS appreciates commenters' feedback. CMS disagrees that the procedure that it described in the initial memorandum would have applied the MFP ceiling twice. However, after consideration of the comments, for initial price applicability period 2026, CMS has revised section 60.2 of the guidance to use the single ceiling per 30-day equivalent supply across all

dosage forms and strengths of the selected drug. This approach aligns with the concept of negotiating an MFP for a whole selected drug across multiple dosage forms and strengths (as identified on the list of NDC-11s of the selected drug in the CMS HPMS, per section 40.2 of this revised guidance) subject to a single MFP ceiling, and then applying that MFP across dosage forms and strengths as required under section 1196(a)(2) of the Act. As discussed in the response to comments under section 60.5 below, CMS intends to monitor the practical effect of its procedures for applying the MFP across the dosage forms and strengths of the selected drug to inform its use of its section 1196(a)(2) authority for initial price applicability years after 2026.

Comment: A few commenters recommended that CMS revise the non-FAMP calculation to use the four quarters of the fiscal year, as opposed to the calendar year, to align with the Veterans Health Care Act of 1992 and reduce burden on manufacturers. Relatedly, commenters recommended that CMS develop mechanisms to account for anomalies in the non-FAMP and to permit restatements of the average non-FAMP due to data or other errors identified after the fact.

Response: Section 1194(c)(6) of the Act defines average non-FAMP to mean "the average of the non-Federal average manufacturer price... for the 4 calendar quarters of the year involved." As a result, the statutory language requires that the calendar year be used to calculate the average non-FAMP. CMS has revised the definition of non-FAMP in Appendix C to clarify that any restatements of the non-FAMP made in any applicable manufacturer non-FAMP submissions to the Department of Veterans Affairs (VA) must be reflected in the non-FAMP submitted to CMS as part of the section 1193(a)(4)(A) manufacturer data submission. Section 50.1.1 and Appendix C of this guidance discuss how manufacturers should report non-FAMP to CMS in cases where there are no data or data are insufficient to calculate non-FAMP for at least one calendar quarter of 2021.

Comment: A few commenters requested clarification as to whether the time period for determining if a selected drug is an extended or long-monopoly drug runs to the start of the applicable initial price applicability year or selected drug publication date. Commenters noted that the initial memorandum is inconsistent, applying the length of time one way when describing the initial delay request made by a biosimilar manufacturer (i.e., to the start of the initial price applicability year) and another when determining the monopoly type as well as the applicable percent specified for the purposes of establishing a ceiling (i.e., to the selected drug publication date).

Response: CMS thanks these commenters for their careful review of the initial memorandum and appreciates their flagging this inconsistency. CMS has revised section 60.2.3 of this guidance to clarify that the time period for determining whether a selected drug is an extended- or long-monopoly drug runs to the start of the applicable initial price applicability year, as specified in sections 1194(c)(4)(A) and 1194(c)(5)(A) of the Act, respectively. However, CMS notes that, as discussed in section 60.2.3 of this guidance, the definition of "extended-monopoly drug" under section 1194(c)(4)(B)(ii) of the Act expressly excludes a selected drug for which a manufacturer has entered into an Agreement with CMS with respect to an initial price applicability year that is before 2030. CMS interprets this to mean that no selected drug will be considered an extended-monopoly drug for purposes of calculating the ceiling prior to initial price applicability year 2030.

Comment: A couple of commenters requested that CMS clarify whether unit refers to non-FAMP units or PDE units in the calculation of the annual non-FAMP for the dosage forms and strengths of the selected drug.

Response: CMS thanks these commenters for their careful review of the initial memorandum and appreciates the requests for clarification. CMS has revised section 60.2.3 of this guidance to clarify that PDE units will be used when averaging non-FAMP across NDC-11s. This is consistent with the use of PDE units to average NDC-9[15] non-FAMP amounts to a whole drug non-FAMP amount.

Comment: A few commenters disagreed with CMS' intent to use DIR data in calculating the "sum of the plan-specific enrollment weighted amounts" for purposes of determining the MFP ceiling. These commenters claim that the "plan specific enrollment weighted amount" is defined by reference to the Part D negotiated price, which does not include price concessions from manufacturers.

Response: Section 1194(c)(2)(A) of the Act states that the "plan-specific enrollment weighted amount" for a Part D or MA-PD plan with respect to a covered Part D drug is calculated using the negotiated price of the drug under the plan "net of all price concessions received by such plan or pharmacy benefit managers on behalf of such plan," and as such CMS plans to use DIR data, including information on manufacturer rebates and other price concessions collected through DIR reporting, in calculating the "sum of the plan-specific enrollment weighted amounts" under section 1194(c)(1)(B) of the Act.

Comment: One commenter recommended that CMS provide manufacturers with an opportunity to review and reconcile CMS' data for the MFP ceiling calculation for a selected drug. One commenter expressed concern that CMS is engaging in various conversion calculations to move from data at the NDC-11 level to the NDC-9 level to the whole drug level without providing sufficient detail to interested parties.

Response: CMS appreciates commenters' feedback. As discussed in section 60.4 of this revised guidance, CMS will provide the Primary Manufacturer information on the calculation of the statutorily-determined ceiling price. However, CMS is not able to provide manufacturers with all data used in ceiling calculations, as some of the calculations use proprietary information.

Comment: One commenter suggested that CMS should consider that the manufacturer-specific factors in section 1194(e)(1) of the Act could constitute the floor for price negotiations while the factors in section 1194(e)(2) could constitute the ceiling, keeping in mind the statutory ceiling in section 1194(c).

Response: As the commenter notes, section 1194(c) of the Act provides a specific formula for the calculation of the ceiling on the MFP for a selected drug, which is further described in section 60.2 of this guidance. The statute also requires CMS to consider the nine factors

[15] In this guidance, the NDC-9 refers to the first two segments of the NDC-11 that represent the labeler code and product portions of the NDC and indicate a drug's dosage, form, and strength regardless of the package size.

described in sections 1194(e)(1) and 1194(e)(2) when developing the initial offer. The statute does not direct CMS to use the manufacturer-submitted data or the section 1194(e)(2) data to establish a floor or ceiling, respectively, for price negotiations.

Methodology for Developing an Initial Offer (Section 60.3)

Comment: Many commenters recommended that CMS set the initial offer at or near the ceiling for all or a subset of selected drugs; for example, drugs that have provided therapeutic advancements, filled an unmet need, or otherwise demonstrated significant patient benefit; drugs under patent protection; small molecule drugs; and all drugs for initial price applicability year 2026 and for several subsequent price applicability years thereafter.

Response: CMS appreciates commenters' input. Section 1194(b)(1) of the Act instructs CMS to develop and use a consistent methodology and process for negotiations that aims to achieve agreement on the lowest MFP for each selected drug and in doing so, to consider the nine factors described in sections 1194(e)(1) and 1194(e)(2) of the Act. Offering the ceiling without a more thorough review of those statutory factors, including manufacturer-submitted data, may not achieve that objective and is inconsistent with the statutory directive.

Comment: CMS received many comments related to the identification of therapeutic alternative(s). Some commenters expressed concern regarding CMS' intent to use the price of the therapeutic alternative(s) in developing the offer starting point, including that drugs would be identified as the therapeutic alternative(s) based on cost rather than clinical appropriateness and that patients' needs will be overlooked when identifying the therapeutic alternative(s). A few commenters also noted that drugs in certain classes have few equivalent or substitutable alternatives. Some commenters were generally supportive of CMS' approach to identifying the therapeutic alternative(s), including limiting comparators to pharmaceutical alternatives, identifying therapeutic alternative(s) by indication, and considering off-label use when appropriate. However, a few commenters opposed CMS' approach to consider off-label use when identifying the therapeutic alternative(s). One commenter recommended that CMS identify no more than two comparators, one of which should be the lowest cost alternative and the other the most commonly used alternative. Another commenter stated that there is variability in how different entities define therapeutic categories, which results in different combinations of drugs in that therapeutic category. Many commenters recommended that CMS provide manufacturers, health care providers, and patients with the opportunity to participate in the selection of the therapeutic alternative(s).

Response: CMS appreciates commenters' feedback. As described in section 60.3.1 of this guidance, CMS will identify the therapeutic alternative(s) based on clinical appropriateness and consideration of various sources of evidence including clinical guidelines, peer-reviewed literature, drug compendia, and data submitted by manufacturers and the public, and not based on the cost of therapeutic alternative(s). CMS also may consult with FDA in the process of identifying other approved therapies for the same indication and with health care providers, patients or patient organizations, and academic experts to ensure that the appropriate therapeutic alternative(s) are selected. CMS expects that the negotiation offer/counteroffer exchange, as well as the negotiation meetings, will offer an opportunity for discussion about the therapeutic

alternative(s) with manufacturers. Further, as described in section 60.4 of this guidance, CMS will provide additional engagement opportunities for interested parties via manufacturer data submission-focused meetings and patient-focused listening sessions after the October 2, 2023 deadline for submission of information on the section 1194(e) data. CMS will provide additional information about these engagement opportunities at a later date.

Comment: Some commenters requested clarification as to whether generic drugs and biosimilars may be included as the therapeutic alternative(s). A few commenters opposed such inclusion because it would enable CMS to undervalue medicines. A few commenters expressed support for including generic and biosimilar therapeutic alternative(s) to establish the starting point for the initial offer.

Response: CMS appreciates commenters' feedback. As described in sections 60.3.1 and 60.3.2 of this guidance, CMS will consider the range of Part D net prices and/or ASPs of therapeutic alternative(s) for the selected drug, including prices of generic and biosimilar therapeutic alternative(s) if clinically appropriate.

Comment: Some commenters expressed support for CMS' proposal to consider the Part D net price or ASP of therapeutic alternative(s) for the selected drug as the starting point for the initial offer. A few commenters had concerns that considering Part D net prices would result in an inflated starting point and recommended CMS use the lowest net price or ASP as the starting point or the manufacturing cost and adjust based on clinical benefit. Another commenter recommended that CMS go beyond the net price of therapeutic alternative(s) to include all health system costs associated with the selected drug and its therapeutic alternative(s). One commenter recommended that if there are multiple therapeutic alternatives, CMS should use the highest-value alternative. Some commenters proposed additional options for the offer starting point, including using the MFP ceiling as the starting point or using comparative effectiveness to establish a price range or threshold for the initial offer.

Response: CMS understands concerns that using the Part D net price or ASP of a therapeutic alternative for the selected drug may result in a higher starting point; however, using net price(s) and ASP(s) of therapeutic alternative(s) enables CMS to start developing the initial offer within the context of the cost and clinical benefit of a group of drugs that treat the same disease or condition. As described in section 60.3.2 of this guidance, CMS will consider the range of Part D net prices and/or ASP(s) of therapeutic alternative(s), which may include consideration of generics and biosimilars as well as on- and off-label use (if such use is included in nationally recognized, evidence-based guidelines and recognized in CMS-approved Part D compendia). Some of the proposed alternatives for determining an offer starting point would not consider the clinical benefit provided by the selected drug relative to its therapeutic alternative(s). For example, if CMS were to use the MFP ceiling for the selected drug as the starting point, all adjustments to the starting point would be decreases, which could limit CMS' ability to adjust the starting point to recognize superior clinical benefit of the selected drug compared to therapeutic alternative(s). Rather than using manufacturing costs as a starting point, CMS will adjust the preliminary price based on manufacturer-specific data elements, including but not limited to the unit costs of production.

Comment: A couple of commenters indicated that CMS' intent to cap the offer starting point at the MFP ceiling is inconsistent with the statute. These commenters noted that the statute only requires that CMS not make an initial offer or accept a counteroffer that is above the statutory ceiling, and that limiting each step of the initial offer development process at the ceiling would lower the amount CMS could subsequently adjust based on other statutory factors (i.e., manufacturer-submitted data and clinical benefit).

Response: CMS appreciates commenters' feedback. CMS believes that the statute grants CMS flexibility to determine the amount of the initial offer, provided that the offer does not exceed the ceiling. Specifically, section 1194(b)(2)(F) of the Act requires that CMS may not make an offer or agree to a counteroffer for an MFP that exceeds the ceiling, but does not prohibit CMS from applying the ceiling when determining the starting point of the initial offer. Further, section 1194(b)(1) of the Act instructs CMS to develop and use a consistent methodology and process for negotiations that aims to achieve agreement on the lowest MFP for each selected drug. CMS' approach of using the Part D net price or ASP of the therapeutic alternative(s), as applicable, as the starting point to determine the initial offer only if it is lower than the ceiling is consistent with this directive. As discussed in section 60.3 of this revised guidance, CMS will further adjust the starting point by the other factors specified in section 1194(e) of the Act.

Comment: CMS received many comments regarding its intent to use the Federal Supply Schedule (FSS) or Big Four price[16] as an offer starting point for selected drugs with no therapeutic alternative(s) or for selected drugs with therapeutic alternative(s) with Part D net prices and/or ASPs greater than the statutory ceiling. Some commenters disagreed with CMS' approach, noting that these prices do not reflect market prices because of certain required discounts. Other commenters were concerned that if Medicare uses these prices, it could put upward pressure on the FSS and Big Four prices, or manufacturers would be less willing to provide price concessions to the Big Four.

Response: CMS thanks these commenters for their remarks and understands the concerns raised. As discussed in section 60.3 of this revised guidance, CMS will use FSS/Big Four prices in situations where the selected drug has no therapeutic alternative(s) or the price of the therapeutic alternative(s) exceeds the ceiling. CMS believes use of FSS/Big Four prices is appropriate in these situations, as these prices are publicly available and are reflective of prices available to other federal payers.

Comment: A commenter requested that CMS limit downward adjustments related to prior Federal financial support to an amount proportional to the amount of prior Federal financial support as a share of total investment in research and development (R&D) in the selected drug.

Response: CMS appreciates these suggestions. As described in section 60.3.4 of this guidance, for each selected drug, CMS may consider each factor outlined in section 1194(e)(1) in isolation or in combination with other factors. With respect to prior Federal financial support specifically,

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[16] The Big Four price is the maximum price a drug manufacturer is allowed to charge the "Big Four" federal agencies, which are the Department of Veterans Affairs (VA), Department of Defense (DoD), the Public Health Service, and the Coast Guard. See section 8126 of title 38 of the U.S. Code. See: https://www.cbo.gov/publication/57007.

CMS will consider the extent to which the Primary Manufacturer benefited from such Federal financial support with respect to the selected drug. For example, CMS may consider adjusting the preliminary price downward if funding for the discovery and development of the drug was received from Federal sources.

Comment: Many commenters indicated the definition of unmet medical need provided in section 60.3.3.1 of the initial memorandum was too narrow and should include situations where patients may not respond to or tolerate available treatments or disease burden remains significant. Some commenters suggested the definition should consider populations with disparities in outcomes or access. Some commenters proposed adopting the definition of unmet need from the FDA's expedited review programs. One commenter suggested looking to the National Comprehensive Cancer Network (NCCN) definition. A couple of commenters suggested looking to the framework used for New Technology Add-On Payments (NTAP). Many commenters recommended incorporating the patient perspective and/or broader societal or public health benefits when determining whether a selected drug fulfills an unmet medical need. A few commenters suggested reviewing unmet medical need across a product's lifecycle. A couple of commenters suggested reviewing unmet medical need at the time of FDA approval.

Response: CMS appreciates commenters' feedback and has reviewed the variety of definitions and frameworks suggested. After consideration of these comments, CMS revised the definition of unmet medical need to further align with section 1194(e)(2)(D) of the Act and FDA's "Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics" to include drugs that may have a therapeutic alternative but the existing alternative does not adequately address the condition or disease indicated (as described in section 60.3.3.1 of this revised guidance). Because the FDA guidance was issued in May 2014 and includes nonbinding recommendations, CMS will consider the guidance a reference and will consider any updates concerning unmet medical need that may be issued by FDA. CMS encourages patients and other interested parties to submit their perspective on how a selected drug meets an unmet medical need through the Negotiation Data Elements ICR submission and in the patient-focused listening sessions that will be held in Fall 2023, per revised section 60.4. More information on patient-focused listening sessions is forthcoming.

CMS also appreciates comments suggesting unmet medical need should be evaluated across a product's lifecycle. CMS will evaluate unmet medical need as of the time the section 1194(e)(2) data is submitted, which aligns with CMS' approach to reviewing manufacturer costs and data, therapeutic alternative(s), and other negotiation factors.

Comment: Many commenters supported using clinical benefit as the primary means for developing the initial offer. A few commenters stated CMS should deemphasize distribution costs when reviewing manufacturer-submitted data. A commenter suggested manufacturer-submitted data only be considered for selected drugs that provide fewer clinical benefits than the therapeutic alternative(s).

Response: CMS appreciates commenters' support for using clinical benefit to inform the initial offer. CMS is required to consider the factors described in section 1194(e) of the Act, as applicable to the selected drug, but there is flexibility to use these factors to inform the initial

offer and final offer, if applicable, in such a way as to recognize the unique characteristics of a selected drug. Regarding distribution costs, as described in section 60.3 of this guidance, CMS will adjust the starting point for the initial offer based on factors related to clinical benefit and then consider manufacturer-submitted data for additional adjustments, as appropriate. CMS also notes that the information submitted by the manufacturer and the public as well as information gathered through CMS' analysis will be considered in totality.

Comment: A few commenters suggested CMS should apply special considerations when evaluating orphan drugs or apply an upward adjustment for drugs with orphan indications, drugs that represent a significant therapeutic advance, and drugs that address an unmet medical need(s).

Response: As noted in the guidance, CMS will consider the totality of evidence when developing the initial offer. If a selected drug represents a significant therapeutic advance or addresses an unmet medical need, all other factors held constant, the initial offer for that selected drug would be higher than if this were not the case. CMS continues to explore whether there are additional actions that can be taken in the Negotiation Program to support orphan drug development, and CMS appreciates continued input from interested parties on this topic.

Comment: Many commenters requested additional detail on how negotiation factors, including those submitted by the Primary Manufacturer, would be weighted and how evidence would be evaluated and prioritized, stating additional transparency is needed. Many commenters suggested developing or adopting an existing framework for evaluating submitted information. A commenter requested CMS define "therapeutic advance."

Response: CMS appreciates commenters' feedback and recognizes the importance of balancing transparency and confidentiality in the negotiation process. CMS believes it is important to maintain flexibility when considering how each negotiation factor contributes to the initial offer and final offer, if applicable, which may be impacted by the unique characteristics of each selected drug, the populations each selected drug is intended to treat, and information that may emerge from meaningful discussions with manufacturers, patients, and patient representatives. Regarding therapeutic advance, CMS will determine whether a selected drug represents a therapeutic advance by examining improvements in outcomes for the selected drug compared to its therapeutic alternative(s) as described in section 60.3.3.1 of this revised guidance. CMS also included considerations for how evidence will be prioritized in section 50.2 of the initial memorandum and this revised guidance.

Comment: Many commenters recommended that real-world evidence,[17] information from clinical experts, and/or patient and caregiver perspectives be prioritized when reviewing negotiation factors. A few commenters suggested both qualitative and quantitative approaches be used to review negotiation factors and develop an initial offer. One commenter noted that CMS

[17] Real-world evidence is clinical evidence about the usage and potential health benefits or risks of a medical product derived from real-world data. Real-world data are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. From *Framework for FDA's Real-World Evidence Program*, December 2018. See: https://www.fda.gov/media/120060/download.

should consider the limitations of real-world evidence, particularly real-world evidence based on patient registry data and the limitations of data from electronic health records and billing records.

Response: CMS agrees with commenters on the importance of real-world evidence as well as the limitations of such evidence, as with any type of data. CMS also agrees with commenters on the importance of the perspective of clinicians, patients, and caregivers. CMS included real-world evidence and consultation with clinical experts and academic researchers in the initial memorandum and, as described in section 60.4 of this revised guidance, CMS will host patient-focused listening sessions that would be open to the public, including patients, beneficiaries, caregivers, consumer and patient advocacy organizations, and other interested parties, to share patient-focused input on therapeutic alternative(s) and other section 1194(e)(2) data regarding selected drugs. CMS may also consider the caregiver perspective to the extent that it reflects directly upon the experience or relevant health outcomes of the patient taking the selected drug. As noted in the initial and revised guidance, CMS will take a qualitative perspective when reviewing a selected drug and consider the evidence, including real-world evidence, clinical input, and patient and caregiver input, in totality. By employing a qualitative approach to information review rather than a more formulaic quantitative approach, CMS is able to preserve flexibility in negotiation, including the ability to consider nuanced differences between different drugs that might not be captured in a more thoroughly pre-specified quantitative approach.

Comment: A few commenters noted that CMS should include the caregiver experience and equity as factors in the negotiation process. A couple of commenters requested that for specific populations, CMS relax data prioritization standards to ensure underserved and underrepresented populations are considered. One commenter recommended that CMS prioritize studies that include individuals from diverse racial and ethnic backgrounds.

Response: CMS thanks these commenters for their feedback. Health equity is the first pillar of the CMS Strategic Plan, which builds health equity into the core functions of CMS, including the Negotiation Program.[18] As noted in the initial memorandum, CMS will consider information related to a selected drug within specific populations. In this revised guidance, CMS clarified that this includes underserved and underrepresented populations, as applicable, that may be experiencing disparities in health outcomes or access to the selected drug. As noted above, CMS will also consider the caregiver perspective to the extent that input reflects directly upon the experience or relevant health outcomes of the patient taking the selected drug. This information will be collected using the Negotiation Date Elements ICR and is open to the public. All applicable negotiation factors will be considered in totality for each selected drug.

Comment: Some commenters suggested that the negotiation factors be expanded to include adherence, convenience, societal impact, caregiver burden, independence, lost wages, travel expenses, costs to patients, medical costs, value of hope, cost of side effects, and other indirect costs. One commenter recommended that CMS de-prioritize or exclude indirect health benefits and instead focus solely on health outcomes to develop the initial offer.

Response: CMS agrees that factors such as adherence and convenience (as applicable to patient experience and outcomes) are important to consider for a selected drug. CMS views such factors

[18] See: https://www.cms.gov/cms-strategic-plan.

as directly related to patient experience and as such, considers these to be included in the factors outlined in the guidance. CMS appreciates commenters' suggestions to add broader societal, economic, and public health factors to those that will be considered during negotiation. Upon reviewing commenters' suggestions for additional factors, CMS revised the guidance to include consideration of both health outcomes and other outcomes when evaluating the benefit of the selected drug and therapeutic alternative(s). Outcomes such as changes to productivity, independence, and quality of life will be considered to the extent that these outcomes correspond with a direct impact on individuals taking the drug and are permitted in accordance with section 1194(e)(2).

Comment: Some commenters recommended using Multi-Criteria Decision Analysis (MCDA) as a framework for evaluating evidence related to a selected drug and its therapeutic alternative(s).

Response: CMS appreciates this suggestion. Due to the statutory timeline, conducting a full MCDA is not feasible. CMS will consider whether the general approach used in MCDA can serve as an informative framework for evaluating evidence.

Comment: A few commenters suggested that CMS share its literature review and other materials related to the selected drug and its therapeutic alternative(s) with the manufacturer of the selected drug.

Response: Per section 1194(b)(2) of the Act and this revised guidance, CMS will provide each manufacturer of a selected drug with an initial offer and a concise justification of the factors used to develop the offer.

Comment: Many commenters stated that CMS should not decrease the initial offer based on existing patents and exclusivities provided by the FD&C Act or PHS Act and recommended the initial offer be increased in cases where a drug has existing patents and exclusivities. Many commenters are concerned that a downward adjustment based on patents and exclusivities will stifle innovation, may impact patient access, disincentivize R&D, and work against the purpose of the patent system. A few commenters believe a downward adjustment based on patents and exclusivities exceeds CMS' statutory authority. A few commenters noted that CMS' action may constitute "a taking requiring just compensation" under the Fifth Amendment's Takings Clause and stated that patents are a constitutionally protected property right.

Response: CMS appreciates commenter feedback on adjusting the initial offer price based on patents and exclusivities provided by the FD&C Act or PHS Act ("exclusivities"). The statute explicitly directs CMS to consider data on approved patents and exclusivities in its determination of the amount of the initial offer. CMS does not believe that its implementation of this statutory mandate constitutes a taking or otherwise implicates or violates the Fifth Amendment Takings Clause. CMS also notes that the example provided in the initial memorandum was intended to provide an illustrative example of how such data could be considered in developing an initial offer. However, as discussed in section 60.3.4 of this revised guidance, following further consideration of the issue, CMS has omitted the example provided in the initial memorandum. This revised guidance clarifies CMS' belief that this information will support CMS' consideration of the 1194(e)(1) and 1194(e)(2) factors described in section 60 of this revised

guidance. For instance, patents and exclusivities may inform CMS' understanding of therapeutic alternatives and other available therapy for the purposes of adjusting for clinical benefit, including consideration of whether the selected drug represents a therapeutic advance or meets an unmet medical need. More specifically, in light of exclusivities, there may be no other available therapy aside from the selected drug that adequately addresses treatment or diagnosis of a condition; consideration of such information would be relevant to CMS' consideration of the extent to which the selected drug addresses an unmet medical need for that condition.

Comment: Many commenters requested that CMS develop additional opportunities for patient, caregiver, and clinician input throughout the negotiation process, particularly to provide input on therapeutic alternative(s) to the selected drug, patient-reported outcomes, health outcomes, whether the drug fulfills an unmet medical need, weighing evidence, and benefits and impacts of the selected drug. Many commenters requested a structured, standardized means for such input to be provided such as roundtables, an advisory or stakeholder panel, listening sessions, town halls, additional meetings, or creating a patient ombudsman to engage with interested parties. A few commenters pointed to FDA's Patient-Focused Drug Development program as one that CMS can adopt or model. Some commenters requested that patients be recognized in this revised guidance as subject matter experts. Some commenters requested that patients and clinical experts be included early and throughout the negotiation process to provide input on therapeutic alternative(s) and negotiation factors such as outcomes of importance and care preferences.

Response: CMS appreciates commenters' recommendation to incorporate additional opportunities for patient, caregiver, and clinician input. In this revised guidance, patients and caregivers have been added as interested parties with whom CMS may consult. CMS will host patient-focused listening sessions that will be open to the public, including patients, beneficiaries, caregivers, consumer and patient advocacy organizations, health care providers, and other interested parties to share patient-focused input on therapeutic alternative(s) and other data on the factors in section 1194(e)(2) for a selected drug and its therapeutic alternative(s). These patient-focused listening sessions will occur in Fall 2023 after the section 1194(e) data submission, which will give patients and other interested parties additional time to prepare their feedback. CMS may draw from the principles and strategies in FDA's "Patient-Focused Drug Development – Collecting Comprehensive and Representative Patient Input" guidance when facilitating patient-focused listening sessions. Additional information is forthcoming.

Negotiation Process (Section 60.4)

Comment: Some commenters suggested that interested parties should be allowed to submit new section 1194(e) data after the October 2, 2023 initial price applicability year 2026 deadline when there is good cause. Commenters also said that not allowing new data submission until the negotiation meetings could result in an inefficient process. One commenter also mentioned that some new data may be in formats that are not conducive to meetings, such as graphs and charts.

Response: CMS recognizes the interest of manufacturers to be involved early in the negotiation process beyond the section 1194(e) data submission due on October 2, 2023. CMS also recognizes the value of current and future patient and other interested parties' input in the negotiation process as well as throughout the implementation of the Negotiation Program. CMS

revised this guidance to allow for meetings after the section 1194(e) data submission deadline of October 2, 2023, where manufacturers can provide context for their submissions, and listening sessions where patients and interested parties can provide input as CMS begins reviewing data.

First, CMS would meet with the Primary Manufacturer of each selected drug once after the October 2, 2023 deadline so that the manufacturer has an opportunity to present its section 1194(e) data submission and share its perspective. These meetings will occur in Fall 2023. Primary Manufacturers may bring materials to facilitate discussion and CMS may request any materials presented afterwards. Primary Manufacturers are limited to sharing 50 pages (or a combination of pages, slides, and/or charts totaling 50 pages) of material, in order to focus the discussion on issues that can reasonably be discussed within the scope of the meeting, anticipating that these materials may contain cross-references to other material, particularly other material already submitted to CMS. This material is meant to provide context on the Primary Manufacturer's 1194(e)(1) submission and may also be used to share any new information regarding the section 1194(e)(2) data that has been identified following the October 2nd data submission.

Second, CMS will host patient-focused listening sessions for the selected drugs that would be open to the public, including patients, beneficiaries, caregivers, consumer and patient organizations, and other interested parties to share patient-focused input on therapeutic alternatives and other section 1194(e)(2) data regarding selected drugs. Interested parties may also use these listening sessions to orally share new information regarding the section 1194(e)(2) data that has been identified since the October 2nd deadline. These patient-focused listening sessions will occur in Fall 2023 after the section 1194(e) data submission deadline, which will give patients and other interested parties additional time to prepare their input. Additional information about these listening sessions will be shared in the future.

Manufacturers are required to provide information on the non-FAMP and information required to carry out negotiation (i.e., the section 1194(e)(1) data), by October 2, 2023 for initial price applicability year 2026. CMS expects Primary Manufacturers to submit information that is complete and accurate by this deadline. Information shared during the Primary Manufacturer meetings described above and materials shared afterwards should only contextualize the Primary Manufacturer's October 2nd section 1194(e)(1) submission; new section 1194(e)(1) data will not be considered. But, as described above, new information on section 1194(e)(2) data will be considered. Similarly, patients, beneficiaries, caregivers, consumer and patient advocacy organizations, and other interested parties may provide contextual information on their October 2nd section 1194(e)(2) data submission and/or share new section 1194(e)(2) data.

Comment: Some commenters recommended that CMS should allow negotiation meetings to happen throughout the negotiation period (i.e., between the publication of the selected drug list through the conclusion of negotiations), and not just in the situation when a manufacturer's counteroffer is rejected. A few commenters suggested specific periods during the negotiation process where CMS should hold meetings with manufacturers of selected drugs, such as after drug selection and prior to the initial offer.

Response: In response to comments requesting the opportunity to provide additional section 1194(e) data submissions to inform CMS' initial offer and negotiations after October 2, 2023, concerns about the tight timeline for data submission, and recommendations to remove any meeting caps and allow meetings throughout the negotiation period, CMS has revised this guidance to allow for manufacturer meetings and patient-focused listening sessions after the October 2, 2023 deadline. CMS would hold one meeting with the Primary Manufacturer of each selected drug to allow the Primary Manufacturer to provide context for the section 1194(e) data submission as CMS reviews the submitted data and develops its initial offer. The patient-focused listening sessions will be open to patients, beneficiaries, caregivers, consumer and patient advocacy organizations, and other interested parties and will invite attendees to share patient-focused input on therapeutic alternatives and other section 1194(e)(2) data regarding selected drugs. Manufacturer meetings and patient-focused listening sessions will occur in Fall 2023. CMS will schedule the meeting with the Primary Manufacturer once the selected drug list is published, and more information will be forthcoming from CMS regarding the patient-focused listening sessions after the selected drug list is published.

Comment: Some commenters stated that limiting negotiation meetings to a maximum of three meetings is restrictive and recommend that CMS allow for more exchanges throughout the negotiation period. One commenter asked that CMS make the meetings more transparent through recorded minutes, records of attendees, and allow any interested party to participate.

Response: The timeline for the negotiations extends from February 1, 2024, the statutory deadline for CMS to make the initial offer on a selected drug to a manufacturer, to July 31, 2024, a total of six months. The statutory deadline for the conclusion of negotiations is August 1, 2024. Up to three negotiation meetings with the manufacturer can occur. During these meetings, the Primary Manufacturer may provide context on the section 1194(e) data submission and additional relevant input on CMS' initial offer and the Primary Manufacturer's counteroffer as CMS reviews data and develops its final offer. Additional meetings (i.e., more than the maximum of three) during the negotiation period after the Primary Manufacturer's counteroffer, if applicable, are not feasible due to time constraints.

As part of the public explanation of the MFP, CMS will publish redacted information on any negotiation meetings that occur if a Primary Manufacturer's counteroffer is rejected.

As mentioned in the responses to the comments directly above, CMS is adding one meeting for each manufacturer and listening sessions for other interested parties after the data submission deadline and before CMS' initial offer is made. These meetings will allow Primary Manufacturers and other interested parties to share their perspectives as CMS reviews data and develops initial offers.

Comment: A few commenters suggested that CMS provide justifications for counteroffer responses and not just initial offers.

Response: CMS thanks these commenters for their feedback. Section 1194(b)(2)(D) of the Act requires that CMS provide the manufacturer with a written response to the manufacturer's counteroffer. CMS believes that if CMS declines the Primary Manufacturer's counteroffer and

offers a meeting, the first meeting between CMS and the Primary Manufacturer will provide an opportunity for CMS to explain its rationale for not accepting the manufacturer's counteroffer.

Comment: Some commenters asked that CMS' justification of its initial offer be meaningful and explain how CMS arrived at the offer. Commenters mentioned that the justification should include sources CMS referenced, section 1194(e) data considered and how they were weighted, therapeutic alternatives considered, interested parties consulted, and benefits and impacts of the drugs considered. One commenter asked that CMS issue a template for the initial offer justification in the final guidance.

Response: CMS thanks these commenters for their feedback and will consider the suggestion to include the information listed in the comment above when developing initial offers and concise justifications for selected drugs. Section 1194(b)(2)(B) of the Act directs CMS to provide a "concise justification" to the Primary Manufacturer when the initial offer is made. CMS will include information that helps the Primary Manufacturer understand the range of evidence and other information submitted pursuant to section 1194(e) that CMS found compelling in developing its initial offer. Because this information will be shared with the Primary Manufacturer, CMS believes the concise justification will be meaningful and provide information that will enable the manufacturer to develop its counteroffer. CMS does not plan on issuing a template for the initial offer or the concise justification but will release redacted information regarding the initial offer with the MFP explanation no later than March 1, 2025.

Comment: One commenter suggested that CMS issue a confidential report to manufacturers alongside the initial offer and concise justification. This confidential report would make manufacturers aware of section 1194(e)(2) data submitted by other interested parties and allow manufacturers to use that information in counteroffers, if applicable, and in future data submissions.

Response: CMS understands that manufacturers may benefit from awareness of section 1194(e)(2) data submitted by other interested parties during the negotiation period and that all interested parties would value receiving access to this information ahead of data submission for initial price applicability year 2027. CMS revised this guidance to state that CMS will aim to share with the Primary Manufacturer of a selected drug the section 1194(e)(2) data received from other interested parties during the negotiation period when feasible. These data will be appropriately redacted and will not include proprietary information, protected health information (PHI) / personally identifiable information (PII), or information that is protected from disclosure under other applicable law. If an MFP is reached during the negotiation period, CMS will issue the public explanation of the MFP no later than March 1, 2025. As part of this public explanation, CMS will share redacted information regarding the section 1194(e) data received, exchange of offers and counteroffers, and the negotiation meetings, if applicable. This redacted information will not contain any proprietary data, as described in section 40.2.1 of this guidance, PHI / PII, or other information that is protected from disclosure under other applicable law. However, as described in section 40.2.1, if a Primary Manufacturer chooses to disclose any material that is made public that CMS has previously deemed to be proprietary information of that Primary Manufacturer, CMS will no longer consider that material proprietary and will not redact it in the public explanation.

Comment: A few commenters asked CMS to commit to responding to counteroffers within 30 days of receipt. Commenters also recommended CMS give manufacturers at least 30 days to review and comment on CMS' response to counteroffers and asked CMS to consider these comments before setting the MFP.

Response: Section 60.4.3 of this revised guidance reaffirms the statement from section 60.4.4 of the initial memorandum that CMS will provide a written response to the manufacturer's counteroffer, if applicable, no later than 30 days after the receipt of the manufacturer's counteroffer. CMS made minor revisions to section 60.4.3 to clarify that CMS will respond in writing no later than 30 days after receipt of a manufacturer's counteroffer regardless of the nature of the response.

CMS declines to revise the guidance to allow manufacturers 30 days to review and comment on CMS' response to counteroffers. If a manufacturer's counteroffer is rejected, negotiation meetings with the Primary Manufacturer and CMS will span from approximately April 1, 2024 to June 28, 2024. This period exceeds 30 days and will give Primary Manufacturers the opportunity to comment on CMS' response to the counteroffer in negotiation meetings.

If applicable, CMS will issue a "Notification of Final Maximum Fair Price Offer" no later than July 15, 2024, and require Primary Manufacturers to respond to this final offer by July 31, 2024. Although this turnaround is less than 30 days, it will come at the end of approximately six months of negotiations (February 2024-July 2024) where there will have been ample opportunity for the Primary Manufacturer to review the initial offer, respond in writing via a counteroffer, and consider the discussions that occurred within the context of up to three negotiation meetings, including any additional proposals for an MFP made by CMS.

Comment: A couple of commenters recommended CMS establish a definition for "meeting" and consider adopting a policy similar to the 2017 FDA guidance "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products: Guidance for Industry," which details meeting criteria and has definitions for different tiers of meetings.

Response: CMS thanks these commenters for their feedback. CMS has updated the description of meeting criteria in section 60.4.3 of this guidance to provide more information on the number of permitted attendees, length of each meeting, meeting scope, and meeting logistics. CMS believes that the meetings as part of the negotiation process under the Negotiation Program have a different purpose than FDA's formal meetings under the user fee agreements and therefore has taken a different approach when defining its meeting standards.

Comment: One commenter suggested CMS allow Secondary Manufacturers to participate in the negotiation process, including negotiation meetings.

Response: CMS thanks this commenter for this feedback. As described in section 60.4.3 of this memorandum, negotiation meetings would be attended solely by representatives of both the Primary Manufacturer and of CMS. CMS will defer to the Primary Manufacturer to identify its preferred representatives it plans to have attend any negotiation meetings.

Comment: One commenter stated that if CMS and a manufacturer engage in bona fide negotiations that result in no agreement, then the MFP should be set at the ceiling.

Response: CMS believes that this suggestion does not align with the statute. The statute envisions a period of negotiations that are expected to result in an agreement between the two parties on MFP by a certain date. The statute does not provide a "default" option if negotiations are not successful. This recommendation is inconsistent with the framework of the statute and would undermine the purpose of the Negotiation Program if manufacturers are assured the ceiling as long as they engage in good faith efforts to negotiate on an MFP.

Comment: One commenter suggested CMS consider issuing further guidance in the future on how data will be used in the negotiation process to determine MFP, as this may promote reaching agreements during negotiations.

Response: CMS will consider the totality of evidence throughout the negotiation period, including when developing the initial offer, reviewing a possible counteroffer, and participating in negotiation meetings when applicable. CMS will leverage the negotiation data described in section 50 to inform the methodology described in section 60.3 and the negotiation process described in section 60.4. Additional documents, such as the various ICRs associated with the Negotiation Program and this revised guidance, provide more detail related to the negotiation process and how data will be used.[19]

Application of the MFP Across Dosage Forms and Strengths (Section 60.5)

Comment: Some commenters indicated that CMS' methodology for calculating the MFP and applying it across dosage forms and strengths is overcomplicated, arbitrary, and inconsistent with the statute. Some commenters also opposed CMS' proposal to use a 30-day equivalent supply to apply the MFP across dosage forms and strengths. A few commenters expressed support for CMS' approach to applying the MFP across dosage forms and strengths, including to new NDAs, BLAs, and NDCs.

Response: CMS appreciates commenters' feedback. The statute requires a single price negotiation to agree upon an MFP for a selected drug, and contemplates that CMS will 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." As such, CMS will identify one MFP for a selected drug, which it will base on the cost of the selected drug per 30-day equivalent supply, weighted across dosage forms and strengths.

Comment: Some commenters opposed CMS' proposed approach to apply the MFP across dosage forms and strengths by calculating a WAC ratio that represents the WAC of a given dosage form and strength compared to the WAC of the whole drug. A few commenters indicated

[19] For ICRs related to the Negotiation Program, see: https://www.cms.gov/inflation-reduction-act-and-medicare/medicare-drug-price-negotiation.

that WAC is a flawed measure because it does not reflect discounts and that it changes over time. A couple of commenters recommended that CMS consider other price metrics such as AMP.

Response: CMS appreciates commenters' concerns regarding the use of the published WAC. For initial price applicability year 2026, CMS will use the WAC ratio to apply the MFP across dosage forms and strengths of a selected drug and will monitor changes to WAC relative to other pricing data, as well as shifts in utilization across dosage forms and strengths. CMS appreciates the commenters' recommendation to use AMP, but is concerned that using AMP prices in place of WAC could potentially disclose manufacturers' proprietary data. CMS recognizes there may be other ways to apply the MFP to dosage forms and strengths and will monitor whether this policy serves the intent of the Negotiation Program. As noted throughout this revised guidance, the policies described for the Negotiation Program are for initial price applicability year 2026, and CMS may consider additional policies for future years of the Negotiation Program.

Comment: Some commenters requested that for purposes of transparency and clarity, CMS provide to manufacturers the data used in MFP calculations, include example calculations in guidance, and publish a decision-making framework.

Response: CMS agrees with commenters about the importance of clarity and transparency in MFP calculations. CMS believes the discussion in sections 60.2 and 60.5 of this revised guidance sufficiently describes the methodologies CMS will use to calculate a single ceiling for a selected drug and to apply the single MFP negotiated for a selected drug across dosage forms and strengths of the selected drug (as identified at the NDC-11 level on the list of NDC-11s of the selected drug in the CMS HPMS, per section 40.2 of this revised guidance) and as such, this revised guidance does not include example calculations. However, as discussed in section 60.4 of this revised guidance, CMS will provide to the Primary Manufacturer information on the calculation of the statutorily-determined ceiling and application of a single MFP across dosage forms and strengths. However, CMS is not able to provide manufacturers with all data used in MFP calculations, as some of the calculations use proprietary pricing information.

Publication of the MFP (Section 60.6)

Comment: Some commenters recommended that the public explanation of the MFP provide details on the negotiation process, what data were considered, and how they were weighted when arriving at the final MFP. Commenters also suggested CMS share information on methodologies, therapeutic alternatives, outcomes metrics, interested parties engaged, and comparative effectiveness research considered. Several commenters also requested CMS explain how patient experience data and real-world evidence were used and how unmet need was factored in when developing the MFP. Commenters also broadly recommended that the public explanation of the MFP be transparent and detailed.

Response: CMS believes that all interested parties should have a transparent understanding of the process and rationale that CMS and the Primary Manufacturer of the selected drug used when negotiating the MFP and how that reasoning evolved over time. In addition to the data elements required by law to be submitted by the Primary Manufacturer regarding the selected drug, CMS expects robust participation by interested parties in submitting information and participating in

the patient-focused listening sessions for the selected drugs. As required under section 1195(a)(1) of the Act, CMS will publish the public explanation of the MFP for each selected drug no later than March 1, 2025. The public explanation, as described in the revised section 60.6.1 of this guidance, will include a narrative explanation of the negotiation process that occurred with that manufacturer and redacted information regarding the section 1194(e) data received, exchange of offers and counteroffers, and the negotiation meetings, if applicable, in alignment with the confidentiality policy described in section 40.2. CMS will also strive to share the section 1194(e)(2) data submitted by the public with the Primary Manufacturer of a selected drug during the negotiation period. This data will be redacted as per the confidentiality standards described in section 40.2 and will not include proprietary information, PHI / PII, or other information that is protected from disclosure under other applicable law. CMS thanks these commenters for their feedback.

Comment: A few commenters recommended CMS make the publication of the MFP and explanation clear, accessible, and transparently available for the public. These comments mention ensuring the information is easy to read, easy to access, and developed in a consumer-friendly format. A couple of commenters suggested CMS include information on how beneficiaries can access the MFP and provide a process to follow if the MFP is not honored. One commenter suggested a webpage that provides the brand name (proprietary name) and generic name (non-proprietary name) for each selected drug where there is an MFP, MFPs for all dosage forms, and the dates the prices are in effect. Another commenter suggested providing a summary in the public explanation so that patients can understand the negotiation process and what to expect when procuring a medication with an MFP.

Response: CMS thanks these commenters for their feedback regarding the publication of the MFPs of the selected drugs and explanations of those MFPs. As described in section 60.6 of this revised guidance, CMS will publish the following on the CMS website by September 1, 2024 for all initial price applicability year 2026 selected drugs where an MFP was agreed upon: the selected drug, the initial price applicability year, and the MFP pricing file for that selected drug. The MFP file will contain the MFP as applied to each selected drug at the single MFP for a 30-day equivalent supply, NDC-9 per unit price, and NDC-11 per package price and will be updated annually to show the inflation-adjusted MFP for the selected drug. CMS will also publish on the CMS website: when a drug is no longer a selected drug and the reason for that change, and situations in which an MFP between a Primary Manufacturer and CMS is not agreed upon. No later than March 1, 2025, CMS will publish the public explanation of the MFP for each initial price applicability year 2026 selected drug. CMS is committed to providing accessible educational materials to beneficiaries, and the pharmacies, mail order services and other dispensers that serve them, about the MFPs for selected drugs and how they can report a violation if they do not believe that they were able to access the MFP for a selected drug.

Comment: Some commenters urged CMS to provide as much information as legally possible when issuing the public explanation of the MFP. These commenters stated that a high level of transparency will garner confidence that the negotiated MFP is the lowest price that CMS could obtain. One commenter asked that CMS release at minimum non-FAMP, R&D costs and recoupment, and unit costs of production, and distribution. Other commenters stated that the only

information that should be withheld from public explanations are R&D costs, unit costs of production, and certain net pricing information.

Response: CMS thanks these commenters for their feedback. CMS is committed to a negotiation process that is transparent and respects confidentiality of proprietary information. CMS appreciates the need to balance both transparency in the negotiation process to assure interested parties and the public that the negotiations were conducted in a fair manner, and that CMS attempted to achieve agreement on the lowest possible MFP for the selected price for Medicare beneficiaries, with the need to maintain the confidentiality of certain information, including manufacturers' proprietary data. As part of the public explanation of the MFP, CMS will release a narrative explanation of the negotiation process and redacted information regarding the section 1194(e) data received, exchange of offers and counteroffers, and the negotiation meetings, if applicable. All information that CMS publishes as part of the public explanation and any other public documents related to the MFP and negotiation process will abide by the confidentiality policy described in section 40.2 and redact proprietary information, PHI / PII, and information that is protected from disclosure under other applicable law.

Comment: One commenter expressed concern that CMS' definition of R&D costs and recoupment was too narrow and suggested that CMS broaden its scope for R&D costs for failed and abandoned products to include all products in the relevant disease state, not just products with the same active moiety / active ingredient as the selected drug. The commenter also felt that CMS' intent to compare R&D costs and global, net revenue reported resulted in an unfair comparison, as global revenue may include products and indications without FDA approval and be supported by separate clinical trials. The commenter asked, if CMS does not revise the definitions, that CMS explain the calculation methodology and inputs in all publications regarding the negotiation process, especially the public explanation of the MFP. The commenter also said CMS should note where its definitions of concepts may differ from others.

Response: CMS thanks this commenter for this feedback. CMS believes that for the purpose of the Negotiation Program, the definition of R&D costs is sufficiently broad, as reflected in the additional revisions and clarifications made to Appendix C, as noted below. To the extent R&D costs and recoupment inform the final MFP for a selected drug, this information and how it was used will be described, with appropriate redactions for proprietary information, as part of the public explanation of the MFP. For more information on CMS' consideration of R&D costs and recoupment definitions, please see the comment and response section for Appendix C.

Comment: One commenter recommended that CMS carefully evaluate what information to include in the public explanation of the MFP and consider whether requests not to disclose some information are to protect business interests or to undermine a transparent process.

Response: CMS thanks the commenter for this feedback. CMS is committed to a transparent process and will follow the confidentiality policy as described in section 40.2 in this revised guidance when developing the public explanation of the MFP. As discussed earlier in this section, as part of the public explanation, CMS will publish redacted information regarding the section 1194(e) data received, exchange of offers and counteroffers, and the negotiation meetings, if applicable. CMS' publication of this information will abide by the confidentiality

policy described in section 40.2 and redact proprietary information, PHI / PII, and information that is protected from disclosure under other applicable law.

Comment: One commenter suggested CMS limit its disclosure of information in the public explanation of the MFP to only information that is already public information.

Response: CMS thanks the commenter for this feedback. CMS is committed to a transparent process and will follow the confidentiality policy as described in section 40.2 in this revised guidance when developing the public explanation of the MFP.

Comment: Some commenters recommended that CMS allow manufacturers to review the explanation for the MFP before it is published so that manufacturers can provide comments and raise concerns about inadvertent disclosure of confidential information.

Response: CMS recognizes the interests of the manufacturers in making sure that certain data they provided to CMS for the negotiation process remain confidential. The statute does not require disclosure of the explanations of the MFP provided to manufacturers before the explanations are made public. Additionally, section 40.2 of this revised guidance describes the information from manufacturers that CMS will consider and maintain as confidential. CMS does not intend to share the explanations of the MFP with manufacturers before releasing the explanations to the public.

Comment: Many commenters suggested that CMS publish the explanation of MFP for all selected drugs with an MFP before the statutorily defined deadline for initial price applicability year 2026 of March 1, 2025. Some commenters recommended that CMS release the explanations along with the first set of MFPs for selected drugs on September 1, 2024, while other commenters did not specify a date. Commenters suggested an earlier publication so that interested parties can review the explanation and understand CMS' negotiation process ahead of submitting section 1194(e) data for initial price applicability year 2027 by the March 1, 2025 deadline.

Response: CMS thanks these commenters for their feedback. According to the statute, the public explanation of the MFP must be published no later than March 1, 2025 for initial price applicability year 2026 selected drugs. CMS understands commenters' interest in reviewing these public explanations in advance of the deadline for manufacturers of drugs selected for negotiation for initial price applicability year 2027 to submit their information, and will strive to release the public explanation of the MFP as soon as practicable. CMS notes that the policies for initial price applicability year 2027 will be shared in future guidance, including whether the policies adopted for section 1194(e)(2) submissions for initial price applicability year 2026 will apply in a similar manner for initial price applicability year 2027, and if so, when those submissions would be due.

Comment: One commenter recommended that, in addition to the public explanation of the MFP, CMS issue a summary report for all negotiated drugs in initial price applicability year 2026 and provide data on various negotiation outcomes. The commenter also suggested a summary report

and using SSR Health and IQVIA data may avoid confidentiality concerns around data from manufacturers.

Response: CMS thanks these commenters for their feedback. In response to comments, CMS revised section 60.6.1 of this guidance so that the public explanation of the MFP now includes a narrative explanation of the negotiation process and redacted information regarding the section 1194(e) data received, exchange of offers and counteroffers, and the negotiation meetings, if applicable. CMS' publication of this information will abide by the confidentiality policy described in section 40.2 and redact any proprietary information, PHI / PII, and information that is protected from disclosure under other applicable law. CMS believes that, with these revisions, the public explanation of the MFP will be sufficiently comprehensive and will achieve the goals suggested by the commenter.

Comment: One commenter recommended that CMS publish the NDCs along with the list of MFPs for selected drugs. One commenter recommended that when CMS releases MFPs and associated data, the list should include selected drug active moieties / active ingredients, their respective NDCs, and unit-level MFPs in a structured and machine-readable format. The commenter also suggested CMS provide additional context on how CMS will use NDC-9s to calculate the unit-level MFPs for every dosage form and strength of the selected drug and how the structure and formatting of the MFP file release will be affected by FDA's proposed rule on the NDC-12 format.[20]

Response: CMS thanks the commenter for this recommendation. CMS will publish by September 1, 2024 the MFP for each drug selected for initial price applicability year 2026 for which CMS and the Primary Manufacturer have reached an agreement on an MFP. Related to this requirement, CMS will publish the following on the CMS website: the selected drug, the initial price applicability year, the MFP file (which will contain the MFP as applied to each selected drug at the single MFP for a 30-day equivalent supply, NDC-9 per unit price, and NDC-11 per package price and will be updated annually to show the inflation-adjusted MFP for the selected drug), and the explanation for the MFP (published at a later date). The MFP file will be machine-readable and in a .CSV format. While CMS understands FDA has issued a proposed rule regarding changes to the format of FDA-issued NDCs, CMS does not believe that this proposed rule is relevant to the Negotiation Program or the establishment of the MFP for initial price applicability year 2026 because the policy, if finalized as proposed, would take effect five years after the final rule is published.

Exclusion from the Negotiation Process Based on Generic or Biosimilar Availability (Section 60.7) and Establishment of MFPs After the Negotiation Deadline (Section 60.8)

CMS solicited comment on these sections, but did not receive any comments that are not otherwise addressed elsewhere (see the "Bona Fide Marketing" section below).

[20] Revising the National Drug Code Format and Drug Label Barcode Requirements, July 25, 2022, available at https://www.federalregister.gov/documents/2022/07/25/2022-15414/revising-the-national-drug-code-format-and-drug-label-barcode-requirements

Removal from the Selected Drug List (Section 70)

Comment: Some commenters recommended CMS not apply the MFP to a selected drug if CMS determines that a generic drug or biosimilar is approved and marketed after the negotiation period but before the start of initial price applicability year 2026. One commenter recommended that CMS replace a selected drug that is removed from the selected drug list. One commenter recommended that, if a generic drug or biosimilar competitor of a selected drug receives FDA approval or licensure before the end of the negotiation period, CMS should establish a grace period after the negotiation period ends (e.g., 30 days) for CMS to consider whether that generic or biosimilar has been bona fide marketed. One commenter asserted that section 1192(e) of the Act requires CMS to remove a selected drug from the selected drug list if a generic drug or biosimilar is approved and marketed before the start of the applicable initial price applicability year.

Response: CMS thanks these commenters for the recommendations. Section 1192(c), not section 1192(e) of the Act, governs the circumstances under which a selected drug would be removed from the selected drug list after the date that that list is published. Section 1192(c) of the Act requires a selected drug that is included on the selected drug list to remain a selected drug for that year and each subsequent year beginning before the first year that begins at least nine months after the date on which CMS determines the statutory criteria in section 1192(c) are met unless CMS makes the determination before or during the negotiation period that a generic drug or biosimilar product for the selected drug is approved or licensed and is marketed. CMS interprets this requirement such that a drug included on the selected drug list published for initial price applicability year 2026 will remain a selected drug for initial price applicability year 2026 unless CMS determines on or before August 1, 2024 that a generic drug or biosimilar product for the selected drug has been approved for marketing by the FDA, and that bona fide marketing exists for the generic drug or biosimilar product. If CMS determines between August 2, 2024 through March 31, 2026 that bona fide marketing exists for the generic drug or biosimilar, the selected drug would cease to be a selected drug after 2026, and no MFP would apply for 2027.

MFP-Eligible Individuals (Section 80)

Comment: One commenter recommended CMS clarify whether an MFP-eligible individual that is enrolled in Part D can receive a selected drug at the MFP if it is paid under Part B. The commenter also requested clarification that the MFP must be made available to an individual with Part D coverage, even if they choose not to use their insurance. One commenter asked CMS to detail how it will ensure access to an MFP for individuals seeking to obtain a selected drug under Part B or Part C. A couple of commenters recommended that CMS clarify that the MFP for initial price applicability year 2026 only applies when the beneficiary receives a selected drug under Part D and that the MFP does not apply when the beneficiary is administered a selected drug under Part B. One commenter stated that the definition of MFP-eligible individual includes an individual enrolled in a Medicare Advantage (MA) Plan who is furnished or administered the selected drug for which payment may be made under Part B.

Response: CMS thanks these commenters for their recommendations. CMS has clarified in section 80 of the guidance that for initial price applicability year 2026, an MFP for a selected

drug must be provided to a Medicare beneficiary who uses their Part D plan (including an MA-PD plan under Medicare Part C or an Employer Group Waiver Plan, but not a plan that receives the Retiree Drug Subsidy) if Part D coverage is provided under such plan for such selected drug. For initial price applicability year 2026, the MFP is not required to be made available to a Medicare beneficiary who uses other sources of prescription drug coverage, prescription drug discount cards, or cash. CMS has made conforming changes throughout this revised guidance to clarify the scope of the requirement to provide access to the MFP for initial price applicability year 2026. For initial price applicability year 2026, CMS does not expect manufacturers to provide access to the MFP of a selected drug to hospitals, physicians, and other providers of services and suppliers with respect to MFP eligible individuals enrolled under Part B, including an individual who is enrolled in an MA plan.

Bona Fide Marketing (Sections 30.1, 60.7, 70, and 90.4)

Comment: Several commenters supported CMS' proposal to determine whether bona fide marketing exists for a generic or biosimilar to (1) determine whether a drug should be selected as a qualifying single source drug, (2) determine whether a selected drug should be deselected, and (3) monitor in cases where a drug is not selected or after it has been deselected to ensure that bona fide marketing is still occurring. These commenters agreed with this approach to ensure that the presence in the market of a generic drug means that there is meaningful competition. Other commenters said that such monitoring is warranted given manufacturers' past market behavior, and identified certain market-limiting agreements that some brand name manufacturers have entered into with generic drug manufacturers to limit the supply of the generic drug and thus inhibit competition. The commenters maintained that such arrangements justify CMS' proposal to determine whether bona fide marketing of a generic or biosimilar is actually occurring. Some commenters suggested that CMS require that manufacturers attest that they have not entered into any agreements that would limit the market share of the generic or biosimilar products, either implicitly or explicitly. One commenter also suggested that CMS require manufacturers submit all agreements provided to the Federal Trade Commission (FTC).

Response: CMS appreciates the support for its reading of the statute to contemplate a determination by the agency that a generic drug or biosimilar is being marketed on a bona fide basis as part of drug selection, deselection, and monitoring of the Negotiation Program. CMS agrees with these commenters that manufacturers' past behavior warrants CMS review on an ongoing basis as to whether a generic drug or biosimilar is being bona fide marketed. Absent this review, a generic drug or biosimilar manufacturer could launch into the market a token or de minimis amount of a generic drug or biosimilar for the selected drug and the manufacturer of that selected drug could claim that the MFP should no longer apply. This result would be inconsistent with the text of the statute as well as its purpose, which is to lower drug prices for Medicare through either negotiation or price competition. Consistent with this statutory purpose, section 1192(e)(1) of the Act requires that a generic drug or biosimilar "is … marketed" in order for a drug or biological product to be excluded from the definition of a qualifying single source drug, and section 1192(c)(1) likewise requires that a generic or biosimilar "is marketed" in order for a selected drug to be deselected. This terminology demonstrates that Congress contemplated that a generic or biosimilar must have a continuing presence on the market in order to affect CMS' determination whether a drug should be selected as a qualifying single source drug or whether a

selected drug should be deselected. Manufacturers are welcome and encouraged to provide information to CMS about the market for generic drugs or biosimilars for the selected drug.

Comment: Many commenters stated CMS lacks statutory authority to define "marketed" for purposes of selected drug eligibility under the statute, including sections 1192(e)(1), 1192(e)(2)(B), and 1192(c) of the Act[21] differently from the first market date reported by the manufacturer to the Medicare Part D Drug Inflation Rebate Program. Further, these commenters stated that CMS lacks statutory authority to address "bona fide marketing" to implement the statutory requirement of determining if a generic or biosimilar is "approved and marketed" or "licensed and marketed" under sections 1192(c) and (e) of the Act. These commenters also asserted that CMS lacks statutory authority to review product utilization or assess "robust and meaningful competition" as part of a determination of whether a generic or biosimilar is "marketed." In addition, these commenters stated that "marketing" is already a term defined in the pharmaceutical industry, including by FDA and CMS, noting that in Appendix C of the initial memorandum, marketing is defined as the "introduction or delivery for introduction into interstate commerce of a drug product." These commenters stated that any review of "marketing" for purposes of drug selection under section 1192(e) of the Act or deselection under section 1192(c) of the Act must be based on the first "market date." One commenter stated that the IRA is not intended to review market performance across an arbitrary period of time but rather whether a generic or biosimilar is marketed at the point in time of CMS' determination of drug selection. Additionally, some commenters suggested that CMS lacks statutory authority to monitor marketing after a drug/biological is determined ineligible for selection or removed from the selected drug list.

Other commenters suggested that CMS clarify the term "bona fide marketing" and its application to the Biosimilar Delay special rule and drug selection and deselection.

Response: Section 1192 of the Act requires CMS to make a determination whether a generic drug or biosimilar "is marketed" in order to determine whether a listed drug / reference product should be selected as a qualifying single source drug or whether a selected drug should be deselected. Congress purposefully used different terminology in section 1192 than it did in section 1860D-14B of the Act, which established the new Medicare Part D Drug Inflation Rebate Program. In the latter provision, Congress referred to the date that a drug is "first marketed." The absence of similar terminology in section 1192 demonstrates that, for purposes of the Negotiation Program, Congress contemplated that a generic drug or biosimilar would have a continuing presence on the market in order to affect the status of a listed drug / reference product.

Consistent with the purpose of the statute to lower prices for Medicare through negotiation or price competition, the statute contemplates that, in making this determination, CMS would consider whether meaningful competition exists on an ongoing basis between a listed drug or

[21] These determinations include whether a drug/biologic is eligible as a qualifying single source drug under section 30.1 of this guidance and whether a selected drug should be removed under sections 60.7 and 70 of this guidance because either (1) the listed drug has an approved generic drug (under section 505(j) of the Federal Food, Drug, & Cosmetic Act) or (2) the reference product has a licensed biosimilar (under section 351(k) of the Public Health Service Act) that is marketed pursuant to that approval or license.

reference product and a generic drug or biosimilar. This determination requires more than solely token or de minimis availability of the products. For example, CMS is aware of situations in which a manufacturer of a brand name drug or biologic has entered into a market-limiting agreement with a manufacturer of a generic drug or biosimilar, where the generic drug manufacturer agrees to limit production or distribution of the generic version of the drug, such that only a nominal quantity of product is allowed to enter the market. The result is a lack of meaningful price competition, and in that circumstance the generic drug or biosimilar is not "marketed" within the meaning of that term as it is used in the IRA.

Given the Negotiation Program is targeted at single source drugs and biologics that have been on the market for some time, for which no generic drug or biosimilar competition currently exists, the statutory directive would not be met if a qualifying single source drug were to avoid selection or be removed from the selected drug list where generic drug or biosimilar availability is limited by the Primary Manufacturer. It is consistent with the purpose of the statute to remove the MFP for a selected drug only when there is evidence that the selected drug or biological product is subject to meaningful competition. For example, Section 1192(e)(2)(A) of the statute provides that an "authorized generic" drug or biosimilar product "shall be treated as the same qualifying single source drug." Although an authorized generic may appear to be competing with the reference drug, authorized generics are typically marketed by the brand name drug company or another company with the brand company's permission, meaning that the relationship between the brand drug and its authorized generic is not meaningful competition in the way envisioned by Congress.

Whether such competition exists between a listed drug or reference product and a generic drug or biosimilar will depend on the totality of circumstances in existence at the time that CMS performs its function of making the determination whether a generic is being marketed. Accordingly, CMS maintains the approach in this guidance of determining if the manufacturer of the generic/biosimilar is engaged in bona fide marketing of the generic/biosimilar.

For a discussion of CMS' approach to the Biosimilar Delay rule, which under section 1192(f)(1)(A) requires CMS to make the statutory determination that there is a "high likelihood" that a biosimilar "will be licensed and marketed" within the relevant statutory time frame, see section 30.3.1 of this revised guidance.

Comment: Some commenters stated CMS lacks statutory authority to establish metrics of "sufficient quantities" and "market share" to assess bona fide marketing. These same commenters suggested these terms are vague and represent arbitrary requirements. A few commenters suggested specific thresholds that CMS could use to determine if meaningful competition exists. For example, one commenter suggested pulling a threshold from literature on competitive generic markets (which the commenter suggested is at least half of the market for small molecule drugs and at least 25 percent for biosimilars) and based on standardized prescriptions (e.g., a 30-day Part D supply) to estimate the generic drug penetration relative to the total volume of products dispensed in Medicare. Specifically, the commenter suggested the calculation of the number of standardized prescriptions dispensed for the generic product divided by the number of standardized prescriptions dispensed for the selected drug aggregated across all dosage forms and strengths, plus the number of standardized prescriptions dispensed for the

generic/biosimilar. Another commenter suggested a generic/biosimilar was effectively marketed when its market share is within a standard deviation of the mean for a given period of time since market entry and/or if its market share is at or above the mean of uptake at the point in time of CMS review regarding selection or deselection of the product.

One commenter requested CMS carefully consider what bar might be too high for a sufficient market share if certain factors of a market share are out of a manufacturer's control and limit competition, for example, this commenter said certain rebates can limit competitive entry.

Response: The statute requires CMS to determine whether a generic drug or biosimilar has been approved or licensed and is marketed pursuant to such approval or licensure for which the selected drug is the listed drug / reference product. Consistent with the purpose of the statute to lower prices for Medicare through negotiation or price competition, the statute contemplates that, in making this determination, CMS would consider whether meaningful competition exists on an ongoing basis between a listed drug or reference product and a generic drug or biosimilar. This determination requires more than solely token or de minimis availability of the products. However, CMS agrees with the commenter than CMS will not set a single specific numeric threshold for meaningful generic drug or biosimilar competition for selected drugs because CMS does not believe there is one specified threshold that would appropriately capture meaningful competition in the market for every selected drug. As described below, CMS will review multiple data sources to inform its determination whether a generic drug or biosimilar is being marketed on a meaningful basis.

CMS clarified in this revised guidance that these data sources will be reviewed holistically to determine if meaningful competition exists in the market for purposes of: (1) the identification of qualifying single source drugs for initial price applicability year 2026 (see section 30.1), (2) removal from the selected drug list before or during negotiation or after an MFP is in effect (see section 70), and (3) monitoring whether a manufacturer of a generic or biosimilar is engaged in bona fide marketing of a drug/biologic determined ineligible as a qualifying single source drug as described in section 30.1 of this guidance or removed from selection as described in section 70 of this guidance because the selected drug was the listed drug or reference biologic for a generic or biosimilar (see section 90.4). Manufacturers can provide evidence to CMS regarding the market for an approved generic drug or biosimilar that references its drug(s) to inform CMS' monitoring for bona fide marketing after a drug is not selected or after deselection.

Comment: Some commenters expressed concern regarding the time difference between the actual date of marketing and the date of CMS' determination of bona fide marketing using PDE data because of the time lag for sales to be captured in PDE data. One commenter suggested that a 12-month review period is arbitrary and CMS failed to explain why this period was selected to establish if a generic/biosimilar is marketed. Another commenter stated that the initial six months of PDE data after market entry reflect a limited uptake because Part D plan sponsors add the drug to their formulary at the 180-day CMS deadline for Part D formulary inclusion, or not at all, and additionally there is a gradual transition for product uptake by providers and patients. Another commenter stated that CMS was relying on the indicator that shows slowest generic drug uptake by relying on PDE data.

Response: CMS thanks these commenters for their feedback regarding the timing of data review. CMS chose to review data over this 12-month time period for initial price applicability year 2026 because it believes that this time range will provide a sufficient window of opportunity to demonstrate whether a generic drug or biosimilar is marketed on a continuing basis while still allowing for sufficient time for that data to inform the selected drug list published on September 1, 2023 in accordance with section 1192(a) of the Act.

While CMS appreciates commenters' concerns regarding the time lag between a generic drug's availability and the ability to detect it in PDE data resulting from filled Part D prescriptions, CMS understands that generally this timing lag is relatively short as Part D plans are instructed to submit original PDEs to CMS within 30 days following the date the claim is received or date of service (whichever is greater)[22] and the average turnaround time to date of submission is fewer days.

Under Medicare Part D rules, 42 C.F.R. § 423.120(b)(5)(iv) permits immediate substitution of a generic drug for a brand name drug on a Part D formulary, and section 1860D-4(b)(3)(I)(ii) of the Act permits removal of a selected drug if permitted by § 423.120(b)(5)(iv) (or any successor regulation). CMS expects that Part D plans would immediately substitute a generic version of the selected drug for the brand version of the selected drug. In addition, Part D sponsors may add new generic drugs and biosimilars to their formularies at any time. Thus, the Part D rules allow for relatively quick formulary substitution of generic drugs for selected drugs and the addition of generic drug and biosimilar versions of selected drugs such that both should be evident in the PDE data relatively quickly.

Nonetheless, to address commenters' concerns about the implications of any lags in timing of data used and its implications on drug selection, CMS will also review AMP[23] data at the time of the initial qualifying single source drug determination under section 30.1 of this revised guidance, any subsequent removal from selection under sections 60.7 and 70 of this revised guidance, and when monitoring whether a manufacturer of a generic drug or biosimilar is engaged in bona fide marketing of a drug/biologic determined ineligible as a qualifying single source drug as described in section 30.1 of this guidance or removed from selection as described in section 70 of this guidance because the selected drug was the listed drug or reference biologic for a generic drug or biosimilar under section 90.4 of this revised guidance. AMP data may capture sales transactions in the supply chain in situations when use of the generic drugs in Part D plans has not yet become evident in the PDE data. A drug's AMP units (which represent manufacturer sales to retail pharmacies and wholesalers that distribute to retail community

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[22] Timely Submission of Prescription Drug (PDE) Event Records and Resolution of Rejected PDEs, Centers for Medicare & Medicaid Services, October 6, 2011, available at: https://www.hhs.gov/guidance/document/revision-previous-guidance-titled-timely-submission-prescription-drug-event-pde-records.

[23] See definition at Section 1927(k)(1) of the Act. Average Manufacturer Price (AMP) is the average price paid to manufacturers by wholesalers for drugs distributed to retail community pharmacies and retail community pharmacies that purchase drugs directly from the manufacturers. AMP was established under the Omnibus Budget Reconciliation Act of 1990 for the Medicaid Drug Rebate Program and is calculated using manufacturer sales transaction data, which include cash discounts, volume discounts, and other reductions in the actual price paid to the manufacturer. CMS receives AMP data from manufacturers that have an agreement with the Secretary of HHS as specified under Section 1927(a)(1) for all Medicaid-covered outpatient drugs on a monthly and quarterly basis, as well as data on the number of units sold by the manufacturer during those time periods.

pharmacies) are reported monthly to CMS as part of a manufacturer's reporting responsibilities under the Medicaid Drug Rebate Program. PDE data and AMP data will be reviewable once the generic drug is listed in the FDA Orange Book (using at least one dosage form and strength of the selected drug as the listed drug) or the biosimilar is listed in the FDA Purple Book (using at least one dosage form and strength of the selected drug as the reference product).

Comment: A few commenters requested CMS include other data sources in addition to PDE data, such as data from NADAC, IQVIA, and DailyMed data; determinations of national market share; presence at distributors and in group purchasing organization (GPO) contracts; and presence on formularies, to determine the presence of a marketed generic or biosimilar for the selection and/or deselection of a drug or biologic. One commenter requested that CMS permit manufacturers to certify the status of the marketing of generic drugs and biosimilars and determine this marketing status on an ongoing basis.

Response: CMS thanks these commenters for these suggestions of additional sources that may include useful information to demonstrate bona fide marketing of a generic drug or biosimilar. The determination whether a generic drug or biosimilar is being bona fide marketed on an ongoing basis is a totality-of-the-circumstances inquiry that will not necessarily turn on any one source of data. Manufacturers of selected drugs can provide evidence to CMS regarding the market for the generic drug or biosimilar versions of their selected drug(s) to inform CMS' monitoring for bona fide marketing before drug selections are made, or after deselection. In addition to also reviewing AMP data, given commenters' suggestions to include additional examples of such other data that may be used, CMS clarified in sections 70 and 90.4 of this guidance (with application to sections 30.1 and 60.7 by way of cross-reference to the discussion of bona fide marketing), that CMS will use multiple sources, including but not limited to, the examples as described in sections 70 and 90.4 of this revised guidance to determine if bona fide marketing exists of the generic drug or biosimilar under review. This monitoring will ensure that drugs and biologicals ineligible for selection or removed from selection are subject to competition from generic drugs and biologicals that are marketed on a meaningful basis. CMS retains the right to consider other data in monitoring if manufacturers of the applicable generic drug or biosimilar continue to engage in bona fide marketing once a selected drug is deselected.

Comment: A few commenters encouraged CMS to monitor for manufacturing and/or marketing arrangements that intend to limit generic competition. One commenter suggested that a drug or biologic should remain eligible as a selected drug, so long as the drug or biologic otherwise qualifies, in the presence of limited distribution agreements. Another commenter suggested CMS publish arrangements that CMS views as limiting competition as a component of monitoring bona fide marketing. A couple of commenters stated that monitoring of market competition is not within CMS' authority and cited FTC and FDA regulatory frameworks to address biosimilar and generic competition.

Response: CMS thanks these commenters for these suggestions. CMS believes that limited-distribution agreements can in fact limit the supply of an available generic drug. CMS reiterates that, for the purposes of the Negotiation Program, the statute instructs CMS to make a determination whether a generic drug or biosimilar "is marketed," which requires a determination whether the generic drug or biosimilar has a continuing presence on the market.

Congress used this language in furtherance of the purpose of the Negotiation Program, which is to lower costs for Medicare through negotiation or price competition. The statute accordingly contemplates that CMS' determination will turn on a finding whether meaningful market competition for such given generic drug or biosimilar biological product exists. While these market-limiting agreements may make CMS aware of a limitation on meaningful market competition, these agreements do not necessarily inform the agency whether such a limitation is manifesting itself in the marketplace. For this reason, CMS intends to monitor actual conditions in the marketplace through PDE and AMP data. However, as commenters suggest, CMS may consult with FTC to identify the types of agreements or arrangements that limit competition. FDA does not receive agreements of this type in the normal course of its operations.

Comment: One commenter asked what action might result if CMS determines through monitoring that a generic drug/biosimilar manufacturer is not engaging in bona fide marketing after CMS determined that there was an applicable generic drug/biosimilar for which the manufacturer was engaged in bona fide marketing.

Response: If the reason for disqualification as a qualifying single source drug is removed, the drug/biologic could be eligible for negotiation in a future price applicability year.

Comment: One commenter requested CMS evaluate whether its monitoring approach accurately captures true competition and whether any specific types of drug marketing/distribution agreements limit generic competition and include in this review the impact on payers, providers and insurers. A few commenters generally expressed concerns about potential impacts they suggested that the Negotiation Program might have on generic drug markets, which they suggested could broadly include reducing the impact to a manufacturer of being the first filer for generics, promoting pricing via negotiation in lieu of market competition, or deterring generic competition and increasing drug pricing costs to payers in certain drug market segments.

Response: CMS thanks these commenters for their input and will keep these comments in mind as CMS implements the Negotiation Program and monitors for bona fide marketing over time.

Monitoring Compliance and Civil Monetary Penalties (Sections 90.1 and 100)

Comment: Many commenters requested additional details regarding the scope and amount of the CMPs, detailed procedures for determining violations and imposing fines, and a review and appeal process for determinations of noncompliance prior to the imposition of CMPs and initiation of the procedures described in section 1128A of the Act. Additionally, some commenters suggested CMS undertake notice and comment rulemaking to provide the process steps and requirements of involved parties prior to imposing any CMPs, and a few commenters requested that CMS use a single notice and comment rulemaking process to capture all instances of CMP triggers under the IRA. A few commenters instructed CMS to look to examples of CMP application in other CMS programs, including Medicare Advantage and the HHS Office of the Inspector General (HHS OIG), when establishing its procedures for the Negotiation Program. A couple of commenters suggested that the dollar amount required by the IRA for a CMP requires rulemaking under the Excessive Fines Clause of the Eighth Amendment of the U.S. Constitution. A few commenters requested a delay in the implementation of CMPs until rulemaking occurs.

Response: CMS appreciates the concern for ensuring that administration of CMPs under section 1197 of the IRA and in accordance with the requirements of section 1128A of the Act is achieved via defined procedures, and appreciates the suggestions offered by commenters. In this revised guidance, CMS has provided additional information about compliance violations that may result in CMPs being issued; the notification process surrounding compliance violations, including reminders, warnings, Notices of Potential Noncompliance, and formal CMP Notifications; and has provided a series of informative example scenarios on the scope and calculation of CMPs when applicable. CMS has also added detail to the CMP Notification process, following the requirements of section 1128A of the Act. CMS directs commenters to section 100 of this guidance for additional information. CMS reviewed examples of CMP processes in other CMS programs to develop the procedures outlined in this guidance. The amounts of CMPs are defined in section 1197 of the IRA and will be applied accordingly. CMS defines the start date and end dates for calculating violations in section 100.2 of this revised guidance.

Sections 11001(c) and 11002(c) of the IRA provide that the Secretary "shall implement" the Negotiation Program "for 2026, 2027, and 2028 by program instruction or other forms of program guidance." Thus, the initial memorandum is not subject to the notice-and-comment requirement of the Administrative Procedure Act or the Medicare statute. Section 1197 of the Act indicates violations that warrant a CMP. This guidance is consistent with the statutory requirement to use program guidance to implement the Negotiation Program for 2026, 2027, and 2028 and to impose certain penalties for violations of the Negotiation Program.

Comment: Some commenters requested that CMS share information with the Primary Manufacturer in advance of the notice of imposition of a CMP and permit the Primary Manufacturer to cure the violation for which a CMP could be imposed. Some commenters also requested a reasonable time period be specified for this cure period and a process be provided to appeal a finding of noncompliance, including as a means to safeguard against a perceived or actual legal or factual error of CMS.

Response: CMS has added in this revised guidance additional details about how Primary Manufacturers will have an opportunity for corrective action in applicable circumstances. For example, CMS revised section 100.2 of this revised guidance to clarify that CMS may request additional information to administer or monitor compliance with the Negotiation Program in accordance with section 1193(a)(5) of the Act. In addition, CMS will issue a written reminder of the impending deadline for submission of information to include a warning of potential liability for a CMP upon failure to comply with the deadline.

Comment: A few commenters expressed support for the IRA's inclusion of CMPs to support the negotiation of the MFP.

Response: CMS thanks these commenters for their feedback.

Comment: Some commenters raised concerns regarding the application of CMPs to Primary Manufacturers due to the actions of a Secondary Manufacturer that does not provide data

required under section 1194(e)(1) of the Act or the action of other third parties, including pharmacies and providers, that do not provide access to the MFP for MFP-eligible individuals. A few commenters requested CMS limit the imposition of CMPs to only a Primary Manufacturers' actions, or alternatively, refrain from enforcement of the CMP on a Primary Manufacturer for a third party's actions in initial price applicability year 2026. One commenter suggested a Primary Manufacturer be able to raise a defense against a CMP when the violation at issue was committed by a Secondary Manufacturer. A few other commenters supported monitoring and imposition of CMPs on third parties via the Primary Manufacturer, and one commenter encouraged CMS to monitor Secondary Manufacturers directly.

Response: CMS appreciates commenters' feedback regarding the imposition of a CMP on the Primary Manufacturer based on the actions of a Secondary Manufacturer or other third party. Per section 40 of this revised guidance, a Secondary Manufacturer is defined as either (1) a manufacturer listed in an NDA or BLA for the selected drug or (2) an entity that has entered into an agreement with the Primary Manufacturer to market the selected drug. A Secondary Manufacturer will include any manufacturer of any authorized generics and any repackager or relabeler of the selected drug that meet these criteria. As such, a Primary Manufacturer may be required to request data from a Secondary Manufacturer including non-FAMP, current unit costs of production and distribution, and certain market data elements. As described in section 1193 of the Act (described in section 40 of this revised guidance) and included in the Manufacturer Agreement, the Primary Manufacturer is also responsible for ensuring access to the MFP for MFP-eligible individuals and to pharmacies, mail order services, and other dispensers that dispense the selected drug to an MFP-eligible individual. Because CMS is entering into the Agreement with the Primary Manufacturer, it is the Primary Manufacturer that will be responsible for adhering to the terms of the Agreement. CMS believes the Primary Manufacturer, based on its arrangements with Secondary Manufacturer(s), can reasonably ensure that the Primary Manufacturer can comply with its Negotiation Program obligations with regards to data submission and ensuring the availability of the MFP for the selected drug sold by a Secondary Manufacturer(s). CMS is not aware of circumstances where a Secondary Manufacturer can operate without a formal arrangement of the Primary Manufacturer, through which the Primary Manufacturer can ensure compliance by the Secondary Manufacturer.

As is clarified in section 100 of this revised guidance, CMS will provide an opportunity for corrective action in certain instances of potential violation prior to imposing CMPs, which may provide Primary Manufacturers an opportunity to mitigate noncompliance related to Secondary Manufacturers in applicable situations.

Comment: One commenter requested CMS identify a pathway by which third parties could provide information regarding potential violations to CMS for investigation, while another commenter suggested an online form and toll-free phone number be established for consumer complaints on MFP availability.

Response: CMS appreciates commenters' feedback. CMS will establish a dedicated telephone line and/or e-mail inbox for interested parties to report any perceived MFP availability violations. Section 90.1 provides additional information regarding monitoring of manufacturer compliance. CMS anticipates providing more information on public monitoring in the future.

Comment: Several commenters requested CMS provide information about how CMS will interpret the term "knowingly" with regard to knowingly providing false information under section 100.3 of this guidance and as applicable to violations of the Agreement under section 100.2 of this guidance. Some commenters requested that CMS interpret "knowingly" based on a plain meaning of the term or uses by other CMS programs, OIG and the False Claims Act, while others requested CMS require "actual knowledge" of the act or omission.

Response: CMS appreciates these comments. After considering the comments received, CMS has adopted a standard for "knowingly" within the context of the Negotiation Program that conforms with the HHS OIG definition at 42 C.F.R. § 1003.110. Specifically, "knowingly" is interpreted to mean that a person, with respect to an act, has actual knowledge of the act, acts in deliberate ignorance of the act, or acts in reckless disregard of the act, and no proof of specific intent to defraud is required. CMS adopts this standard for "knowingly" in section 100.3 of this revised guidance for purposes of whether a manufacturer knowingly provides false information under the procedures to apply the aggregation rule in section 1192(d)(2)(B) of the Act for the Small Biotech Exception and whether any Biosimilar Manufacturer knowingly provides false information under the procedures to apply the aggregation rule in section 1192(f)(1)(C) of the Act for the Biosimilar Delay, as provided in section 1197(d) of the Act.

In applying CMPs, CMS intends to use discretion such that CMPs are reserved for instances of substantive noncompliance. These violations do not necessarily require the violation to be "knowing." Based on statutory requirements, CMS has clarified in section 100.2 that CMS maintains the authority to issue CMPs for substantive violations of the Agreement even in cases that violations are not "knowing."

Comment: Several commenters raised concerns that the detailed and numerous Primary Manufacturer data submission requirements under the Agreement will result in violations of compliance unintended by the Primary Manufacturer unless CMS allows for Primary Manufacturers to submit data based on a reasonable assumption of the IRA statutory data requirements.

Response: CMS appreciates commenters' feedback regarding the perceived potential for CMP liability based on unintended noncompliance with data submission requirements as set forth in section 1194(e)(1) and section 50 and Appendix C of the initial memorandum. As previously noted, CMS clarified in section 100 of this revised guidance that CMS will provide manufacturers with an opportunity, via the Notice of Potential Noncompliance, for corrective action in certain instances of potential violation prior to determining whether to impose a CMP. CMS has also provided responses regarding data submissions within the responses to Appendix C comments, including revisions to Appendix C definitions in response to commenters' requests for clarifications (e.g., unit type for non-FAMP, patents to be included). CMS also directs commenters to the 30-day notice for public comment on the Negotiation Data Elements ICR (CMS-10847 / OMB 0938-NEW), which incorporates revisions to instructions in response to comments CMS received in response to the 60-day notice for public comment. CMS is not adopting the recommendation that Primary Manufacturers submit a statement of reasonable assumptions with submissions under section 1194(e)(1) of the Act or otherwise use reasonable

assumptions in lieu of the definitions in Appendix C of this revised guidance. Submitted data must align with the instructions in CMS' Negotiation Data Elements ICR and the definitions in Appendix C of this guidance to ensure that the data submitted by Primary Manufacturers are based on consistent definitions and scope.

Part D Formulary Inclusion of Selected Drugs (Section 110)

Comment: Many commenters expressed support for requiring selected drugs to be included on Part D formularies. Several other commenters noted that the IRA does not detail how selected drugs should be included on formularies; therefore, CMS should confirm plan formulary flexibilities for selected drugs. A few commenters also requested CMS clarify when the formulary inclusion requirement would not apply, such as when a selected drug is excluded from negotiation because of the introduction of a generic or biosimilar competitor. Additionally, a couple of commenters expressed concern that mandating inclusion of selected drugs on Part D formularies—without establishing guardrails to ensure beneficiary access—could create perverse incentives because plans could place selected drugs on less favorable tiers compared to non-selected drugs. Finally, a couple of commenters requested CMS clarify that it will not require that Part D formularies include every dosage form and strength of a selected drug, noting that plans could comply with the IRA if only one dosage form and strength of the selected drug is included. One commenter stated Congress did not intend that every dosage form and strength of a selected drug be included on formularies.

Response: CMS appreciates commenters' feedback and agrees with commenters about the importance of ensuring meaningful beneficiary access to selected drugs and their MFPs and ensuring that plans do not engage in gaming behavior. CMS shares concerns that Part D sponsors may be incentivized in certain circumstances to disadvantage selected drugs by placing selected drugs on less favorable tiers compared to non-selected drugs, or by applying utilization management that is not based on medical appropriateness to steer Part D beneficiaries away from selected drugs in favor of non-selected drugs. CMS expects Part D sponsors to provide their enrollees with meaningful access to selected drugs and will use its comprehensive formulary review process to assess any practices that may undermine beneficiary access to selected drugs, as discussed in section 110 of this guidance. CMS maintains a robust, clinical formulary review process to ensure that all Part D plan formularies comply with statutory and regulatory requirements, including the requirement under section 1860D-11(e)(2)(D)(i) of the Act that CMS may only approve a Part D plan if it "does not find that the design of the plan and its benefits (including any formulary and tiered formulary structure) are likely to substantially discourage enrollment by certain Part D eligible individuals under the plan." Further, if CMS identifies that Part D sponsors are not providing beneficiaries with meaningful access to selected drugs, CMS may consider implementing new requirements for future contract years. CMS believes this approach will provide Part D sponsors with the flexibility to continue to manage costs when clinically appropriate while allowing CMS to monitor practices that may undermine enrollee access to selected drugs and inform further action, as necessary.

Section 1860-D-4(b)(3)(I) of the Act requires Part D plan formularies to include each covered Part D drug that is a selected drug under section 1192 of the Act for which an MFP is in effect with respect to the year. Accordingly, all dosage forms and strengths of the selected drug that

constitute a covered Part D drug and for which the MFP is in effect must be included on formulary. In response to the comments requesting clarification on when the formulary inclusion requirement would cease to apply, CMS refers readers to section 70 of this revised guidance, which, in accordance with section 1192(c) of the Act, details when a selected drug will cease to be a selected drug because CMS determines that a generic or biosimilar competitor to the selected drug has been approved or licensed and marketed pursuant to such approval or licensure. CMS notes that, as specified by section 1860D-4(b)(3)(I)(ii) of the Act, nothing shall prohibit a Part D sponsor from removing a selected drug from a formulary if such removal would be permitted under 42 C.F.R. § 423.120(b)(5)(iv) (or any successor regulation).

Comment: A couple of commenters stated CMS should require selected drugs to be placed on lower (preferred) formulary tiers, noting that this would reduce out-of-pocket costs for beneficiaries. A couple of commenters recommended CMS ensure parity between selected drugs and non-selected drugs, such as requiring plans to cover selected drugs on the most favorable tier as any brand name drug in the therapeutic class. One commenter stated CMS should require plans to place selected drugs on lower or equivalent tiers as their competitors. A few commenters indicated that selected drugs should be placed on formulary tiers with copayments rather than coinsurance to help beneficiaries plan for their drug expenses. One of these commenters added CMS should prohibit plans from placing selected drugs on tiers that require coinsurance. Finally, one commenter recommended CMS use the specialty tier cost threshold to determine tier placement of selected drugs. Specifically, selected drugs with monthly costs less than the specialty tier threshold could be placed on the lowest generic tier and selected drugs with monthly costs greater than the threshold could be placed on higher copayment tiers.

Response: CMS appreciates commenters' feedback. For contract year 2026, CMS is not implementing explicit tier placement requirements for selected drugs, but section 110 of this revised guidance indicates how CMS will use its formulary review process to assess potentially concerning review findings. CMS generally expects that Medicare beneficiaries taking selected drugs will benefit from the lower negotiated MFPs. While CMS understands that not all selected drugs and drug classes will present Part D sponsors and their Pharmacy & Therapeutics (P&T) Committees with the same formulary considerations and might not warrant the same formulary placement in all situations, CMS is concerned that Part D sponsors may be incentivized in certain circumstances to disadvantage selected drugs by placing selected drugs on less favorable tiers compared to non-selected drugs. To help ensure that beneficiaries have meaningful access to selected drugs and consistent with the agency's statutory obligation to monitor plan compliance with all applicable formulary requirements, CMS will use its formulary review process to assess any instances where Part D sponsors place selected drugs on non-preferred tiers or where a selected drug is placed on a higher tier than non-selected drugs in the same class. As discussed in section 110 of this revised guidance, as part of the annual bid review process, CMS will expect Part D sponsors to provide CMS with a reasonable justification to support the submitted plan design that includes any such practices. This justification should address applicable clinical factors, such as clinical superiority, non-inferiority, or equivalence of the selected and non-selected drugs, as well as the plan design's compliance with applicable statutory and regulatory requirements (e.g., the requirement to have a cost-effective drug utilization management program that bases decisions on the strength of the clinical evidence and standards of practice). As CMS reviews Part D plan formularies to ensure they comply with statutory and regulatory

requirements, pursuant to section 1860D-11(e)(2)(D)(i) of the Act, CMS will only approve a Part D plan bid submitted by a Part D plan sponsor if CMS does not find that the design of the plan and its benefits (including any formulary and tiered formulary structure) are likely to substantially discourage enrollment by certain Part D eligible individuals under the plan. CMS believes this approach will provide Part D sponsors with the flexibility to continue to manage costs through tier placement in a clinically appropriate manner, while allowing CMS to monitor practices that may undermine beneficiary access to selected drugs and inform new requirements for future contract years.

Comment: Many commenters expressed concern that plans will use utilization management not based on medical appropriateness to steer Part D beneficiaries away from selected drugs in favor of non-selected drugs that may be associated with higher rebates. Therefore, commenters suggested CMS should limit or prohibit utilization management for selected drugs. A few commenters asserted that maintaining the ability to use utilization management will best ensure that plans can negotiate effectively with interested parties to lower prescription drug costs.

Response: CMS appreciates commenters' feedback. For contract year 2026, CMS is not implementing explicit utilization management requirements for selected drugs, but section 110 of this revised guidance indicates how CMS will use its formulary review process to assess potentially concerning review findings. CMS shares the commenters' concerns that Part D sponsors may be incentivized in certain circumstances to disadvantage selected drugs by applying utilization management that is not based on medical appropriateness to steer Part D beneficiaries away from selected drugs in favor of non-selected drugs. To help ensure that beneficiaries have meaningful access to selected drugs and consistent with the agency's statutory obligation to monitor plan compliance with all applicable utilization management requirements, CMS will use its formulary review process to assess any instances where Part D sponsors require utilization of an alternative brand drug prior to a selected drug with an MFP (i.e., step therapy) or where Part D sponsors impose more restrictive utilization management (i.e., step therapy and/or prior authorization) for a selected drug compared to a non-selected drug in the same class. As discussed in section 110 of this guidance, as part of the annual bid review process, CMS will expect Part D sponsors to provide CMS with a reasonable justification to support the submitted plan design that includes any such practices. This justification should address applicable clinical factors, such as clinical superiority, non-inferiority, or equivalence of the selected and non-selected drugs, as well as the plan design's compliance with applicable statutory and regulatory requirements (e.g., the requirement to have a cost-effective drug utilization management program that bases decisions on the strength of the clinical evidence and standards of practice). CMS reviews all Part D plan formularies to ensure they comply with statutory and regulatory requirements and, pursuant to section 1860D-11(e)(2)(D)(i) of the Act, will only approve a Part D plan bid submitted by a Part D plan sponsor if CMS does not find that the design of the plan and its benefits (including any formulary and tiered formulary structure) are likely to substantially discourage enrollment by certain Part D eligible individuals under the plan. CMS believes this approach will provide Part D sponsors with the flexibility to continue to manage costs through utilization management in a clinically appropriate manner, while allowing CMS to monitor practices that may undermine beneficiary access to selected drugs and inform new requirements for future contract years.

Comment: Many commenters expressed concern that price negotiation, combined with changes in interested party liability from Part D redesign, will have significant impacts on the structure of Part D and could negatively impact patient access to medicines. These commenters recommended CMS monitor plan formularies and the extent to which plans are using utilization management and tiering for selected drugs. Some commenters also recommended CMS update rules and guidance around plan coverage decisions and create safeguards to ensure patient access to a selected drug.

Response: CMS thanks these commenters for sharing their concerns regarding patient access to selected drugs. CMS agrees with commenters about the importance of beneficiaries having meaningful access to selected drugs. As such, as discussed in section 110 of this guidance and consistent with the agency's statutory obligation to monitor plan compliance with all applicable formulary requirements, CMS will use its formulary review process to assess (1) any instances where Part D sponsors place selected drugs on non-preferred tiers, (2) any instances where a selected drug is placed on a higher tier than non-selected drugs in the same class, (3) any instances where Part D sponsors require utilization of an alternative brand drug prior to a selected drug with an MFP (i.e., step therapy), or (4) any instances where Part D sponsors impose more restrictive utilization management (i.e., step therapy and/or prior authorization) for a selected drug compared to a non-selected drug in the same class. As CMS reviews Part D plan formularies to ensure they comply with statutory and regulatory requirements, pursuant to section 1860D-11(e)(2)(D)(i) of the Act, CMS will only approve a Part D plan if it does not find that the design of the plan and its benefits (including any formulary and tiered cost-sharing structure) are likely to substantially discourage enrollment by certain Part D eligible individuals under the plan. While CMS is not implementing additional tier placement or utilization management requirements for selected drugs for contract year 2026, if CMS identifies that Part D sponsors are not providing beneficiaries with meaningful access to selected drugs, CMS may consider implementing new requirements for future contract years to ensure that Part D sponsors are not undermining beneficiary access to selected drugs.

Application of Medicare Part B and D Prescription Drug Inflation Rebate Programs to Selected Drugs (Section 120)

Comment: A few commenters stated that selected drugs should not be subject to inflation rebates. These commenters pointed to the Part B inflation rebate calculation in statute to assert that Congress did not intend for rebates to apply to selected drugs.

Response: The statute provides that the inflation rebates apply to selected drugs.[24] Specifically, the rebate calculation specified in section 1847A(i)(3)(A)(ii)(l) of the Act references section 1847A(b)(1)(B) of the Act, which includes payment for selected drugs. That is, there is no statutory exemption from inflation rebates for selected drugs. Note that CMS intends to issue final guidance relating to the Part B and Part D inflation rebates later in 2023.

Comment: Commenters requested clarification regarding the application of inflation rebates to selected drugs. One commenter asked CMS to clarify how MFPs will be factored into the inflation rebate calculations for selected drugs under the Part B and Part D programs. Another

[24] See sections 1847A(i) and 1860D-14B of the Act.

commenter urged CMS to issue guidance to ensure that the Negotiation Program and Part B Inflation Rebate Program do not have an interactive effect, and that inflation rebates should only apply when the manufacturer has increased its price.

Response: Section 120 of this guidance clarifies that the MFP for a selected drug is not included in the AMP for the selected drug and thus will not affect the Part D inflation rebate calculation.[25] CMS will provide additional information about how Part B inflation rebates apply to selected drugs in future guidance.

Appendix C: Definitions for Purposes of Collecting Manufacturer-Specific Data

Comment: Some commenters stated that the proposed framework for CMS' data collection and corresponding definitions to capture information required in sections 1194(e)(1) and (2) of the Act lacks the flexibility necessary to accommodate unique characteristics of different drugs/products that will be reviewed through the Negotiation Program. These commenters requested CMS rescind the proposed definitions and permit manufacturers to provide statutorily required data submissions based on reasonable assumptions along with a justification of such assumptions when interpreting the applicable IRA statutory requirements. Some commenters stated that because of the assumptions inherent in responding to a data request, CMS must use notice-and-comment rulemaking to provide information about required data. A few commenters raised concerns about differences between the definitions proposed in the initial memorandum and other pharmaceutical industry and/or government reporting requirements with related terms, and some commenters included specific term examples of these situations (included in other comments below). A couple of commenters expressed broad support for the definitions in Appendix C. Additionally, some commenters requested CMS allow manufacturers to provide supplemental data without text limits. Another commenter requested CMS establish a uniform starting point across data collections and not require data prior to this point because it could unfairly penalize manufacturers for previous pricing practices and data collection before the IRA went into effect.

Response: CMS thanks these commenters for articulating the considerations they will need to address when preparing to conform data submissions to the definitions provided in Appendix C of this guidance. CMS consulted with subject matter experts and federal agencies regarding the terms defined in this guidance. As already discussed herein, CMS engaged (and continues to engage) with interested parties through various platforms since passage of the IRA in August 2022. CMS has considered recommendations and suggestions in revising the definitions included in Appendix C of this guidance, which serve as the basis for the information to be collected under sections 1194(e)(1) and (2) of the Act. CMS is not adopting the recommendation that Primary Manufacturers submit a statement of reasonable assumptions with submissions under section 1194(e)(1) of the Act or otherwise use reasonable assumptions. CMS believes it is important that data submissions reflect the application of consistent standards and definitions to permit appropriate consideration of such data, timely execution of the negotiation process, and enforcement actions, as warranted. As such, data submitted in response to this revised guidance must be based on consistent definitions and scope, as reflected in Appendix C of this revised guidance. CMS appreciates the resources required to meet these submission requirements. On

[25] See section 1927(k)(1)(B)(i)(VI) of the Act.

March 21, 2023, CMS released the Negotiation Data Elements ICR (CMS-10847 / OMB 0938-NEW) to detail the specific data that CMS is requesting for purposes of implementing the negotiation process to determine the MFP. The comment period in response to the 60-day notice closed on May 22, 2023. CMS is releasing a revised version of the Negotiation Data Elements ICR on June 30, 2023, and the 30-day comment period will close on July 31, 2023. The revised ICR is available here: https://www.cms.gov/regulations-and-guidance/legislation/paperworkreductionactof1995/pra-listing/cms-10847. Comments must be submitted through www.regulations.gov.

Additionally, as explained in response to comments received regarding CMS' statutory authority to issue program instruction, sections 11001(c) and 11002(c) of the IRA state that CMS "shall implement" the Negotiation Program "for 2026, 2027, and 2028 by program instruction or other forms of program guidance"; thus, this revised guidance and corresponding data collection requirements are not subject to the notice-and-comment requirements of the Administrative Procedure Act or the Medicare statute. However, CMS is following requirements pursuant to the Paperwork Reduction Act of 1995 for information collection requests related to the administration of the Negotiation Program.

Comment: A few commenters asked for clarification on the requested data elements related to R&D costs. Some commenters expressed concern that CMS' definition of R&D costs is too narrow and excludes relevant costs such as those related to acquisition, ongoing studies or monitoring of a drug, and costs related to investments in technology that may apply to multiple drugs. One commenter recommended CMS exclude from the definition of R&D costs post-marketing clinical trials that were not completed and limit consideration of spending on abandoned and failed projects to those that were conducted within a narrower timeframe. One commenter expressed concern that the 8.1 percent capital rate specified in the guidance is too low. A few commenters stated CMS' approach for calculating recoupment of R&D costs by comparing global net lifetime revenue for the selected drug with R&D costs attributable to FDA-approved indications of the selected drug is imprecise or flawed and disadvantages the manufacturer.

Response: CMS thanks these commenters for their feedback. After consideration of the comments on this guidance and the Negotiation Data Elements ICR, CMS has revised Appendix C to consolidate several R&D cost categories. Specifically, as revised, the category "Post-Investigational New Drug (IND) Application Costs" includes costs for completed, FDA-required post-marketing trials, which were previously in their own category. The category "All Other R&D Direct Costs" includes costs associated with post-marketing trials that were not completed or were conducted for the purposes of marketing claims, which were previously in their own category. In addition, CMS revised the guidance to require reporting of acquisition costs as part of R&D costs rather than market data and revenue and sales volume data. CMS also revised the definition of basic pre-clinical research costs to clarify that the relevant time period for reporting such costs begins on the later of the date of initial discovery or the date the Primary Manufacturer acquired the right to hold the NDA(s) / BLA(s) of the selected drug. This revision was made to clarify that CMS does not expect the Primary Manufacturer to submit R&D costs for the time period prior to its acquisition of the rights to the selected drug.

Acknowledging that not all costs are mutually exclusive among products and that manufacturer investments can include failed drug candidates, CMS believes that for the purpose of the Negotiation Program, the definition of R&D costs is sufficiently broad. As required in section 1194(e)(1)(A), CMS must consider R&D "costs of the manufacturer related to the [selected] drug." Expanding the definition of such costs to include failures of products with different active moieties / active ingredients or mechanisms of action or in different therapeutic classes or other non-specific innovation-related costs goes beyond considering costs related to the R&D of the selected drug and does not provide a clear accounting of drug-specific R&D expenditures. In defining R&D costs, CMS considered a multitude of sources including government reports, literature searches, the FDA website, and discussions with experts. The definition is intended to be sufficiently broad to accommodate differences in accounting policies and cost allocations across different manufacturers. Manufacturers should submit additional R&D costs not included in other R&D definitions as part of "All Other R&D Direct Costs", as applicable. The 8.1 percent capital rate is consistent with assumptions used by the Congressional Budget Office in an April 2021 study on R&D in the pharmaceutical industry.[26]

CMS appreciates commenters sharing their concerns regarding comparisons of global, lifetime net revenue for the selected drug with R&D costs attributable to FDA-approved indications of the selected drug. CMS understands that R&D occurs globally and, as stated in the Negotiation Data Elements ICR instructions, the Primary Manufacturer must report R&D costs incurred in other countries that are related to the FDA-approved indication of a selected drug. As noted in the ICR and Appendix C of this revised guidance, R&D costs exclude costs associated with applying for and receiving foreign regulatory approvals. In response to commenters' concerns, CMS has revised Appendix C of this guidance, as well as the ICR, to clarify that CMS will consider both a Primary Manufacturer's global and also U.S. revenue when determining whether to adjust the preliminary price based on manufacturer-submitted data. Further, to align reporting of U.S. revenue with global total lifetime net revenue, CMS has (1) eliminated reporting of quarterly gross U.S. revenue and (2) replaced reporting of quarterly net revenue for the selected drug with U.S. lifetime net revenue for the selected drug.

Comment: Some commenters recommended CMS remove federal tax credits from the definition of prior Federal financial support and limit consideration of prior Federal financial support to only products with a patent application containing a Government Interest Statement and/or research where a patent assignee was a U.S. government agency. One commenter recommended that prior Federal financial support exclude indirect federal funding (e.g., provision of funding to a third party which then provides funding to the manufacturer). One commenter suggested including tax credits provided under the Orphan Drug Act and similar subsidies in addition to grants and contracts. Another commenter recommended CMS use broad definitions for "preclinical" and "novel discovery" to capture prior Federal financial support that occurs before a manufacturer acquires a viable drug product.

Response: CMS thanks these commenters for their feedback. CMS disagrees that tax credits should be excluded from the definition of prior Federal financial support. The federal government supports drug research through tax incentives. The statute does not require that CMS

[26] Congressional Budget Office, "Research and Development in the Pharmaceutical Industry," April 2021, available at https://www.cbo.gov/publication/57126.

only consider direct expenditures in prior Federal financial support or only government interest patents. CMS believes that the definition of prior Federal financial support appropriately captures industry and/or government standards in a manner that is consistent with the statutory requirements to use such information.

Comment: Several commenters raised concerns about challenges with obtaining requested information about current unit costs of production and distribution at the drug-specific level, which they stated is inconsistent with reporting requirements of other governmental bodies such as the SEC. One commenter recommended CMS allow manufacturers to use reasonable assumptions based on existing audited financial reports submitted to the SEC and/or generally accepted accounting principles. One commenter noted that it may not be able to obtain some of these data from Secondary Manufacturers. One commenter recommended CMS include channel fees in its definition of distribution costs. Several commenters recommended CMS allow manufacturers discretion to include production and distribution costs that are available to them and provide a narrative rationale for any factors they are not able to include.

Response: CMS appreciates commenters' concerns and feedback. In response to comments, CMS revised Appendix C to note that costs should be determined and reported in accordance with generally accepted accounting principles. CMS believes the Primary Manufacturer, based on its arrangements with Secondary Manufacturer(s), can reasonably ensure that the Primary Manufacturer can comply with its negotiation program obligations with regarding to data submission and ensuring the availability of MFP for selected drug sold by Secondary Manufacturer(s). CMS notes that because the agreement is between CMS and the Primary Manufacturer, it is the Primary Manufacturer's responsibility to submit certain data that will serve as the basis for offers and counteroffers. CMS declines to explicitly include channel fees in its definition of costs of distribution and notes that the definition generally refers to all (direct and allocation of indirect) costs related to packaging, labeling, and shipping operating costs for facilities and transportation. CMS refers commenters to the Negotiation Data Elements ICR for information about submitting explanations of various calculations, including unit production and distribution costs. Finally, CMS notes that the definitions of unit costs of production and distribution are intended to be sufficiently broad to account for various costs associated with producing and distributing drugs or biological products.

Comment: One commenter noted that manufacturers define kits differently than the National Council for Prescription Drug Programs (NCPDP) Billing Unit Standards that are referenced in Appendix C. This commenter recommended including the definition to avoid confusion.

Response: This revised guidance includes a footnote to provide clarification with respect to the definition of kits to be clear that CMS is adopting the NCPDP definition for kits.

Comment: Some commenters disagreed with the scope of patent and exclusivity information that CMS proposed to collect and recommended CMS clarify and narrow the scope of these reporting requirements to, for example, include only U.S. patents and applications directly related to the Primary Manufacturer and/or selected drug. Some commenters also disagreed with the patent-related definitions adopted by CMS. A few commenters requested clarity with respect to certain terms used in this section, including the meaning of patents "linked to" or "relating to"

the selected drug. One commenter recommended removing required reporting of reference product exclusivity for biologics, stating that FDA only makes this determination if there is a regulatory necessity (as opposed to at the time of approval). A few commenters also recommended CMS obtain information about approved patent applications and marketing applications from FDA resources such as the Orange Book and Purple Book and that manufacturers be allowed to reference those sources in their submissions to CMS to reduce burden. One commenter recommended CMS align its terminology and standards with other federal laws and regulations such as those of FDA.

Response: CMS thanks these commenters for their suggestions. In drafting the Patents, Exclusivities, and Approvals section of Appendix C and the Negotiation Data Elements ICR, CMS consulted with the United States Patent and Trademark Office (USPTO) and reviewed the FD&C Act and FDA regulations. After consideration of the comments, CMS has revised Appendix C of this guidance to remove certain definitions and provide additional information about the types of patents and patent applications that CMS considers to be "related to" the selected drug. While CMS understands that certain patent information is submitted to other agencies and is publicly available in the FDA Orange and Purple Books, section 1194(e)(1)(D) of the Act requires that manufacturers submit patent information to CMS. Although some of the requested data may be publicly available, CMS may not be able to ensure that such data are complete or up-to-date. Further, other information required by section 1194(e)(1)(D) of the Act, for example, information about pending patent applications, may not be publicly available. CMS understands that FDA has not made a determination of first licensure for each 351(a) biological product included in the Purple Book and that the absence of a date of first licensure in the Purple Book does not mean that a biological product on the list is not, or was not, eligible for the periods of exclusivity described under the PHS Act. CMS expects that the Primary Manufacturer will report any periods of reference product exclusivity for the selected drug to the extent the determination of exclusivity is listed in the Purple Book.

Comment: A few commenters raised concerns that CMS' definitions in the Market Data Revenue and Sales Volume Data section were too broad and burdensome given the timeframe to collect data from all Secondary Manufacturers. Some commenters opposed CMS' intent to collect certain metrics such as "U.S. commercial average net unit price" and "manufacturer average net unit price to Part D plan sponsors." A few commenters requested CMS withdraw or clarify these metrics. Some commenters also were concerned with CMS requesting data on patient assistance, noting that patient assistance is not a form of price concession or remuneration. One commenter requested CMS remove all reporting of patient assistance or, minimally, clarify that patient assistance programs are defined as charitable free drug programs. One commenter noted the definitions included vague timeframes, which could lead to data discrepancies, and recommended CMS consider including firm dates in definitions. For example, the commenter suggested clarifying "quarterly total U.S. unit volume" and providing a specific quarter on which to report, including which specific quarter in the past five years. One commenter stated that the information collected pursuant to the definitions are considered confidential and proprietary information.

Response: CMS appreciates commenters' concerns. The statute requires CMS to broadly consider market data and revenue and sales data. As noted in guidance, CMS considers these

data to include WAC, Medicaid best price, AMP, FSS price, Big Four price, and U.S. commercial average net unit price, among other data. Data related to these definitions will be considered, in part, as the basis for offers and counteroffers. CMS clarified in Appendix C that patient assistance programs include manufacturer-run patient assistance programs that provide financial assistance such as coupons or copayment assistance or free drug products. In response to comments, CMS removed the metrics "manufacturer average net unit price to Part D plan sponsors" and "quarterly total U.S. unit volume." CMS removed "manufacturer average net unit price to Part D plan sponsors" because CMS does not plan to consider this information for the purposes of developing the initial offer. CMS removed "quarterly total U.S. volume" because CMS collects this information in other questions in the Negotiation Data Elements ICR (CMS-10847 / OMB 0938-NEW). CMS refers interested parties to the revised version of the Negotiation Data Elements ICR that is open for a 30-day public comment period through July 31, 2023. With respect to the comment about confidential and proprietary information, proprietary information, including trade secrets and confidential commercial or financial information, CMS will protect the confidentiality of any proprietary information from Primary Manufacturers or Secondary Manufacturers (described in section 40.2.1) as required under section 1193(c) of the Act and other applicable law.

Timeline for Medicare Drug Price Negotiation Program Initial Price Applicability Year 2026

Date	Milestone
June 30, 2023	Revised Negotiation Program guidance is published by CMS.
July 3, 2023	Latest date to submit Small Biotech Exception request to CMS for initial price applicability year 2026.
September 1, 2023*	CMS publishes list of up to 10 selected drugs for initial price applicability year 2026 of the Negotiation Program.
October 1, 2023*	Latest date for manufacturers of selected drugs to enter into a Medicare Drug Price Negotiation Program Agreement with CMS. Manufacturers of selected drugs without an Agreement in place are referred to IRS.
October 2, 2023*	Manufacturers' section 1194(e)(1) data submissions due to CMS. All voluntary submissions of section 1194(e)(2) data are also due on this date.
Fall 2023	CMS meets with the manufacturer of each selected drug to review data submissions, subject to manufacturer's interest in such meeting.
Fall 2023	CMS holds listening sessions with patients, consumer groups, and other interested parties to obtain input on selected drugs.
February 1, 2024*	Latest date for CMS initial offers to manufacturers for selected drugs, including concise justification of the initial offer.
March 2, 2024*	Latest date for counteroffers from manufacturers, if applicable, assuming initial offer sent to manufacturer by CMS on February 1, 2024.
April 1, 2024	Latest date for CMS to act on manufacturer counteroffer, assuming counteroffer is received by CMS on March 2, 2024. CMS may accept or decline such counteroffer.
April 1, 2024	Latest date for first CMS-manufacturer negotiation meeting to be scheduled if CMS declines the counteroffer, assuming initial offer was sent by CMS on February 1, 2024.

~April 1, 2024 through June 28, 2024	Up to three possible negotiation meetings between the manufacturer and CMS to negotiate MFP for the selected drug. Meetings can begin in late March or April depending on when CMS declines the counteroffer, if applicable, and scheduling.
July 15, 2024	Latest date for final CMS MFP offers to manufacturers if MFP not agreed to during negotiations.
July 31, 2024	Manufacturer response due to CMS regarding final CMS MFP offer.
August 1, 2024*	End of negotiation period for initial price applicability year 2026. Manufacturers of selected drugs without an MFP in place are referred to IRS.
September 1, 2024*	MFPs published for up to 10 selected drugs for 2026 for which MFP agreement has been reached with the manufacturer. CMS will publish the following on the CMS website: the selected drug, the initial price applicability year, and the MFP file (which would be updated annually to show the inflation-adjusted MFP for a selected drug).
March 1, 2025*	CMS publishes explanation of MFP for each selected drug for which MFP agreement has been reached with the manufacturer. CMS will also release redacted information regarding the section 1194(e) data received, exchange of offers and counteroffers, and the negotiation meetings, if applicable.
January 1, 2026*	MFPs for the selected drugs for which MFP agreement has been reached with the manufacturer go into effect.

*Denotes statutory dates

D. Revised Guidance on Medicare Prescription Drug Negotiation Program

10. Introduction

The purpose of this revised guidance is to provide interested parties with information regarding CMS' implementation of sections 11001 and 11002 of the Inflation Reduction Act (IRA) (P.L. 117-169), signed into law on August 16, 2022, which establish the Medicare Drug Price Negotiation Program (hereafter the "Negotiation Program") to negotiate maximum fair prices (MFPs)[27] for certain high expenditure, single source drugs and biological products. The requirements for this program are described in sections 1191 through 1198 of the Social Security Act (hereafter "the Act") as added by sections 11001 and 11002 of the IRA.

Sections 11001(c) and 11002(c) of the IRA direct the Secretary of the Department of Health and Human Services (hereafter "the Secretary") to implement the Negotiation Program for 2026, 2027, and 2028 by program instruction or other forms of program guidance. In accordance with the law, the Centers for Medicare & Medicaid Services (CMS) is issuing this revised guidance for implementation of the Negotiation Program for initial price applicability year 2026.

[27] In accordance with section 1191(c)(3) of the Social Security Act, maximum fair price means, with respect to a year during a price applicability period and with respect to a selected drug (as defined in section 1192(c) of the Act) with respect to such period, the price negotiated pursuant to section 1194 of the Act, and updated pursuant to section 1195(b) of the Act, as applicable, for such drug and year.

This revised guidance is not subject to the notice-and-comment requirements of the Administrative Procedure Act ("APA") or the Medicare statute, due to the requirement in sections 11001(c) and 11002(c) of the IRA to implement the Negotiation Program for 2026, 2027, and 2028 by program instruction or other forms of program guidance. The terms "program instruction" and "program guidance" are terms of art that Congress routinely uses in Medicare statutes to refer to agency pronouncements other than notice-and-comment rulemaking. The statutory directive in sections 11001(c) and 11002(c) thus specifies that CMS shall follow policymaking procedures that differ from the notice-and-comment procedures that would otherwise apply under the APA or the Medicare statute. Congress underscored this directive by placing the Negotiation Program in the newly-enacted Part E of Title XI of the Social Security Act.

Moreover, as explained in the initial memorandum, to the extent that this revised guidance establishes or changes any substantive legal standard, CMS found that notice and public procedure on this revised guidance would be impracticable, unnecessary, and contrary to the public interest in light of the statutory requirement to implement the Negotiation Program for 2026 by program instruction and in light of the complexity of the preparation that must be undertaken in advance of the publication by September 1, 2023 of the selected drug list for initial price applicability year 2026. In particular, manufacturers need to take a number of actions well in advance of September 1, 2023, to prepare for the possibility that a drug that they manufacture might be included on the selected drug list for initial price applicability year 2026. For example, manufacturers may need to engage in internal discussions regarding whether the manufacturer would choose to participate in the Negotiation Program if its drug is included among the selected drug list published on September 1, 2023, review the template Medicare Drug Price Negotiation Program Agreement and guidance to understand Negotiation Program requirements for participating manufacturers in advance of the statutory deadline for entering agreements of October 1, 2023, and gather information for potential submission to CMS by the statutory deadline of October 2, 2023. In addition, for the reasons explained below, the deadline for a biosimilar manufacturer to submit a delay request under section 1192(f) was May 22, 2023. CMS could not have proceeded through notice-and-comment rulemaking and still provided interested parties with guidance sufficiently far in advance of these statutory deadlines to allow them adequate time to complete their preparations for participation in the Negotiation Program. Thus, CMS concluded that there was good cause to issue certain specified parts of the initial memorandum as final (i.e., section 30) without public comment and without a delayed effective date. Although CMS has endeavored to solicit public comment and to respond to comments to the extent that it would be feasible to do so consistent with the statutory deadlines for implementation of the Negotiation Program, CMS also concludes that there is good cause to issue this revised guidance as final without the 60-day period for public comment under the Medicare statute, and without a delayed effective date, in order to meet the statutory deadlines of the Negotiation Program and consistent with the authority provided to CMS in sections 11001(c) and 11002(c) of the IRA. *See* 5 U.S.C. § 553(b)(B) & (d)(3); *see also* section 1871(b)(2)(C) of the Act.

In this revised guidance, CMS has made clarifications and changes to the policies described in the initial memorandum in response to comments and based on CMS' further consideration of the relevant issues, including policies on which CMS did not expressly solicit comment.

This revised guidance describes how CMS will implement the Negotiation Program for initial price applicability year 2026 (January 1, 2026 to December 31, 2026), and specifies the requirements that will be applicable to manufacturers of drugs that are selected for negotiation and the procedures that may be applicable to drug manufacturers, Medicare Part D plans (both Prescription Drug Plans (PDPs) and Medicare Advantage Prescription Drug (MA-PD) Plans), pharmacies, mail order services, and other dispensing entities that dispense drugs covered under Medicare Part D.

If any provision in this revised guidance is held to be invalid or unenforceable, it shall be severable from the remainder of this revised guidance, and shall not affect the remainder thereof, or the application of the provision to other persons or circumstances.

The table of contents for this revised guidance is as follows:

20. Overview

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 Medicare drugs. 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.

As noted above, in order to facilitate the timely implementation of the Negotiation Program, CMS issued section 30 of the initial memorandum as final, without a comment solicitation (with the exception of the Small Biotech Exception Information Collection Request (ICR),[28] as discussed in section 30.2.1 of this revised guidance). To allow for public input, CMS voluntarily solicited comments on all other sections of the initial memorandum except for section 90.3 (which states that the Treasury Department will issue guidance relating to the excise tax in the coming weeks), and specifically on certain topics in the initial memorandum, including:

- Terms and conditions contained in the manufacturer agreement, including the manufacturer's and CMS' responsibilities (included in section 40 of this revised guidance);

[28] This ICR was approved on May 26, 2023. Small Biotech Exception (CMS-10844; OMB Control No. 1938-1443).

- Approach for considering (1) the manufacturer-reported data elements and (2) evidence about alternative treatments (included in section 60 of this revised guidance);
- Process for the offer and counteroffer exchange between CMS and manufacturers (included in section 60 of this revised guidance);
- Content of an explanation for the MFP (included in section 60 of this revised guidance);
- Method for applying the MFP across different dosage forms and strengths of a selected drug (included in section 60 of this revised guidance);
- Dispute resolution process for specific issues that are not exempt from administrative and judicial review under section 1198 (included in section 40.5 of this revised guidance); and
- Processes for compliance monitoring and imposition of CMPs for violations (included in sections 90 and 100 of this revised guidance).

In this revised guidance, CMS has made clarifications and changes in response to comments and based on CMS' further consideration of the relevant issues, including policies on which CMS did not expressly solicit comment.

30. Identification of Selected Drugs for Initial Price Applicability Year 2026

In order to facilitate the timely implementation of the Negotiation Program in accordance with statutory deadlines, CMS issued section 30 of the initial memorandum as final, without a comment solicitation (with the exception of the Small Biotech Exception ICR, as described in section 30.2.1 of this revised guidance). While CMS did not solicit comment in response to section 30, CMS did receive many thoughtful comments, and based on these comments and further consideration of the relevant issues, CMS identified certain policies where revisions to clarify the policy described in the initial memorandum would facilitate the implementation of the Negotiation Program for initial price applicability year 2026. CMS has noted in section 30, and in the summary of key changes and clarifications, where clarifying revisions were made.

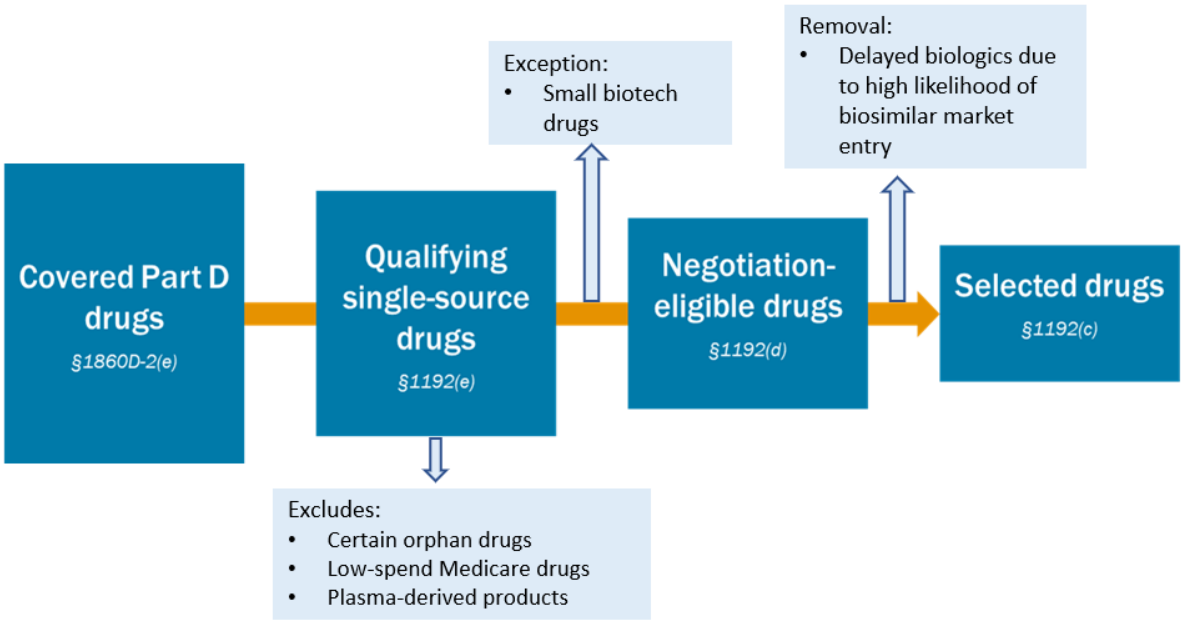
Section 1192 of the Act establishes the requirements governing the identification of qualifying single source drugs, the identification of negotiation-eligible drugs, the ranking of negotiation-eligible drugs and identification of selected drugs, and the publication of the list of selected drugs for 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 revised 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 Expenditures[29] under Part D of Title XVIII for these qualifying single source drugs calculated using Part D prescription drug event (PDE) data for dates of service between June 1, 2022, and May 31, 2023, and other information described below, CMS will identify negotiation-eligible drugs for initial price applicability year

[29] For the purposes of the Negotiation Program, Total Expenditures under Part D of Title XVIII are defined in section 1191(c)(5) 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 the initial memorandum, CMS indicated that it had proposed to update this regulatory definition of gross covered prescription drug costs to eliminate any potential ambiguity in the regulation text and help to ensure there is a consistent understanding of the term for purposes of both the Part D program and the IRA. Since the initial memorandum was issued, CMS has issued a final rule adopting the proposed revisions to 42 C.F.R. § 423.308. (See Contract Year 2024 Policy and Technical Changes to the Medicare Advantage and Medicare Prescription Drug Benefit Programs Final Rule (0938-AU96), 88 Fed. Reg. 22,120, 22,259 (Apr. 12, 2023)).

2026 as described in section 30.2 of this revised guidance (in this step, CMS will also exclude certain drugs in accordance with section 1192(d)(2) and (3) of the Act).

In accordance with section 1192(d)(1) of the Act, CMS will rank negotiation-eligible drugs for initial price applicability year 2026 according to the Total Expenditures for such drugs under Part D of Title XVIII for the 12-month period described above (described in section 30.3 of this revised 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 the 10 negotiation-eligible drugs with the highest Total Expenditures under Part D of Title XVIII for negotiation for initial price applicability year 2026 (described in section 30.3 of this revised guidance) and publish a list of those ten selected drugs not later than September 1, 2023 (described in section 30.4 of this revised guidance). Figure 1 provides a visual depiction of this process, and detailed guidance pertaining to this process for initial price applicability year 2026 is included below.

Figure 1: Diagram of Process for Selecting Drugs for Negotiation for Initial Price Applicability Year 2026



30.1 Identification of Qualifying Single Source Drugs for Initial Price Applicability Year 2026

For initial price applicability year 2026, 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."

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 drug[30] 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)[31], inclusive of products that are marketed pursuant to different NDAs. 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 sentence that are: (1) repackaged and relabeled products that are marketed pursuant to such NDA(s), (2) authorized generic drugs that are marketed pursuant to such NDA(s), and (3) multi-market approval (MMA) products imported under section 801(d)(1)(B) of the FD&C Act that are marketed pursuant to such NDA(s);
- 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),[32] inclusive of products that are marketed pursuant to different BLAs. 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 sentence that are: (1) repackaged and relabeled products that are marketed pursuant to such BLA(s), (2) authorized biologic products that are marketed pursuant to such BLA(s), and (3) MMA products imported under section 801(d)(1)(B) of the FD&C Act that are marketed pursuant to such BLA(s).

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[30] Throughout this revised 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 NDA(s) / BLA(s) for the active moiety / active ingredient as outlined in section 30.1 of this revised guidance.
[31] As described in section 505(c) of the FD&C Act.
[32] As described in section 351(a) of the PHS Act.

As an example, 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 a subcutaneous injectable 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.

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 new dosage forms or different routes of administration of the same active moiety / active ingredient have been submitted by the same NDA / BLA holder and approved 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 Act[33] 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.

If a drug is a fixed combination drug[34] 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 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 long-acting 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 long-acting corticosteroid inhaler would be considered as a separate potential qualifying single source drug from the fixed combination inhaler.

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[33] 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.

[34] For purposes of the Negotiation Program, the term "fixed combination drug" has the meaning specified in 21 C.F.R. § 300.50.

Applying statutory criteria for qualifying single source drugs:
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 U.S. Food and Drug Administration (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 2026 is September 1, 2023, as specified in section 1191(d)(1) of the Act. As such, for initial price applicability year 2026, the initial approval for a drug product to be considered a qualifying single source drug must have been on or before September 1, 2016, and the date of initial licensure for a biological product to be considered a qualifying single source drug must have been on or before September 1, 2012.

For example, if 12 years had elapsed between the original approval for NDA-1 cited in the previous example above and September 1, 2023, 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 September 1, 2023), consistent with the statutory directives 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 Book[35] and Purple Book,[36] to determine whether a generic drug or biosimilar biological product 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 2026.

In accordance with section 1192(c) and (e) of the Act for the purpose of identifying qualifying single source drugs for initial price applicability year 2026, CMS is clarifying in this revised guidance that it will review PDE data for the 12-month period beginning August 16, 2022 and ending August 15, 2023, using PDE data available on August 16, 2023, as well as Average Manufacturer Price (AMP)[37] data for the 12-month period beginning August 1, 2022 and ending July 31, 2023, using the AMP data available on August 16, 2023, for a given generic drug or biosimilar biological product for which a potential qualifying single source drug is the listed drug or reference product. 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

[35] See: https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.
[36] See: https://purplebooksearch.fda.gov/.
[37] 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.

will be informative for that determination. CMS will consider a generic drug or biosimilar biological product to be marketed when the totality of the circumstances, including these data, reveals that the manufacturer of that drug or product is engaging in bona fide marketing of that drug or product (see section 70 of this revised guidance for additional details). 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 to inform the selected drug list published by September 1, 2023 in accordance with section 1192(a) of the Act.

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 biological products that CMS determines are approved and marketed based on the process described in this revised guidance, the potential qualifying single source drug will not be considered a qualifying single source drug for initial price applicability year 2026. If CMS determines that the potential qualifying single source drug will not be considered a qualifying single source drug for initial price applicability year 2026 because a manufacturer of such generic drug or biosimilar biological product has engaged in bona fide marketing of the generic drug or biosimilar biological product, CMS will monitor to ensure continued bona fide marketing of the generic drug or biosimilar biological product based on the approach described in section 90.4 of this revised 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 ("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) 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. CMS is clarifying in this revised guidance that a drug that has orphan designations for more than one rare 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 further clarifies that it 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.

In order 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 revised guidance must meet the criteria for exclusion. CMS will use the FDA Orphan Drug Product designation database[38] and approvals on the FDA website[39] 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 needed, including to determine whether a drug is designated for, or approved for indications for, one or more rare disease(s) or condition(s). In this revised guidance, CMS is clarifying that, in the event that a drug or biological product loses Orphan Drug Exclusion status,

[38] See: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/.
[39] See: https://www.accessdata.fda.gov/scripts/cder/daf/.

pursuant to sections 1192(e)(1)(A)(ii) and (B)(ii) of the Act, CMS will use the date of the earliest approval or licensure of the drug or 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.

As noted in the initial memorandum, CMS is considering whether there are additional actions CMS can take in its implementation of the Negotiation Program to best support orphan drug development, and CMS appreciates continued input from interested parties on this topic. Additional information about how CMS will consider the impact of a selected drug (and its therapeutic alternative(s)) on specific populations as well as the extent to which the selected drug (and its therapeutic alternative(s)) meets an unmet medical need in CMS' development of an initial offer is in section 60.3.3 of this revised guidance.

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 also exclude low-spend Medicare drugs or biological products with less than $200,000,000 in combined expenditures under Medicare Parts B and D when identifying qualifying single source drugs ("the Low-Spend Medicare Drug Exclusion"). For initial price applicability year 2026, 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 June 1, 2022, and ending May 31, 2023. 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 service described above that have been submitted no later than 30 days[40] after May 31, 2023, i.e., by June 30, 2023. 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 May 31, 2023, i.e., by June 30, 2023.
- For each potential qualifying single source drug as described in section 30.1 of this revised guidance, CMS will use the PDE data to calculate the Total Expenditures under Part D and CMS will use the 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. CMS is clarifying in this revised guidance that 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 2026 any drugs for which the sum of Total Expenditures under Part D and Part B is less than $200 million.

[40] For purposes of this revised guidance, CMS defines all days as calendar days unless otherwise specified in statute, guidance, or regulation.

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 revised 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 products,[41] and will refer to the FDA Online Label Repository[42] to verify if the product is derived from human whole blood or plasma. CMS will also consult with FDA as needed.

30.2 Identification of Negotiation-Eligible Drugs for Initial Price Applicability Year 2026

In accordance with sections 1192(a) and 1192(d)(1) of the Act, a negotiation-eligible drug for initial price applicability year 2026 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 2026 as follows:

- CMS will identify all qualifying single source drugs for initial price applicability year 2026 using the process described in section 30.1 of this revised guidance. CMS will exclude any drugs that qualify for the exclusions listed in sections 30.1.1 – 30.1.3 of this revised guidance.
- CMS will identify PDE data for each NDC-11 of a qualifying single source drug for dates of service during the 12-month period beginning June 1, 2022, and ending May 31, 2023. 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 May 31, 2023, i.e., by June 30, 2023.
- 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 subject to the exception for small biotech drugs, described in section 30.2.1 of this revised guidance; (2) rank the remaining qualifying single source drugs by Total Expenditures under Part D during the applicable 12-month period; and (3) 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 2026.

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(ies) / active ingredient(s), until CMS has identified 50 negotiation-eligible drugs. CMS believes that this approach would not be likely to alter which drugs are selected drugs because a maximum of 10 drugs will be selected for initial price applicability year 2026 (see section 30.3 of this revised guidance for details).

[41] See: https://www.fda.gov/vaccines-blood-biologics/blood-blood-products/approved-blood-products.
[42] See: https://labels.fda.gov/.

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 Exception"). The statute requires that CMS consider, for Part D drugs, Total Expenditures under Part D for all covered Part D drugs during 2021, Total Expenditures for the qualifying single source drug under Part D during 2021, and Total Expenditures under Part D for all covered Part D drugs for which the manufacturer that had a Coverage Gap Discount Program (CGDP) agreement in effect under section 1860D-14A of the Act for the qualifying single source drug during 2021 also had a CGDP agreement in effect during 2021.[43] To identify and exclude such small biotech drugs, CMS will consider whether, for dates of services in calendar year 2021, the Total Expenditures under Part D for the qualifying single source drug (1) were equal to or less than one percent of the Total Expenditures under Part D for all covered Part D drugs; and (2) were equal to at least 80 percent of the Total Expenditures under Part D for all covered Part D drugs for which the manufacturer of the qualifying single source drug had a CGDP agreement in effect during 2021.

For the purposes of the Small Biotech Exception for initial price applicability year 2026, the aggregation rule at section 1192(d)(2)(B)(i) of the Act requires that CMS treat as a single manufacturer all entities that, as of December 31, 2021, were treated as a single employer under subsection (a) or (b) of section 52 of the Internal Revenue Code (IRC) of 1986 with the entity that had the CGDP agreement for the qualifying single source drug on that date. However, CMS does not have information about which entities were treated as a single employer under the applicable IRC provisions. Therefore, a manufacturer that seeks the Small Biotech Exception for its qualifying single source drug ("Submitting Manufacturer") must submit information to CMS about the company and its products in order for the drug to be considered for the exception. To the extent that more than one entity meets the statutory definition of a manufacturer of a qualifying single source drug, only the holder of the NDA(s) / BLA(s) for the qualifying single source drug may be the Submitting Manufacturer. CMS made this decision to ensure that only the entity with which CMS would negotiate in the event that the qualifying single source drug is selected for negotiation, as described in section 40 of this revised guidance, is able to seek the Small Biotech Exception.

On January 24, 2023, CMS released the Small Biotech Exception ICR (CMS-10844 / OMB 0938-1443) to detail the specific data that CMS is requesting for purposes of implementing this exception. The comment period in response to the 60-day notice closed on March 27, 2023. CMS released a revised version of the Small Biotech Exception ICR on April 24, 2023, and the comment period in response to the 30-day Federal Register notice closed on May 24, 2023. CMS published the final, approved version of the Small Biotech Exception ICR on May 26, 2023.[44]

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[43] For the purposes of this determination, a manufacturer that participated in the CGDP in 2021 by means of an arrangement whereby its labeler codes were listed on another manufacturer's CGDP agreement would be considered to have had an agreement in effect during 2021.

[44] To view the Small Biotech ICR Form, a summary of changes made to the Small Biotech ICR in response to comments received during the 60-day and 30-day notice periods, as well as comments received on the Small Biotech ICR and CMS' responses to those comments, see https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202304-0938-016.

The Small Biotech Exception ICR addresses the collection of information for initial price applicability year 2026 only. For initial price applicability year 2026, Sections 1191(a) and 1192(d) of the Act require CMS to evaluate whether a qualifying single source drug qualifies as a negotiation-eligible drug under 1192(d) based on Total Expenditures under Part D only, including with respect to the Small Biotech Exception. As a result, this ICR addresses the collection of information relevant to Total Expenditures only under Part D. Additionally, this ICR does not address the collection of information relevant to the statutory limitation found in section 1192(d)(2)(B)(ii) of the Act (which precludes the application of the Small Biotech Exception to a qualifying single source drug if the manufacturer of that drug is acquired after 2021 by a manufacturer that does not meet the definition of a specified manufacturer under section 1860D–14C(g)(4)(B)(ii) because the earliest effective date specified in that limitation (January 1, 2025) has no impact until initial price applicability year 2027 (the first initial price applicability year with a selected drug publication date after January 1, 2025).

As CMS announced on May 26, 2023, after approval of the ICR, to receive consideration for the Small Biotech Exception for initial price applicability year 2026, the Submitting Manufacturer must submit the Small Biotech Exception ICR Form using the CMS Health Plan Management System (CMS HPMS) by July 3, 2023.[45] CMS will notify the Submitting Manufacturer in September 2023 of the determination of whether the Submitting Manufacturer's qualifying single source drug qualifies for the Small Biotech Exception for initial price applicability year 2026. CMS is clarifying in this revised guidance that information in a Small Biotech Exception ICR Form that is a trade secret or confidential commercial or financial information will be protected from disclosure if the information meets the requirements set forth under Exemptions 3 and/or 4 of the Freedom of Information Act (FOIA) (5 U.S.C. § 552(b)(3), (4)).

CMS will not consider incomplete submissions. Upon receipt of a complete Small Biotech Exception ICR Form, CMS will take the following approach to identify whether a qualifying single source drug qualifies for the Small Biotech Exception:

- CMS will identify the manufacturer that had a CGDP agreement for the qualifying single source drug in effect as of December 31, 2021 ("2021 Manufacturer") based on the information submitted in the Small Biotech Exception ICR Form.
- CMS will use the information submitted in that form to identify the complete set of 11-digit National Drug Codes (NDC-11s)[46] for which any member of the 2021 Manufacturer's controlled group as of December 31, 2021 had a CGDP agreement as of December 31, 2021. "Controlled group" means all corporations or partnerships, proprietorships and other entities treated as a single employer under 26 U.S.C. § 52(a) or (b).
- Using the complete set of NDC-11s for which the 2021 Manufacturer or any member of the 2021 Manufacturer's controlled group had a CGDP agreement in effect on December

[45] On June 2, 2023, CMS released the Small Biotech Exception functionality in CMS HPMS, and manufacturers could begin submitting their requests on that date. To view instructions for requesting the Small Biotech Exception in CMS HPMS, see https://www.cms.gov/files/document/small-biotech-exception-guidance-6223.pdf.

[46] 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.

31, 2021, CMS will identify PDE data for dates of service during the 12-month period beginning January 1, 2021 and ending December 31, 2021.

- Using the PDE data for (1) the qualifying single source drug, (2) the complete set of covered Part D drugs for which the 2021 Manufacturer or any member of the 2021 Manufacturer's controlled group had a CGDP agreement as of December 31, 2021, and (3) all covered Part D drugs, CMS will determine whether:
    - The Total Expenditures under Part D for the qualifying single source drug were equal to or less than one percent of the Total Expenditures under Part D for all covered Part D drugs; and
    - The Total Expenditures under Part D for the qualifying single source drug were equal to at least 80 percent of the Total Expenditures under Part D for all covered Part D drugs for which the 2021 Manufacturer or any member of the 2021 Manufacturer's controlled group had a CGDP agreement in effect during 2021.

  CMS is clarifying in this revised guidance that the Total Expenditures under Part D for all covered Part D drugs will be determined using PDE data for all covered Part D drugs. The Total Expenditures under Part D for the qualifying single source drug and the Total Expenditures under Part D for all covered Part D drugs for which the 2021 Manufacturer or any member of the 2021 Manufacturer's controlled group had a CGDP agreement in effect during 2021 will only include PDE data for NDC-11s with labeler codes associated with the 2021 Manufacturer or any member of the 2021 Manufacturer's controlled group.

For initial price applicability year 2026, the term "negotiation-eligible drug" will exclude any covered Part D drugs that are qualifying single source drugs that meet these criteria to qualify for the Small Biotech Exception.

A determination by CMS that a given qualifying single source drug qualifies for the Small Biotech Exception for initial price applicability year 2026 does not mean that this drug will continue to qualify for the Small Biotech Exception for future initial price applicability years. The Submitting Manufacturer must resubmit a request for the drug to be considered for the exception for initial price applicability years 2027 and 2028. The process for resubmitting a request will be addressed in future guidance.

In this revised guidance, CMS is clarifying that it will publish the number of drugs that applied for and received the Small Biotech Exception for initial price applicability year 2026 as part of publishing the selected drug list on September 1, 2023.

30.3 Selection of Drugs for Negotiation for Initial Price Applicability Year 2026

In accordance with sections 1192(a) and 1192(b) of the Act, CMS will select 10 (or all, if such number is less than 10) negotiation-eligible drugs for initial price applicability year 2026 as follows:

- CMS will rank the 50 negotiation-eligible drugs identified in section 30.2 of this revised guidance by Total Expenditures under Part D (based on the data described in section 30.2 of this revised guidance) in descending order: the negotiation-eligible drug with the highest Total Expenditures under Part D will be listed first and the negotiation-eligible drug with the lowest Total Expenditures under Part D will be listed last.

- CMS will remove any biological products that qualify for delayed selection under section 1192(f) of the Act as described in section 30.3.1 of this revised guidance.
- CMS will select for negotiation the 10 (or all, if such number is less than 10) highest ranked negotiation-eligible drugs remaining on the ranked list for initial price applicability year 2026.
    - In the event that two or more negotiation-eligible drugs have the same Total Expenditures under Part D to the dollar and such Total Expenditures are the 10th highest among negotiation-eligible drugs, CMS will rank those negotiation-eligible drugs based on which drug has the earlier approval or licensure date, as applicable, associated with the initial FDA application number for its active moiety(ies) / active ingredient(s), and select based on that ranking until there are 10 selected drugs (or until all drugs are selected if the number of negotiation-eligible drugs is less than 10).

30.3.1 Delay in the Selection and Negotiation of Certain Biologics with High Likelihood of Biosimilar Market Entry

In accordance with section 1192(b)(1)(C) of the Act, CMS will remove from the ranked list of 50 negotiation-eligible drugs described in section 30.3 of this revised guidance any negotiation-eligible drug for which the inclusion on the selected drug list is delayed in accordance with section 1192(f) of the Act. This section 30.3.1 describes the implementation of section 1192(f) of the Act (the "Biosimilar Delay").

Under section 1192(f)(1)(B) of the Act, the manufacturer of a biosimilar biological product ("Biosimilar Manufacturer" of a "Biosimilar") may submit a request, prior to the selected drug publication date, for CMS' consideration to delay the inclusion of a negotiation-eligible drug that includes the reference product for the Biosimilar (such a negotiation-eligible drug is herein referred to as a "Reference Drug") on the selected drug list for a given initial price applicability year. The Biosimilar Manufacturer eligible to submit the request is the holder of the BLA for the Biosimilar or, if the Biosimilar has not yet been licensed, the sponsor of the BLA submitted for review by FDA. CMS believes that this approach is appropriate because (1) it clearly identifies one manufacturer that may submit a Biosimilar Delay request for a given Biosimilar, avoiding the possibility that CMS would receive two such requests naming the same Biosimilar for the same initial price applicability year, and (2) the status of the application for licensure for the Biosimilar is material to CMS' consideration of a Biosimilar Delay request, as described in this section 30.3.1.

Section 1192(f) of the Act contemplates two potential requests under the Biosimilar Delay: (1) a request to delay the inclusion of a Reference Drug by one initial price applicability year ("Initial Delay Request"), as stated in section 1192(f)(1)(B)(i)(I) of the Act; and (2) a request to delay the inclusion of a Reference Drug for which an Initial Delay Request has been granted for a second initial price applicability year ("Additional Delay Request") as stated in section 1192(f)(1)(B)(i)(II) of the Act.

The following subsections of this section 30.3.1 include details on the implementation of the Biosimilar Delay for initial price applicability year 2026. Topics related to future initial price applicability years (including Additional Delay Requests) will be covered in future guidance.

30.3.1.1 Requirements for Granting an Initial Delay Request for Initial Price Applicability Year 2026

The statute specifies that the following requirements must be met in order for CMS to grant an Initial Delay Request:

1. In accordance with section 1192(f)(1)(A) of the Act, it is required that the Reference Drug would be, absent the Biosimilar Delay, a selected drug for the initial price applicability year.
    - Biosimilar Manufacturers that think that a Reference Drug for their Biosimilar may be a selected drug for initial price applicability year 2026 may submit an Initial Delay Request, and CMS will disregard that application if the Reference Drug would not, in fact, be a selected drug for initial price applicability year. Biosimilar Manufacturers are encouraged to consult publicly available data on expenditures for covered Part D drugs, including data published by CMS, which may allow them to determine the likelihood that a given drug may be a selected drug.
2. In accordance with section 1192(f)(1)(A) of the Act, it is required that the Reference Drug would be an extended-monopoly drug, as defined in section 1194(c)(4) of the Act, included on the selected drug list for the initial price applicability year, absent the Biosimilar Delay. For Initial Delay Requests submitted with respect to initial price applicability year 2026, this means that the Reference Drug must have received its initial BLA licensure between January 1, 2010, and January 1, 2014.
    - Section 1194(c)(4)(B)(ii) of the Act specifies that selected drugs for which a manufacturer had an agreement under the Negotiation Program for an initial price applicability year prior to 2030 are excluded from the definition of extended-monopoly drugs. Importantly, however, an Initial Delay Request must be submitted by a Biosimilar Manufacturer before the selected drug publication date for an initial price applicability year and before the Primary Manufacturer (as defined in section 40 of this revised guidance) of the Reference Drug ("Reference Manufacturer") would have entered into an agreement under the Negotiation Program. Therefore, CMS believes the exception to the definition of "extended-monopoly drug" in section 1194(c)(4)(B)(ii) of the Act will not apply at the time that a delay would be requested for initial price applicability years 2026 through 2029. Accordingly, CMS believes that the Biosimilar Delay under section 1192(f) of the Act is applicable beginning with initial price applicability year 2026. As such, Biosimilar Manufacturers may submit an Initial Delay Request for initial price applicability year 2026, provided that the Reference Drug named in the request will have been licensed for between 12 and 16 years prior to the start of the initial price applicability year on January 1, 2026.
3. In accordance with section 1192(f)(1)(A) of the Act, the Reference Drug must include the reference product identified in the Biosimilar's application for licensure under section 351(k) of the PHS Act that has been approved by the FDA or accepted for review, as described below in section 30.3.1.2 of this revised guidance.
    - Please note that in order for CMS to grant an Initial Delay Request, the licensure application for the Biosimilar does not need to include all of the dosage forms, strengths, and indications for which the Reference Drug has received approval.

4. In accordance with section 1192(f)(2)(D)(iii) of the Act, an Initial Delay Request cannot be granted if more than one year has elapsed since the licensure of the Biosimilar and marketing of the Biosimilar has not commenced.
    - For Initial Delay Requests submitted with respect to initial price applicability year 2026, this requirement means that if the Biosimilar has already received approval by the FDA for its application for licensure under section 351(k) of the PHS Act, the date of such licensure must be on or after September 1, 2022 for a delay to be granted. If the Biosimilar is already licensed and marketed by September 1, 2023, the selected drug publication date for initial price applicability year 2026, the Reference Drug would by definition no longer be a qualifying single source drug and therefore would fail requirement #1 on this list. If the Biosimilar was licensed prior to September 1, 2022 and is not marketed before September 1, 2023, more than one year would have elapsed since the licensure of the Biosimilar without marketing of the Biosimilar having commenced.
5. In accordance with section 1192(f)(2)(D)(iv) of the Act, the Biosimilar Manufacturer must not be the same as the Reference Manufacturer and must not be treated as being the same pursuant to section 1192(f)(1)(C) of the Act.
    - For the purposes of this determination, all persons treated as a single employer under subsection (a) or (b) of section 52 of the IRC of 1986, or in a partnership, shall be treated as one manufacturer, as stated in section 1192(f)(1)(C) of the Act.
    - For the purposes of this determination, "partnership" is defined at section 1192(f)(1)(C)(ii) of the Act as a syndicate, group, pool, joint venture, or other organization through or by means of which any business, financial operation, or venture is carried on by the Reference Manufacturer and the Biosimilar Manufacturer.
6. In accordance with section 1192(f)(2)(D)(iv) of the Act, the Biosimilar Manufacturer and the Reference Manufacturer must not have entered into an agreement that either:
    - requires or incentivizes the Biosimilar Manufacturer to submit an Initial Delay Request; or
    - directly or indirectly restricts the quantity of the Biosimilar that may be sold in the United States over a specified period of time. For Initial Delay Requests submitted with respect to initial price applicability year 2026, CMS will consider any agreement between the Biosimilar Manufacturer and the Reference Manufacturer that directly or indirectly restricts the quantity of the Biosimilar that the Biosimilar Manufacturer may sell during any period of time on or after September 1, 2023 as violating this requirement.
7. In accordance with section 1192(f)(1)(A) of the Act and as described in detail in section 30.3.1.2 of this revised guidance, CMS must determine that there is a high likelihood that the Biosimilar will be licensed and marketed before the date that is two years after the selected drug publication date for the initial price applicability year.

30.3.1.2 High Likelihood

In accordance with section 1192(f)(1)(A) of the Act, CMS will review Initial Delay Requests to determine whether there is a high likelihood that the Biosimilar will be licensed and marketed before the date that is two years after the selected drug publication date for the initial price applicability year. Accordingly, for Initial Delay Requests submitted with respect to initial price

applicability year 2026, CMS must find a high likelihood that the Biosimilar will be licensed and marketed before September 1, 2025, in order to grant the request. If CMS does not find that there is a high likelihood that the Biosimilar will be licensed and marketed before September 1, 2025, based on the criteria described below, CMS will deny the Initial Delay Request.

In accordance with section 1192(f)(3) of the Act, Initial Delay Requests must demonstrate both of the following in order meet the high likelihood threshold:

1. An application for licensure under section 351(k) of the PHS Act for the Biosimilar has been accepted for review or approved by the FDA.[47]
    - For Initial Delay Requests submitted with respect to initial price applicability year 2026, the Biosimilar's application for licensure must be approved or accepted for review by the FDA no later than August 15, 2023, in order to permit CMS time to review the information and finalize the selected drug list prior to the selected drug publication date of September 1, 2023.
    - Please note that if the Biosimilar's application for licensure has not been accepted for review by August 15, 2023, including in the case where the Biosimilar Manufacturer has submitted an application for licensure that has not been accepted for review by the FDA or for which a filing determination is pending, CMS will deny the Initial Delay Request for initial price applicability year 2026.
2. Clear and convincing evidence that the Biosimilar will be marketed before September 1, 2025 (the date that is two years after the selected drug publication date for the initial price applicability year), based on the information from the items described in sections 1192(f)(1)(B)(ii)(I)(bb) and (III) of the Act as submitted to CMS.

For Initial Delay Requests submitted for initial price applicability year 2026, to demonstrate clear and convincing evidence that the Biosimilar will be marketed before September 1, 2025, CMS requires that the information from the items described in sections 1192(f)(1)(B)(ii)(I)(bb) and (III) of the Act as submitted to CMS by the Biosimilar Manufacturer as part of its Initial Delay Request demonstrates both (1) that patents related to the Reference Drug are unlikely to prevent the Biosimilar from being marketed and (2) that the Biosimilar Manufacturer will be operationally ready to market the Biosimilar. These requirements address the two primary contributing factors to delays in marketing of biosimilars approved in the U.S. to date, and so CMS believes that evidence showing that a Biosimilar meets these two requirements is sufficient to establish clear and convincing evidence that the Biosimilar will be marketed.

First, the Initial Delay Request must clearly demonstrate that patents related to the Reference Drug are unlikely to prevent the Biosimilar from being marketed before September 1, 2025. CMS is clarifying in this revised guidance that, in its evaluation of whether this requirement is met, CMS will only consider patents relating to the reference product included in the Reference Drug that are applicable to the Biosimilar. Specifically, CMS will consider this requirement met if (1) there are no unexpired patents relating to the reference product included in the Reference

[47] CMS is clarifying in this revised guidance that it will consider an application for licensure under section 351(k) of the PHS Act that has been accepted for review and that received a Complete Response letter to meet the section 1192(f)(3)(A) requirement that an application for licensure under section 351(k) for the biosimilar biological product has been accepted for review by FDA.

Drug that are applicable to the Biosimilar; (2) one or more court decisions establish the invalidity, unenforceability, or non-infringement of any potentially applicable unexpired patent relating to the reference product included in the Reference Drug that the patent holder asserted was applicable to the Biosimilar; or (3) the Biosimilar Manufacturer has a signed legal agreement with the Reference Manufacturer that permits the Biosimilar Manufacturer to market the Biosimilar before September 1, 2025, without imposing improper constraints on the Biosimilar Manufacturer.[48] CMS will deny all Initial Delay Requests for Biosimilars that do not meet this requirement with respect to at least one reference product included in the Reference Drug. However, active litigation related to another reference product included in the Reference Drug that is not applicable to the Biosimilar will not be disqualifying.

Second, the Initial Delay Request must clearly demonstrate that the Biosimilar Manufacturer will be operationally ready to market the Biosimilar before September 1, 2025. To assess this requirement, CMS will consider the Biosimilar Manufacturer's progress against the actions, activities, and milestones that are typical of the normal course of business leading up to the marketing of a drug as evidenced by both: (1) disclosures about capital investment, revenue expectations, and actions consistent with the normal course of business for marketing of a biosimilar biological product before September 1, 2025, and (2) a manufacturing schedule that is consistent with the public-facing statements and, as clarified in this revised guidance, demonstrates readiness to meet revenue expectations. CMS chose these criteria because they are indicative of operational readiness and should be available in the elements that CMS must consider in making this determination as required by section 1192(f)(1)(B)(ii) of the Act.

In determining whether an Initial Delay Request satisfies the high likelihood threshold, CMS may use all the information described in section 30.3.1.3 of this revised guidance to determine whether an application for licensure under section 351(k) of the PHS Act for the Biosimilar has been accepted for review or approved by the FDA. In accordance with section 1192(f)(3)(B) of the Act, CMS is required to use information from the following items when assessing whether there is clear and convincing evidence that the Biosimilar will be marketed before September 1, 2025:

- All agreements related to the Biosimilar filed with the Federal Trade Commission or the Assistant Attorney General pursuant to subsections (a) and (c) of section 1112 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003;
- The manufacturing schedule for the Biosimilar submitted to the FDA during its review of the application for licensure under section 351(k) of the PHS Act for the Biosimilar; and
- Disclosures (in filings by the Biosimilar Manufacturer with the Securities and Exchange Commission required under section 12(b), 12(g), 13(a), or 15(d) of the Securities Exchange Act of 1934 about capital investment, revenue expectations, and actions taken by the manufacturer that are typical of the normal course of business in the year (or the two years, as applicable) before marketing of a biosimilar biological product) that pertain to the marketing of the Biosimilar, or comparable documentation that is distributed to the shareholders of privately held companies.

[48] As described in section 30.3.1.1 of this revised guidance, an Initial Delay Request will not be granted if the Biosimilar Manufacturer enters into an agreement with the Reference Manufacturer that requires or incentivizes the Biosimilar Manufacturer to submit an Initial Delay Request or directly or indirectly restricts the quantity of the Biosimilar sold in the United States on or after September 1, 2023.

In accordance with section 1198(2) of the Act, there will be no administrative or judicial review of CMS' determinations under section 1192(f) of the Act.

30.3.1.3 Submitting an Initial Delay Request for Initial Price Applicability Year 2026

A Biosimilar Manufacturer intending to submit an Initial Delay Request for initial price applicability year 2026 was required to submit a complete request by 11:59 pm PT on May 22, 2023. The process for Biosimilar Manufacturers to submit an Initial Delay Request, including the required documentation, for initial price applicability year 2026 is detailed below.

A Biosimilar Manufacturer should have submitted an Initial Delay Request for initial price applicability year 2026 only if it (1) plans for its Biosimilar to be licensed and marketed before September 1, 2025, (2) believes its request will satisfy the statutory requirements for granting an Initial Delay Request, as described in section 30.3.1.1 of this revised guidance, and (3) believes that its request demonstrates that there is a high likelihood that the Biosimilar will be licensed and marketed before September 1, 2025, based on the criteria described in section 30.3.1.2 of this revised guidance.[49]

CMS has designed the process for Initial Delay Request submission for initial price applicability year 2026 to allow CMS time to adjudicate all requests in advance of September 1, 2023, the selected drug publication date, and to be operationally feasible. For initial price applicability year 2026, CMS accepted Initial Delay Requests submitted via email and Box[50] as described below, whereas, for future initial price applicability years, CMS plans to issue guidance on use of the CMS HPMS to receive and process these requests. Accordingly, Initial Delay Requests for initial price applicability year 2026 were able to be submitted via the following process:

1. The Biosimilar Manufacturer emailed IRARebateandNegotiation@cms.hhs.gov to indicate its intention to submit an Initial Delay Request for initial price applicability year 2026. The Biosimilar Manufacturer was encouraged to use the template, including subject line and body content, described in Appendix A of this revised guidance. Emails must have been received by 11:59 pm PT on May 10, 2023.
2. Within 5 business days of receipt, CMS responded by providing the Biosimilar Manufacturer with (1) a fillable template for the Initial Delay Request form, available in Appendix B of this revised guidance, and (2) access to a Box folder specific to the Biosimilar Manufacturer's Initial Delay Request. No parties other than the Biosimilar Manufacturer and CMS and its contractors have access to this folder.
3. The Biosimilar Manufacturer must have uploaded a complete Initial Delay Request with the following documentation to the Box folder or using an alternative submission approach approved by CMS by 11:59 pm PT on May 22, 2023. CMS deemed an Initial Delay Request to be complete if it included:

[49] For initial price applicability year 2026, an Initial Delay Request should have been submitted by a Biosimilar Manufacturer that anticipated the reference product for its Biosimilar will be included in one of the ten covered Part D Drugs that will be a selected drug for this initial price applicability year. Biosimilar Manufacturers are encouraged to consult publicly available data on expenditures for covered Part D drugs, including data published by CMS, which may allow them to determine the likelihood that a given drug may be a selected drug for a future initial price applicability year.

[50] See: https://www.box.com/; if a Biosimilar Manufacturer is unable to use Box, it should have included an explanation in its email in step #1 below and request an alternative submission method.

a. A complete Initial Delay Request form using the fillable template that the Biosimilar Manufacturer received from CMS. This template allowed submission of:
    i. information used to identify the Biosimilar Manufacturer, the Biosimilar, the Biosimilar's reference product, and the Reference Manufacturer;
    ii. attestations that the Initial Delay Request meets the statutory requirements listed in section 30.3.1.1 of this revised guidance; and
    iii. information on the status of licensure for the Biosimilar under section 351(k) of the PHS Act;
b. All agreements related to the Biosimilar filed with the Federal Trade Commission or the Assistant Attorney General pursuant to subsections (a) and (c) of section 1112 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003;
c. The manufacturing schedule for the Biosimilar submitted to the FDA during its review of the application for licensure under section 351(k) of the PHS Act, to the extent available; and
d. Disclosures (in filings by the Biosimilar Manufacturer with the Securities and Exchange Commission required under section 12(b), 12(g), 13(a), or 15(d) of the Securities Exchange Act of 1934 about capital investment, revenue expectations, and actions taken by the manufacturer that are typical of the normal course of business in the year (or the two years, as applicable) before marketing of a biosimilar biological product) that pertain to the marketing of the Biosimilar, or comparable documentation that is distributed to the shareholders of privately held companies, to the extent available.

In accordance with section 1192(f)(1)(B)(ii) of the Act, Initial Delay Requests for initial price applicability year 2026 that were not submitted by 11:59 pm PT on May 22, 2023 or that did not include all elements will be denied. CMS is clarifying in this revised guidance that information in an Initial Delay Request that is a trade secret or confidential commercial or financial information will be protected from disclosure if the information meets the requirements set forth under Exemptions 3 and/or 4 of the FOIA (5 U.S.C. § 552(b)(3), (4)).

30.3.1.4 Process and Timing After Submission of an Initial Delay Request for Initial Price Applicability Year 2026

Within 5 business days after the Biosimilar Manufacturer uploaded the required documentation to its Box folder or using an alternative submission approach approved by CMS, CMS sent an email confirming receipt to the email address used by the Biosimilar Manufacturer in its initial email to CMS expressing its intent to submit an Initial Delay Request. In accordance with section 1192(f)(1)(B)(ii)(II) of the Act, after reviewing an Initial Delay Request, inclusive of the materials submitted therein, CMS may request additional information from the Biosimilar Manufacturer as necessary to make a determination with respect to the Initial Delay Request. For initial price applicability year 2026, CMS made any such follow-up request in writing to the Biosimilar Manufacturer via the same email address on or before June 20, 2023. Any such written request specified the additional information required, the format and manner in which the Biosimilar Manufacturer must provide the additional information, and the deadline for providing such information, which will be no later than July 3, 2023. The one exception to these deadlines

is as follows: per section 30.3.1.2 of this revised guidance, for CMS to determine that there is a high likelihood of the Biosimilar being licensed and marketed prior to September 1, 2025, the Biosimilar's application for licensure must be accepted for review or approved by the FDA no later than August 15, 2023. CMS will permit the Biosimilar Manufacturer to update CMS on the status of the Biosimilar's application for licensure before 11:59 pm Pacific Time (PT) on August 15, 2023, in order to enable CMS to use the most recent possible data to make this determination while still allowing for sufficient time to inform the selected drug list published on September 1, 2023, in accordance with section 1192(a) of the Act.

Prior to September 1, 2023, the selected drug publication date for initial price applicability year 2026, CMS will review each Initial Delay Request in the following manner. First, CMS will review each Initial Delay Request to determine whether it includes all of the elements for an Initial Delay Request and was submitted by the applicable deadline in accordance with section 30.3.1.3 of this revised guidance. Second, if an Initial Delay Request includes all required elements and was timely submitted, CMS will review the Initial Delay Request to determine if it meets all of the statutory requirements described in section 30.3.1.1 of this revised guidance, with the exception of the high likelihood requirement. Third, if the Initial Delay Request meets all statutory requirements other than the high likelihood requirement, CMS will review the Initial Delay Request to determine whether it demonstrates a high likelihood that the Biosimilar will be licensed and marketed by September 1, 2025, as described in section 30.3.1.2 of this revised guidance. In considering an Initial Delay Request, CMS will cease consideration upon finding that the Initial Delay Request has failed to meet any of these requirements. For example, if CMS determines an Initial Delay Request was not submitted by the established deadline, CMS will not review that request against other statutory requirements; if CMS determines an Initial Delay Request fails to meet one or more of the statutory requirements described in section 30.3.1.1 of this revised guidance, with the exception of the high likelihood requirement, CMS will not consider whether that Initial Delay Request demonstrates a high likelihood that the Biosimilar will be licensed and marketed before September 1, 2025.

The list of selected drugs published for initial price applicability year 2026 will reflect the results of CMS' determinations with respect to any Initial Delay Requests that are submitted, i.e., a Reference Drug that, absent a successful Initial Delay Request, would have been selected, will not appear on the selected drug list published by September 1, 2023 if it is named in a successful Initial Delay Request.

After completing its review, CMS will notify each Biosimilar Manufacturer that submits an Initial Delay Request for initial price applicability year 2026 in writing of CMS' determination regarding such request. This notification will occur on or after September 1, 2023, but no later than September 30, 2023, and will include a brief summary of CMS' determination, including:

- Whether the Initial Delay Request was successful or unsuccessful; and
- If unsuccessful, the reason CMS determined that the Initial Delay Request was unsuccessful, including but not limited to:
    - failure to submit all elements of the Initial Delay Request by the applicable deadline;
    - failure to meet another statutory requirement for granting a request (other than the high likelihood requirement), including in the case that the Reference Drug would

not have been a selected drug for initial price applicability year 2026 absent the Initial Delay Request; or

- failure to demonstrate a high likelihood that the Biosimilar will be licensed and marketed before September 1, 2025.

CMS will also notify each Reference Manufacturer named in a successful Initial Delay Request using the CMS HPMS to identify the relevant point(s) of contact. Such notification will be in writing and will identify the Reference Drug that would have been a selected drug in initial price applicability year 2026, absent the successful Initial Delay Request. Reference Manufacturers named in unsuccessful Initial Delay Requests will not be notified. In this revised guidance, CMS is clarifying that it will publish the number of Reference Drugs that would have been selected drugs for initial price applicability year 2026, absent successful Initial Delay Requests, as part of publishing the selected drug list on September 1, 2023.

In accordance with section 1192(f)(2)(B) of the Act, CMS must determine whether each Biosimilar named in a successful Initial Delay Request is licensed and marketed during the initial delay period. For successful Initial Delay Requests submitted with respect to initial price applicability year 2026, CMS will make this determination by mid-2024; CMS is still determining the appropriate date by which this determination should be made and plans to publish a specific date in future guidance. The timing, content, and format of this notification will be specified in future guidance.

The following table provides a summary of key dates related to implementation of the Biosimilar Delay for initial price applicability year 2026, as specified in this section 30.3.1:

Date	Deadline / milestone
11:59 pm PT on May 10, 2023	Deadline for Biosimilar Manufacturer to email CMS regarding intent to submit Initial Delay Request for initial price applicability year 2026
11:59 pm PT on May 22, 2023	Deadline for Biosimilar Manufacturer to submit the documentation for its Initial Delay Request as specified in section 30.3.1.3 of this revised guidance
June 20, 2023	Deadline for CMS to request follow-up information for a submitted Initial Delay Request, if applicable
July 3, 2023	Deadline for Biosimilar Manufacturer to submit any follow-up information requested by CMS, if applicable
11:59 pm PT on August 15, 2023	Deadline for Biosimilar application for licensure to be accepted for review or approved by the FDA; deadline for Biosimilar Manufacturer to submit any follow-up information requested by CMS related to the Biosimilar application for licensure
September 1, 2023	Statutory deadline for CMS to publish the selected drug list for initial price applicability year 2026. Along with the selected drug list, CMS will publish the number of drugs that would have been selected drugs, absent successful Initial Delay Requests.
September, 2023	CMS informs each Biosimilar Manufacturer that submitted an Initial Delay Request of the results of such request, in writing; for successful Initial Delay Requests, CMS also informs the Reference Manufacturer
Mid-2024[51]	For successful Initial Delay Requests, CMS determines whether the Biosimilar has been licensed and marketed during the initial delay period

Information on other policies related to section 1192(f) of the Act will be included in future guidance, including, but not limited to:

- the deadline and process for submitting an Initial Delay Request for initial price applicability year 2027;
- the deadline and process for submitting an Additional Delay Request for initial price applicability year 2027, in the event an Initial Delay Request for initial price applicability year 2026 is granted and CMS determines by mid-2024 that the Biosimilar was not licensed and marketed during the initial delay period;[52]
- the criteria for adjudicating Additional Delay Requests;
- the impact of Initial Delay Requests and Additional Delay Requests on the selected drug list for initial price applicability year 2027; and
- the application and calculation of rebates for a Reference Drug for 2026, as applicable.

30.4 Publication of the Selected Drug List

In accordance with section 1192(a) of the Act, CMS will publish the selected drug list for initial price applicability year 2026 no later than September 1, 2023. This list will include the 10 (or all, if such number is less than 10) drugs selected for negotiation for initial price applicability year 2026, including the active moiety / active ingredient for each selected drug, and the list of NDC-9s and NDC-11s for the selected drug that either had PDE utilization in the 12-month period

[51] CMS plans to publish a specific date in future guidance.
[52] CMS plans to publish a specific date in future guidance.

beginning June 1, 2022 and ending May 31, 2023 or that CMS believes are likely to have PDE utilization in the future (for example, NDC-11s associated with recently approved NDAs / BLAs).[53] CMS will post the selected drug list on the CMS IRA webpage and update this list in accordance with the process described in section 40.2 of this guidance.[54]

40. Requirements for Manufacturers of Selected Drugs for Initial Price Applicability Year 2026

In accordance with section 1193(a) of the Act, the Secretary shall enter into agreements with manufacturers of selected drugs. In section 1191(c)(1) of the Act, the Negotiation Program statute adopts the definition of "manufacturer" established in section 1847A(c)(6)(A) of the Act. Section 1193(a)(1) of the Act establishes that CMS will negotiate an MFP with "the manufacturer" of the selected drug. To the extent that more than one entity meets the statutory definition of manufacturer for a selected drug for purposes of initial price applicability year 2026, CMS will designate the entity that holds the NDA(s) / BLA(s) for the selected drug to be "the manufacturer" of the selected drug (hereinafter "Primary Manufacturer").

Likewise, for initial price applicability year 2026, CMS will refer to any other entity that meets the statutory definition of manufacturer for a drug product included in the selected drug and that either (1) is listed as a manufacturer in an NDA or BLA for the selected drug or (2) markets the selected drug pursuant to an agreement with the Primary Manufacturer but is not listed on the NDA or BLA as a "Secondary Manufacturer." A Secondary Manufacturer will include any manufacturer of any authorized generics and any repackager or relabeler of the selected drug that meet these criteria. A manufacturer that is not listed as a manufacturer on the NDA / BLA and without an agreement in place with the Primary Manufacturer would not be considered a Secondary Manufacturer.

In the example described in section 30.1 of this revised guidance, if the potential qualifying single source drug described was selected for negotiation, entity "A" would be considered the Primary Manufacturer while entity "B" would be considered a Secondary Manufacturer either because it was listed as a manufacturer in NDA-1 or if it was not listed as a manufacturer in NDA-1 because it markets the three strengths of the immediate release tablets manufactured by entity A pursuant to an agreement with entity A.

CMS will sign an agreement (a "Medicare Drug Price Negotiation Program Agreement," herein referred to as an "Agreement") with the willing Primary Manufacturer of each selected drug and believes this approach aligns with the statute's requirement to negotiate to determine an MFP with "the manufacturer" of a selected drug in accordance with section 1193(a) of the Act. This Agreement, as described in this section 40, will set forth requirements of the Primary Manufacturer with respect to its participation in the Negotiation Program, including with respect to section 1193(a)(5) of the Act, which requires the Primary Manufacturer to comply with

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[53] CMS acknowledges that, for some selected drugs, the list of NDC-9s and NDC-11s might not reflect all NDCs marketed pursuant to the approved NDA(s) / BLA(s). For example, if a selected drug includes one NDC-9 that has no current or future Part D PDE utilization (e.g., the NDC-9 is utilized only in Part B settings of care), that NDC-9 and associated NDC-11s would not be included on the published list of NDC-9s and NDC-11s of the selected drug for initial price applicability year 2026.

[54] See: https://www.cms.gov/inflation-reduction-act-and-medicare.

requirements set forth in this revised guidance, which CMS has determined are necessary for purposes of administering and monitoring compliance with the Negotiation Program.

CMS will not enter into an Agreement with any Secondary Manufacturer of a selected drug with respect to that drug. As such, under section 1193(a)(4), a Primary Manufacturer that enters into an Agreement must collect and report necessary information applicable to any Secondary Manufacturer(s) as described in section 40.2 of this revised guidance. As the entity that is party to the Agreement, the Primary Manufacturer will be solely responsible for compliance with all provisions of the Agreement and will be accountable for ensuring compliance with respect to units of the selected drug manufactured by the Secondary Manufacturer or marketed by any Secondary Manufacturer pursuant to an agreement with the Primary Manufacturer. In accordance with section 1193(a)(1) of the Act and section 40.4 of this revised guidance, the Primary Manufacturer must ensure that any Secondary Manufacturer(s) make the MFP available to MFP-eligible individuals and to pharmacies, mail order services, and other dispensers. For initial price applicability year 2026, the scope of Primary Manufacturer responsibility to provide access to the MFP for the selected drug is limited to units of such drug sold by the Primary Manufacturer or a Secondary Manufacturer. CMS reiterates that the requirement for Primary Manufacturers to provide access to the MFP applies to all sales of the selected drug to MFP-eligible individuals and to pharmacies, mail order services, and other dispensers that are providing a selected drug to an MFP-eligible individual, as described in section 80 of this revised guidance. Failure to comply with obligations to make the MFP available may result in civil monetary penalties being assessed on the Primary Manufacturer pursuant to section 1197(a) of the Act.

CMS requires that for initial price applicability year 2026, the Primary Manufacturer of a selected drug is the entity that does each of the following:

1. Signs the Agreement with CMS, as described in section 40.1 of this revised guidance;
2. Collects and reports all data required for negotiation under section 1193(a)(4) of the Act, including the negotiation data elements, as described in section 40.2, section 50.1, and Appendix C of this revised guidance;
3. Negotiates an MFP with CMS, as described in section 40.3 of this revised guidance;
4. Ensures the MFP is made available to all MFP-eligible individuals and to pharmacies, mail order services, and other dispensers that dispense the selected drug to those individuals, as described in section 40.4 of this revised guidance; and
5. Responds to CMS requests within specified timeframes with documentation demonstrating compliance and remedial actions, as applicable, pursuant to reports of noncompliance or other CMS compliance and oversight activities, and pays any CMPs for violations, including: violating the terms of the Agreement; providing false information under the procedures to apply the aggregation rule for the Small Biotech Exception or the Biosimilar Delay; failing to pay the rebate amount for a biological product for which inclusion on the selected drug list was delayed but which has since undergone negotiation as described in section 1192(f)(4) of the Act; or not providing access to the MFP to MFP-eligible individuals, pharmacies, mail order services, and other dispensers, as described in section 40.5, section 90, and section 100 of this revised guidance.

Termination of an Agreement for the Negotiation Program is described in section 40.6 of this revised guidance, and other relevant provisions from the Agreement are described in section 40.7. of this revised guidance.

40.1 Entrance into an Agreement with CMS and Alternatives

Section 1193(a) of the Act instructs CMS to enter into agreements with manufacturers of selected drugs for a price applicability period. The deadline for the Primary Manufacturer of a selected drug to enter into an Agreement for initial price applicability year 2026 is October 1, 2023. The Primary Manufacturer must use the CMS HPMS to identify relevant authorized representative(s) and effectuate the Agreement.[55]

CMS recommends, but does not require, that within five days following publication by CMS on September 1, 2023 of the list of selected drugs for an initial price applicability year, the Primary Manufacturer submit to CMS the name(s), title(s), and contact information for the representative(s) authorized to execute the Agreement. CMS recommends taking this action as soon as possible to facilitate timely communication and effectuation of the Agreement. The authorized representative(s) must be legally authorized to bind the Primary Manufacturer to the terms and conditions contained in the Agreement, including any Addenda. The authorized representatives should follow instructions made available on the CMS HPMS webpage to gain access to the CMS HPMS. To be eligible for electronic signature access in CMS HPMS, an authorized representative must be the Primary Manufacturer's Chief Executive Officer, Chief Financial Officer, an individual with equivalent authority to a Chief Executive Officer or Chief Financial Officer, or an individual that has been granted direct delegated authority to perform electronic signatures on behalf of one of the individuals previously noted. CMS notes that it is a requirement of the CMS HPMS that the person accessing the CMS HPMS have a Social Security Number (SSN). An authorized representative of the Primary Manufacturer must access the CMS HPMS and sign the Agreement by October 1, 2023.

The negotiation period for initial price applicability year 2026 will begin on the earlier of two dates: the date on which the Agreement is executed (i.e., signed by both CMS and the Primary Manufacturer) or October 1, 2023. If an Agreement is fully executed before October 1, 2023, the negotiation period (as defined in section 1191(b)(4) of the Act) will begin on the date on which the Agreement is signed by the last party to sign it. If the Agreement is not fully executed by October 1, 2023, then pursuant to 26 U.S.C. § 5000D(b)(1), a period will begin on October 2, 2023, during which the manufacturer could be exposed to potential excise tax liability. CMS will make reasonable efforts to make the final text of the Agreement available to the public before the selected drug list for initial price applicability year 2026 is published.

Section 11003 of the IRA expressly connects a Primary Manufacturer's financial responsibilities under the voluntary Negotiation Program to that manufacturer's voluntary participation in the Medicaid Drug Rebate Program, the Medicare Coverage Gap Discount Program, and the Manufacturer Discount Program. If a Primary Manufacturer decides it is unwilling to enter into an Agreement for the Negotiation Program, it may expedite its exit from the Medicare Coverage Gap Discount Program and the Manufacturer Discount Program by submitting to CMS a notice that incorporates both: (1) a notice of decision not to participate in the Negotiation Program; and

[55] See: https://hpms.cms.gov/app/ng/home/.

(2) a request for termination of the Primary Manufacturer's applicable agreements under the Medicaid Drug Rebate Program, the Medicare Coverage Gap Discount Program, and the Manufacturer Discount Program. When a Primary Manufacturer submits such a notice, CMS will find good cause to terminate the Primary Manufacturer's agreement(s) under the Medicare Coverage Gap Discount Program and the Manufacturer Discount Program, as applicable, pursuant to section 1860D-14A(b)(4)(B)(i) and section 1860D-14C(b)(4)(B)(i) of the Act to expedite the date on which none of the drugs of the Primary Manufacturer are covered by an agreement under section 1860D-14A or section 1860D-14C. CMS has determined (and hereby provides notice) that it will automatically grant such termination requests upon receipt, and that it will expedite the effective date of the Primary Manufacturer's termination of its Medicare Coverage Gap Discount Program and/or Manufacturer Discount Program agreements consistent with the statutory limitation that termination shall not be effective earlier than 30 calendar days after the date of notice to the manufacturer of such termination.

If a Primary Manufacturer has determined it would not be willing to enter into an Agreement for the Negotiation Program if one of its drugs is listed as a selected drug and has submitted a notice of its decision and its request for termination as described above, CMS shall, upon written request from such Primary Manufacturer, provide a hearing concerning its termination request. Such a hearing will be held prior to the effective date of termination with sufficient time for such effective date to be repealed. Such a hearing will be held solely on the papers; because CMS' determination that there is good cause for termination depends solely on the Primary Manufacturer's request for termination to effectuate its decision not to participate in the Negotiation Program, the only question to be decided in the hearing is whether the Primary Manufacturer has asked to rescind its termination request prior to the effective date of the termination. CMS will automatically grant such request from the Primary Manufacturer to rescind its termination request.

40.2 Submission of Manufacturer Data to Inform Negotiation

After entering into an Agreement with CMS and in accordance with section 1193(a)(4) of the Act, the Primary Manufacturer of each selected drug must submit to CMS the following information with respect to the selected drug: information on the non-Federal average manufacturer price ("non-FAMP") (defined in section 8126(h)(5) of title 38, United States Code), as described in section 50.1.1 and Appendix C of this revised guidance, and any information that CMS requires to carry out negotiation, including but not limited to the factors listed in section 1194(e)(1) of the Act, as described in section 50.1 and Appendix C of this revised guidance. This information must be submitted by the Primary Manufacturer to CMS no later than October 2, 2023, for initial price applicability year 2026.

The Agreement must be fully executed, meaning both the Primary Manufacturer and CMS have signed the Agreement, before the Primary Manufacturer may submit the data elements described in this section. While these data elements may not be submitted prior to execution of the Agreement, Primary Manufacturers will be able to access the data elements template in the CMS HPMS, and CMS believes Primary Manufacturers will be able to gather these data prior to the Agreement being executed. By signing the Agreement, a Primary Manufacturer agrees to use the CMS HPMS and comply with all relevant procedures and policies set forth in the CMS HPMS for utilizing the system.

Certain data, as described in section 50.1 and Appendix C of this revised guidance, must reflect any products included in the selected drug marketed by a Secondary Manufacturer(s), and the Primary Manufacturer is responsible for collecting such data from such Secondary Manufacturer(s) and including this information in its submission to CMS.

For each selected drug for initial price applicability year 2026, CMS will populate the CMS HPMS with the list of the NDC-11s published in accordance with section 30.4 of this revised guidance, meaning those NDC-11s of the selected drug that either had Part D PDE utilization in the 12-month period beginning June 1, 2022 and ending May 31, 2023 or which CMS believes are likely to have PDE utilization in the future (for example, NDC-11s associated with recently approved NDAs / BLAs). This list will include any NDC-11s of the selected drug marketed by the Primary Manufacturer and any Secondary Manufacturer. CMS will transmit the list to the Primary Manufacturer of the selected drug. In connection with the data submission described in section 50.1 of this revised guidance, the Primary Manufacturer must provide CMS with information regarding the NDC-11s that may be appropriate to ensure the list is complete and accurate, including but not limited to, whether any NDC-11s associated with the NDA(s) / BLA(s) of the selected drug are missing from the list (e.g., because they are new NDC-11s), including any missing NDC-11s of a Secondary Manufacturer of the selected drug; whether any of the listed NDC-11s are marketed or controlled solely by a manufacturer that is not the Primary Manufacturer or a Secondary Manufacturer; and whether any of the listed NDC-11s have been discontinued. CMS will collect this information in the CMS HPMS as part of the collection of the other data elements described in section 50.1 of this revised guidance and update this list as necessary (e.g., based on supplements from the Primary Manufacturer or other updates).

This list of NDC-11s constitutes the baseline of NDCs of the selected drug as described in section 30 of this revised guidance that will be subject to the negotiation process for initial price applicability year 2026. The NDC-11s on this list will be included in ceiling calculations for initial price applicability year 2026 as described in section 60.2, to the extent data are available to support such calculations. CMS will also use the NDC-11s on this list for the calculations used to apply the MFP across dosage forms and strengths of the selected drug for initial price applicability year 2026 as described in section 60.5 of this revised guidance. In addition, CMS will use the information supplied by the Primary Manufacturer about discontinued NDC-11s as additional context for the data elements described in section 50.1 of this revised guidance (e.g., notice that an NDC-11 has been discontinued may explain why a Primary Manufacturer submitted partial year data for a particular NDC-11 of a selected drug).

The Primary Manufacturer has an ongoing obligation to timely report any changes in this information to ensure the list of NDC-11s of the selected drug in the CMS HPMS remains complete and accurate consistent with this revised guidance and any future guidance and regulations. For example, a Primary Manufacturer must report to CMS any new NDC-11s of the selected drug at least 30 days prior to their first marketed date for any Primary Manufacturer or any Secondary Manufacturer(s) of such selected drug; if CMS believes these new NDC-11s are likely to have PDE utilization in the future, these NDC-11s will be added to the list of NDC-11s of the selected drug. The Primary Manufacturer also must report to CMS the delisting of any NDC-11 of the selected drug that is no longer marketed by the Primary Manufacturer or any

Secondary Manufacturer(s) within 30 days after its discontinuation. Failure of the Primary Manufacturer to provide timely information material to the accuracy of the list of NDC-11s of the selected drug as described in this section 40.2 of the revised guidance will be considered a violation of the Agreement pursuant to section 1193(a)(5) of the Act and may cause the Primary Manufacturer to be subject to civil monetary penalties per section 1197(c) of the Act.

40.2.1 Confidentiality of Proprietary Information

Section 1193(c) of the Act states that CMS must determine which information submitted to CMS by a manufacturer of a selected drug is proprietary information of that manufacturer. Information that is deemed proprietary shall only be used by CMS or disclosed to and used by the Comptroller General of the United States for purposes of carrying out the Negotiation Program. Proprietary information, including trade secrets and confidential commercial or financial information, will also be protected from disclosure if the proprietary information meets the requirements set forth under Exemptions 3 and/or 4 of the FOIA (5 U.S.C. § 552(b)(3), (4)).[56]

CMS will implement a confidentiality policy that is consistent with existing federal requirements for protecting proprietary information, including Exemptions 3 and/or 4 of the FOIA, and that strikes an appropriate balance between (1) protecting the highly sensitive information of manufacturers and ensuring that manufacturers submit the information CMS needs for the Negotiation Program, and (2) avoiding treating information that does not qualify for such protection as proprietary. Thus, for initial price applicability year 2026, CMS will treat information on non-FAMP as proprietary.

For initial price applicability year 2026, CMS will also treat certain data elements submitted by a Primary Manufacturer of a selected drug in accordance with section 1194(e)(1) and section 1194(e)(2) of the Act as proprietary if the information constitutes confidential commercial or financial information of the Primary Manufacturer or a Secondary Manufacturer. Specifically, CMS will treat research and development costs and recoupment, unit costs of production and distribution, pending patent applications, market data, revenue, and sales volume data as proprietary, unless the information that is provided to CMS is already publicly available, in which case it would be considered non-proprietary. CMS will treat the data on prior Federal financial support and approved patent applications, exclusivities, and applications and approvals under section 505(c) of the FD&C Act or section 351(a) of the PHS Act as non-proprietary because CMS understands these data are publicly available.

Pursuant to section 1195(a)(2) of the Act, CMS is required to publish the explanation of the MFP by March 1, 2025, for initial price applicability year 2026 (see section 60.6.1 of this revised guidance). In this public explanation and any other public documents discussing the MFP, CMS will make public the section 1194(e)(1) and section 1194(e)(2) data submitted by the Primary Manufacturer and the public that are determined to be non-proprietary, but will not include any protected health information (PHI) or personally identifiable information (PII). CMS will also make public high-level comments about the section 1194(e)(1) and section 1194(e)(2) data submitted to CMS that are determined to be proprietary, without sharing any PHI / PII or any proprietary information reported to CMS under section 1193(a)(4) for purposes of the negotiation. For example, CMS will not make public the research and development costs

[56] See: https://www.justice.gov/oip/doj-guide-freedom-information-act-0.

reported by a Primary Manufacturer, as CMS would treat that data as proprietary, but CMS may say "the manufacturer has recouped its research and development costs." Any proprietary information obtained during the course of an audit will also remain confidential, except as necessary to use that information in the course of a judicial enforcement proceeding.

40.2.2 Data and Information Use Provisions and Limitations

CMS will not publicly discuss ongoing negotiations with a Primary Manufacturer, except as outlined below. As described in section 60.6.1, CMS will make public a narrative explanation of the negotiation process and share redacted information regarding the section 1194(e) data received, exchange of offers and counteroffers, and the negotiation meetings, if applicable.

Primary Manufacturers may choose to publicly disclose information regarding its ongoing negotiations with CMS at its discretion. If a Primary Manufacturer discloses information that is made public regarding any aspect of the negotiation process prior to the explanation of the MFP being released by CMS, CMS reserves the right to publicly discuss the specifics of the negotiation process regarding that Primary Manufacturer. If a Primary Manufacturer chooses to disclose any material that is made public that CMS has previously deemed to be proprietary information of that Primary Manufacturer, CMS will no longer consider that material proprietary consistent with section 40.2.1 of this guidance. For example, if a Primary Manufacturer chooses to publicly disclose the unit cost of production, CMS will no longer consider the unit cost of production to be proprietary. If the Primary Manufacturer chooses to disclose proprietary information prior to the explanation of the MFP, then it will not be redacted in the explanation of the MFP. Primary Manufacturers negotiating an MFP with CMS pursuant to the process set forth in section 60 are reminded that statements to or discussions with other Primary Manufacturers also engaged in the MFP negotiation process with CMS could negatively impact the competitive process for each independent MFP negotiation. Information exchanges concerning confidential and strategic business negotiations may violate the antitrust laws under certain circumstances and lead to other anticompetitive agreements. Primary Manufacturers should consider the antitrust implications of any such actions.

CMS will prohibit audio or video recording of any negotiation meetings between CMS and a Primary Manufacturer. CMS will maintain written records of the negotiation process, including negotiation meetings, in compliance with applicable federal law, including the Federal Managers Financial Integrity Act and the Federal Records Act. A Primary Manufacturer can maintain its own written record of these exchanges.

40.2.3 Opportunity for Corrective Action Following Information Submission

Recognizing the substantial role that manufacturer-submitted information will play in the negotiation process and in administering and monitoring the Negotiation Program, CMS will provide an opportunity for corrective action in the event a submission is incomplete or inaccurate. Upon receipt of Primary Manufacturer-submitted information – for example, information on the section 1194(e)(1) factors – CMS will review the submission for completeness and accuracy. Should CMS determine a submission is incomplete or contains inaccurate information, CMS will provide a written request that the Primary Manufacturer take corrective action and resubmit the information. CMS will provide five business days for the Primary Manufacturer to correct the submission and/or provide additional information to validate

the accuracy/completeness of the original submission. Following resubmission, CMS may follow up with the Primary Manufacturer to clarify any information included in the resubmission and confirm full accuracy and completeness of the required information.

To facilitate the corrective action process, CMS will provide the Primary Manufacturer with a written request for the corrected information, which will be transmitted to the Primary Manufacturer following CMS' discovery of any inaccurate or incomplete submissions. The written request will include a deadline for resubmitting the information (i.e., the end of the five-business day period). CMS will make efforts to be available to engage with the Primary Manufacturer about the specifics of the request for corrected information and to answer questions and provide clarification. Note that failure to engage in timely corrective action may result in the Primary Manufacturer being subject to civil monetary penalties as authorized under section 1197(c) for failure to submit required information.

40.3 Negotiation and Agreement to an MFP and Renegotiation in Later Years

CMS will use the CMS HPMS to share the initial offer and concise justification, any subsequent offer and justification, and to receive any counteroffer(s) from the Primary Manufacturer of a selected drug. A Primary Manufacturer that signs the Agreement will be required to adhere to the process and deadlines described in section 60 of this revised guidance. CMS will also use the CMS HPMS to share and receive an Addendum to the Agreement, as applicable, in order for CMS and the Primary Manufacturer to effectuate agreement upon the MFP that results from the negotiation process. For example, concurrent with the agency's provision of the initial offer, CMS will populate an Addendum in the CMS HPMS containing the MFP identified in the initial offer; if a Primary Manufacturer wishes to accept CMS' initial offer, it can sign the Addendum in the CMS HPMS. Similarly, concurrent with the Primary Manufacturer's submission of a written counteroffer, the Primary Manufacturer will populate an Addendum in the CMS HPMS containing the MFP identified in the counteroffer and sign the Addendum; if CMS wishes to accept the counteroffer, it will countersign the Addendum in the CMS HPMS. CMS will determine that negotiations have concluded upon execution by both parties of the Addendum setting forth the agreed-upon MFP.

Pursuant to section 1194(f) of the Act, CMS and a Primary Manufacturer may renegotiate the MFP for a selected drug, beginning with 2028. CMS plans to release guidance related to the renegotiation process in future years.

40.4 Providing Access to the MFP

After entering into an Agreement with CMS and in accordance with section 1193(a) of the Act, the manufacturer of a selected drug must provide access to the MFP to MFP-eligible individuals (defined in section 1191(c)(2)(A) of the Act and section 80 of this revised guidance) and to pharmacies, mail order services, and other dispensers with respect to such MFP-eligible individuals who are dispensed that drug during a price applicability period. That is, the manufacturer is required to provide access to the MFP for all dosage forms, strengths, and package sizes of the selected drug (i.e., NDCs included in the MFP file published in accordance with section 60.6 of this revised guidance), including any additional such dosage forms, strengths, and package sizes that may be further included in the MFP file, if coverage is being provided for such dosage forms, strengths, and package sizes under a prescription drug plan

under Medicare Part D or an MA–PD plan under Medicare Part C (including an Employer Group Waiver Plan).

Under section 1860D-2(d)(1)(D) of the Act, as amended by section 11001(b) of the IRA, the negotiated prices used in payment by each Part D plan sponsor for each selected drug must not exceed the MFP plus any dispensing fees for such drug. In Part D, the negotiated price of a drug is the basis for determining beneficiary cost-sharing and for benefit administration at the point of sale. Therefore, the requirement that the price used for beneficiary cost-sharing and benefit administration cannot exceed the MFP (plus dispensing fees) helps to ensure that Part D MFP-eligible individuals will have access to the MFP at the point of sale. Therefore, while section 1193(a) of the Act requires manufacturers to provide access to the MFP to MFP-eligible individuals, as a practical matter, this would be facilitated by Part D plan sponsors in the normal course.

However, section 1193(a) of the Act also requires that the manufacturer of a selected drug provide access to the MFP for the selected drug to pharmacies, mail order services, and other dispensers with respect to MFP-eligible individuals who are dispensed such drugs. CMS requires that the Primary Manufacturer ensures that entities that dispense drugs to MFP-eligible individuals, including pharmacies, mail order services, and other dispensers, have access to the MFP for the selected drug in accordance with section 1193(a) of the Act and as further described in section 90.2 of this revised guidance. CMS defines "providing access to the MFP" as ensuring that the amount paid by the dispensing entity for the selected drug is no greater than the MFP.

Primary Manufacturers must provide access to the MFP in one of two ways: (1) prospectively ensuring that the price paid by the dispensing entity when acquiring the drug is no greater than the MFP; or (2) providing retrospective reimbursement for the difference between the dispensing entity's acquisition cost and the MFP. As part of this obligation, the Primary Manufacturer must ensure the MFP is made available to pharmacies, mail order services, and other dispensers for units of the selected drug for which there is a Secondary Manufacturer. With respect to the second option, CMS plans to issue further information regarding the specific calculation that the manufacturer could use in the determination of the refund to the dispenser. CMS is exploring whether manufacturers could offer a standardized refund amount, such as the Wholesale Acquisition Cost (WAC) of the selected drug minus the MFP (WAC-MFP), in order to meet this obligation.

CMS intends to engage with a Medicare Transaction Facilitator (MTF) to facilitate the exchange of data between pharmaceutical supply chain entities to support the verification of an MFP-eligible individual who is dispensed a selected drug. CMS intends to continue to work with interested parties to identify existing processes and any new processes that would be the most viable for the supply chain to operationalize to ensure that pharmacies, mail order services, and other dispensers have access to the MFP during the price applicability period. CMS will consult with pharmacies, mail order services, and other dispensers, as well as with industry standard development organizations (SDOs), 340B covered entities and related organizations, pharmaceutical/biotechnology manufacturers, and other supply chain participants to understand existing data flows and identify opportunities for increased connectivity and data sharing. CMS is also exploring options to facilitate retrospective payment exchange between manufacturers and

dispensing entities to help effectuate access to the MFP. CMS plans to release more information in advance of initial price applicability year 2026 regarding such issues related to ensuring access to the MFP, including how CMS might support and facilitate data exchange between pharmaceutical supply chain entities.

A Primary Manufacturer must ensure that pharmacies, mail order services, and other dispensers are reimbursed timely. That is, CMS requires that the MFP must be passed through to the dispensers within 14 days of the manufacturer receiving sufficient information to verify that an individual is eligible for access to the MFP. Neither Primary Manufacturers nor their contracted entities shall charge any transaction fees for the data exchanges that would be facilitated through an MTF. Regardless of whether existing processes or new processes are used to facilitate access to the MFP, manufacturers are expected to comply with existing applicable data privacy and security laws. Primary Manufacturers must work with any Secondary Manufacturer of a selected drug to determine how the MFP will be passed through in a manner that complies with applicable data privacy and security laws.

Further, CMS requires that a Primary Manufacturer submit its process for making the MFP available, including to 340B covered entities, for the selected drug in writing to CMS at least 30 days before the start of the initial price applicability year for the selected drug. CMS intends to publish these processes on the CMS IRA website. For initial price applicability year 2026, a Primary Manufacturer of a selected drug must send its process for ensuring MFP availability to CMS in writing by December 2, 2025. A Primary Manufacturer must notify CMS of any changes to its process for making the MFP available at least 30 days before the change goes into effect. CMS will monitor for compliance, and will audit as needed, to ensure that the MFP is being made available for the selected drug (see section 90.2 of this revised guidance for additional details). A Primary Manufacturer must retain for at least ten years from the date of sale any records relating to sales of the selected drug to entities that dispense the selected drug to MFP-eligible individuals, including pharmacies, mail order services, and other dispensers for units of selected drug, in alignment with the statute of limitations period under the False Claims Act.

CMS notes that the Agreement would not restrict the Primary Manufacturer or Secondary Manufacturer(s) from offering to the Part D plans a price lower than the MFP that would be passed through to the beneficiary by the dispenser. CMS reiterates that Primary Manufacturers are responsible for ensuring that the MFP is made available to pharmacies, mail order services, and other dispensers that dispense the selected drug to MFP-eligible individuals, including ensuring that MFP is available for units of the selected drug for which there is a Secondary Manufacturer. Commercial and other payers will continue to have discretion to consider Medicare payment rates among other considerations in establishing their own payment policies.

40.4.1 Nonduplication with 340B Ceiling Price

In accordance with 1193(d) of the Act and as further described in section 90.2 of this revised guidance, the Primary Manufacturer of a selected drug is not required to provide access to the MFP for a selected drug to MFP-eligible individuals who are eligible to be dispensed such selected drug at a covered entity described in section 340B(a)(4) of the PHS Act if the selected drug is subject to an agreement described in section 340B(a)(1) of the PHS Act and the 340B

ceiling price (defined in section 340B(a)(1) of the PHS Act) is lower than the MFP for such selected drug.

A manufacturer that provides an MFP on a selected drug is not also required to provide a 340B discount on that same drug. That is, these price concessions are not cumulative. CMS expects that the ingredient cost component of all Part D prescriptions filled for a selected drug will be no greater than the drug's MFP, including when those prescriptions are filled at 340B covered entities and their contract pharmacies. CMS understands that 340B covered entities and their contract pharmacies currently use different inventory management processes for 340B drugs, such as separate physical drug inventories or a retrospective replenishment model. Regardless of the specific inventory management process used, the same policies regarding the MFP will apply, including that the manufacturer must provide access to the lower of the MFP or 340B ceiling price, such as through a replenished 340B inventory or an MFP refund within 14 days of determining that the selected drug was dispensed to an MFP-eligible individual.

CMS intends to work with the Health Resources and Services Administration, which administers the 340B Drug Pricing Program, to help to ensure that the MFP is made available to 340B covered entities where appropriate and that there is no duplication with the 340B ceiling price.

40.5 Compliance with Administrative Actions and Monitoring of the Drug Price Negotiation Program

Pursuant to CMS' statutory obligation under sections 1191(a)(4), 1196, and 1197 of the Act, CMS will establish a robust program for monitoring compliance with the Negotiation Program. After entering into an Agreement with CMS and in accordance with section 1193(a)(5) of the Act, the Primary Manufacturer must comply with requirements determined by CMS to be necessary for purposes of administering the Negotiation Program and monitoring compliance with the Negotiation Program. For example, CMS anticipates engaging in auditing processes to verify the accuracy and completeness of any information provided by the Primary Manufacturer under the requirements of section 1193(a)(4) of the Act. CMS also may audit any data related to the Primary Manufacturer providing access to the MFP, including where the selected drug is provided by a Secondary Manufacturer. CMS will document all requests for information required to administer or monitor compliance with the Negotiation Program in accordance with section 1193(a)(5) of the Act. Written requests from CMS to the Primary Manufacturer will include a date by which the requested information shall be submitted to CMS. If the Primary Manufacturer fails to submit complete and accurate information to CMS by the deadline stated in a request for information, CMS will consider the Primary Manufacturer in violation of the Agreement and the Manufacturer may be subject to civil monetary penalties as outlined in section 1197(c) of the Act.

CMS will allow a Primary Manufacturer that believes in good faith that CMS has made an error in the calculation of the ceiling or the computation of how CMS will apply a single MFP across dosage forms and strengths to submit a suggestion of error for CMS' consideration. As feasible, CMS will provide information on these calculations to the Primary Manufacturer within 60 days of the Primary Manufacturer's submission of data that complies with the requirements described in section 50.1. A Primary Manufacturer will have 30 days to submit a suggestion of error and may do so by submitting the request via email to IRARebateandNegotiation@cms.hhs.gov with

the subject line "Suggestion of Error for [name of the selected drug]." This notification should include supporting information documenting why the Primary Manufacturer believes that CMS made a mathematical error in its calculations and corresponding steps that should be reviewed. CMS will review and respond within 30 days of receiving the suggestion of error from the Primary Manufacturer if feasible. The suggestion of error process does not imply that a Primary Manufacturer need not comply with Negotiation Program requirements and will not affect any timelines or requirements of the Negotiation Program.

40.6 Termination of the Agreement

In accordance with section 1193(b) of the Act, when the Primary Manufacturer enters into the Agreement described in section 40.1 of this revised guidance, the Agreement will remain in effect, including through renegotiation, as applicable, until the selected drug is no longer considered a selected drug under section 1192(c) of the Act as described in section 70 of this revised guidance unless the Agreement is terminated sooner by the Primary Manufacturer under the conditions specified below. Accordingly, the Agreement will have an effective date as of the date the Agreement is signed by both parties (the "Effective Date"), and the term of the Agreement will be from the Effective Date of the Agreement to the earlier of the first year that begins at least 9 months after the date on which CMS determines that the selected drug is no longer a selected drug under section 1192(c) of the Act or the Agreement is terminated by either party in accordance with this section (the "Termination Date").

In accordance with section 1193(a)(5) of the Act, a Primary Manufacturer may terminate its Agreement with respect to a selected drug with respect to a price applicability period, before reaching an agreement with CMS as to the MFP for the selected drug or after such an MFP is agreed to, if the Primary Manufacturer meets certain conditions for termination consistent with the provisions in 26 U.S.C. § 5000D(c). Specifically, a Primary Manufacturer seeking to terminate its Agreement with respect to a selected drug must submit to CMS a notice of request to terminate. As noted in section 40.1, section 11003 of the IRA expressly connects a Primary Manufacturer's financial responsibilities under the voluntary Negotiation Program to that manufacturer's voluntary participation in the Medicaid Drug Rebate Program and the Medicare Coverage Gap Discount Program and the Manufacturer Discount Program. The provisions enacted at 26 U.S.C. § 5000D give the Primary Manufacturer choices with regard to the Negotiation Program. The Primary Manufacturer may participate in the Negotiation Program. The Primary Manufacturer may opt out of the Negotiation Program and pay the excise tax on the sale of the selected drug during defined periods. Alternatively, the Primary Manufacturer may opt out of the Negotiation Program and avoid the excise tax on sales of the selected drug during the period for which the manufacturer does not have applicable agreements with the Medicare and Medicaid programs and none of its drugs are covered by an agreement under section 1860D-14A or section 1860D-14C of the Act. Promoting continuity in the administration of the Negotiation Program warrants extending parallel options to a Primary Manufacturer with respect to potential CMP liability. A Primary Manufacturer with an Agreement with respect to the price applicability period with respect to a selected drug may opt out of the Negotiation Program and pay CMPs associated with violations of program requirements. Alternatively, a Primary Manufacturer seeking to cease participation in the Negotiation Program through the end of the price applicability period for a selected drug may avoid CMP liability by terminating its Agreement if it also ceases participation in the Medicaid Drug Rebate Program and the Medicare

Coverage Gap Discount Program and the Manufacturer Discount Program through the end of the price applicability period for the selected drug.

Thus, in accordance with section 1193(a)(5) of the Act, CMS has determined that the Primary Manufacturer's notice of termination of the Agreement must incorporate both (1) a request for termination of the Primary Manufacturer's applicable agreements under the Medicaid Drug Rebate Program and the Medicare Coverage Gap Discount Program and the Manufacturer Discount Program, consistent with the requirements as set forth in 26 U.S.C. § 5000D(c)(1)(A)(i), and (2) an attestation that through the end of the price applicability period for the selected drug, the Manufacturer (a) shall not seek to enter into any subsequent agreement with any such program and (b) shall not seek coverage for any of its drugs under the Medicare Coverage Gap Discount Program under section 1860D-14A of the Act or the Manufacturer Discount Program under section 1860D-14C of the Act, consistent with the requirements as set forth in 26 U.S.C. § 5000D(c)(1)(B). A Primary Manufacturer later seeking to re-enter any applicable agreement or obtain coverage for any of its drugs under the Medicare Coverage Gap Discount Program or the Manufacturer Discount Program would be deemed to have provided an invalid attestation that was a condition of termination, and the Agreement would once again become operative as of the date of re-entry into the applicable agreements or coverage for any of its drugs under the Medicare Coverage Gap Discount Program or the Manufacturer Discount Program. If a Primary Manufacturer terminated its Agreement prior to completing the negotiation process and agreeing to an MFP, such process will be initiated or resumed in accordance with the negotiation process described in section 60 of this revised guidance. In addition, the timing of the Primary Manufacturer's decision to resume participation in the Negotiation Program may implicate the renegotiation process beginning with 2028, for which guidance will be forthcoming for future years of the Negotiation Program.

If the conditions for termination of the Agreement for the Negotiation Program described above are met, CMS will terminate such Agreement effective on the first date on which the notices of termination for all applicable agreements have been received and none of the drugs of the Primary Manufacturer are covered by an agreement under the Medicare Coverage Gap Discount Program or the Manufacturer Discount Program. As is noted above, section 11003 of the IRA expressly connects a Primary Manufacturer's financial responsibilities under the voluntary Negotiation Program to that manufacturer's voluntary participation in the Medicaid Drug Rebate Program and the Medicare Coverage Gap Discount Program and the Manufacturer Discount Program. If a Primary Manufacturer determines after executing its Agreement that it is unwilling to continue its participation in the Negotiation Program and provides a termination notice that complies with the requirements in this section 40.6, CMS will find good cause to terminate the Primary Manufacturer's agreement(s) under the Medicare Coverage Gap Discount Program and the Manufacturer Discount Program, as applicable, pursuant to section 1860D-14A(b)(4)(B)(i) and section 1860D-14C(b)(4)(B)(i) of the Act to expedite the date on which none of the drugs of the Primary Manufacturer are covered by an agreement under section 1860D-14A or section 1860D-14C and thus facilitate an expedited Termination Date.

Moreover, consistent with the process described in Section 40.1 above, if a Primary Manufacturer has determined it is unwilling to continue its participation in the Negotiation Program and provides a termination notice that complies with the requirements in this section

40.6, CMS shall, upon written request from such Primary Manufacturer, provide a hearing concerning its termination request for its applicable agreements under the Medicare Coverage Gap Discount Program and the Manufacturer Discount Program, as applicable. Such a hearing will be held prior to the effective date of termination with sufficient time for such effective date to be repealed. Such a hearing will be held solely on the papers; because CMS' determination that there is good cause for termination depends solely on the Primary Manufacturer's request for termination to effectuate its decision not to participate in the Negotiation Program, the only question to be decided in the hearing is whether the Primary Manufacturer has asked to rescind its termination request prior to the effective date of the termination. CMS will automatically grant such request from the Primary Manufacturer to rescind its termination request.

Notwithstanding any termination of the Agreement, the MFP shall continue to apply for any selected drugs that were dispensed prior to the Termination Date. Also, notwithstanding the termination of the Agreement, any confidentiality, record retention, and/or data requirements and any requirements for Primary Manufacturer participation in audit and other Negotiation Program oversight activities shall continue to apply.

40.7 Other Provisions in the Agreement

Additional terms in the Agreement set forth general provisions in accordance with requirements determined by CMS to be necessary for purposes of administering or monitoring compliance with the Negotiation Program. For example, any notice required to be given by the manufacturer or CMS must be sent in writing via email to CMS- and manufacturer-designated email addresses. CMS retains the authority to amend the Agreement to reflect changes in law, regulation, or guidance, and, when possible, CMS will give the Manufacturer at least 60-day notice of any change to the Agreement.

In accordance with section 1193(a)(5) of the Act, if, after entering in an Agreement with CMS, the Primary Manufacturer of a selected drug transfers ownership of one or more NDAs / BLAs of the selected drug to another entity, the Primary Manufacturer remains responsible for all requirements of the Agreement, including the requirement to provide access to the MFP, associated with the transferred NDAs / BLAs unless and until the Primary Manufacturer transfers all the NDAs / BLAs of the selected drug that it holds to an entity and such acquiring entity assumes responsibility as the new Primary Manufacturer. Those steps must be evidenced by a novation to the transferring Primary Manufacturer's original Agreement for the Negotiation Program. The transferring Primary Manufacturer remains responsible for any outstanding Negotiation Program rebate liabilities related to the biosimilar delay provision under section 1192(f) of the Act unless and until such liabilities are transferred to the acquiring entity as the new Primary Manufacturer. The transferring Primary Manufacturer shall provide CMS at least 30 calendar days written notice before the effective date of any such transfer and, if applicable, any novation.

If the Primary Manufacturer of a selected drug transfers all NDAs / BLAs of the selected drug pursuant to the preceding paragraph, such that an acquiring entity assumes responsibility as the new Primary Manufacturer of the selected drug for purposes of the Negotiation Program, CMS recognizes that this transfer of ownership could affect the Primary Manufacturer's potential excise tax liability as well as the impact on the Primary Manufacturer of the statutory suspension

of excise tax provisions and the termination process as described in section 40.6 of this revised guidance. CMS recognizes that whether this transfer of ownership would have these impacts would depend on whether the transfer of the NDAs / BLAs was made to an entity that is not a related party (e.g., not treated as part of the same employer under subsections (a) and (b) of section 52 of the Internal Revenue Code of 1986) and complied with relevant principles of tax law.

If any provision of the Agreement is found to be invalid by a court of law, the Agreement will be construed in all respects as if the invalid or unenforceable provision(s) were eliminated, and without any effect on any other provisions.

50. Negotiation Factors

In accordance with sections 1193(a)(4) and 1194(b)(2)(A) of the Act, the Primary Manufacturer of a selected drug that has chosen to sign the Agreement must submit, in a form and manner specified by CMS, information on the non-FAMP for the selected drug (described in section 50.1.1 of this revised guidance). The Primary Manufacturer must also submit information on certain factors (described in section 1194(e)(1) of the Act and described further in section 50.1 of this revised guidance). The Primary Manufacturer will be responsible for aggregating and reporting information from any applicable Secondary Manufacturer(s). In addition, the statute prescribes that CMS also consider available evidence about therapeutic alternatives to the selected drug(s) (described in section 1194(e)(2) of the Act and described further in section 50.2 of this revised guidance).

While the statute requires that CMS consider manufacturer-specific data for the factors described at section 1194(e)(1) of the Act, the statute does not specify what sources CMS must use for the factors described at section 1194(e)(2) regarding therapeutic alternatives to a selected drug. CMS will consider evidence about therapeutic alternatives relevant to the factors described in section 1194(e)(2) of the Act submitted by members of the public, including manufacturers, Medicare beneficiaries, academic experts, clinicians, caregivers, and other interested parties. CMS believes that by allowing any interested party to submit data, CMS will be best positioned to identify all available, relevant evidence for the factors described at section 1194(e)(2).

CMS published the Negotiation Data Elements ICR in the Federal Register on March 21, 2023. The Negotiation Data Elements ICR describes how CMS will collect the data outlined in sections 1193(a)(4)(A), 1194(e)(1), and 1194(e)(2) of the Act. This ICR includes instructions on how Primary Manufacturers and members of the public may submit relevant data. The comment period for the Negotiation Data Elements ICR closed on May 22, 2023. CMS is releasing a revised version of the Negotiation Data Elements ICR on June 30, 2023, and the 30-day comment period will close on July 31, 2023.

The definitions that CMS is adopting for the purposes of describing the data to be collected for use in the Negotiation Program under sections 1193(a)(4)(A) and 1194(e)(1) of the Act are specified in Appendix C of this revised guidance.

In accordance with sections 1191(d)(5)(A), 1194(b)(2)(A), and 1193(a)(4)(B) of the Act, the data described in sections 50.1 and 50.2 of this revised guidance for drugs selected for initial price applicability year 2026 must be submitted to CMS by October 2, 2023. CMS' determination to

require public submission on the same date as manufacturer submission (i.e., October 2, 2023) serves to enable CMS to consider all submitted evidence in totality and meet the statutory deadline for the initial offer, pursuant to general program administration authority.

50.1 Manufacturer-Specific Data

Section 1194(e) of the Act directs CMS, for purposes of negotiating the MFP for a selected drug with the Primary Manufacturer, to consider certain factors, as applicable to the selected drug, as the basis for determining its offers, as described in section 60 of this revised guidance. These factors include data submitted by the Primary Manufacturer, as specified in section 1194(e)(1) of the Act. Submission of these data by the Primary Manufacturer is required if an Agreement is signed; details related to the submission process are described in section 40.2 of this revised guidance.

These data include the following and are required to be reported by the Primary Manufacturer to CMS by October 2, 2023:

1. Research and development (R&D) costs of the Primary Manufacturer for the selected drug and the extent to which the Primary Manufacturer has recouped those costs;
2. Current unit costs of production and distribution of the selected drug, averaged across the Primary Manufacturer and any Secondary Manufacturer(s);
3. Prior Federal financial support for novel therapeutic discovery and development with respect to the selected drug;
4. Data on pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the FD&C Act or section 351(a) of the PHS Act for the selected drug; and
5. Market data and revenue and sales volume data for the selected drug in the United States for the Primary Manufacturer and any Secondary Manufacturer(s).

The Primary Manufacturer should submit information in the CMS HPMS for the NDC-11s of the selected drug, inclusive of any NDC-11s that the Primary Manufacturer submits for the list of NDC-11s pursuant to section 40.2 of this revised guidance. As noted above, CMS requires the Primary Manufacturer to aggregate data from both the Primary Manufacturer and any Secondary Manufacturer(s) for the following: non-FAMP, current unit costs of production and distribution, and certain data pertaining to market data and revenue and sales volume data for the selected drug.

Please see Appendix C of this revised guidance for a list of definitions that apply for purposes of describing these data to be collected for use in the Negotiation Program.

50.1.1 Non-FAMP Data

The Primary Manufacturer must submit data on non-FAMP for the selected drug for the Primary Manufacturer and any Secondary Manufacturer(s), as required under section 1193(a)(4)(A) of the Act. CMS will be collecting these data through the Negotiation Data Elements ICR described above. Specifically, for initial price applicability year 2026, the Primary Manufacturer must submit the non-FAMP, unit type, and total unit volume for each NDC-11 of the selected drug for the four quarters of calendar year 2021, or in the case that there is not an average non-FAMP price available for such drug for 2021, the non-FAMP, unit type, and total unit volume for each

NDC-11 of the selected drug for the four quarters of the first full calendar year following market entry of such drug. For purposes of determining the applicable year, CMS will consider the average non-FAMP price to be available for a selected drug for calendar year 2021 if the Primary Manufacturer reports at least one quarter of non-FAMP data for at least one NDC-11 of the selected drug in calendar year 2021. As described in Appendix C, when there are at least 30 days of commercial sales data but less than a calendar quarter of data to calculate the non-FAMP in calendar year 2021 (or the first full year following market entry of such drug, when applicable) for a given NDC-11 of such drug, the non-FAMP reported by the manufacturer to CMS for that calendar quarter should reflect the temporary non-FAMP predicated upon the first 30 days of commercial sales data. The temporary non-FAMP should be calculated following the same methodology used to calculate the temporary non-FAMP amount used to determine the Temporary Federal Ceiling Price as described in the Department of Veterans Affairs' (VA) 2023 Updated Guidance for Calculation of Federal Ceiling Prices (FCPs) for New Drugs subject to Public Law 102-585. Any restatements of the non-FAMP made in any manufacturer non-FAMP submissions to the VA must be reflected in the non-FAMP submitted to CMS. The use of these data to calculate the ceiling for the MFP is further described in section 60.2 of this revised guidance. Details on how CMS defines the parameters of the non-FAMP data collection are included in Appendix C of this revised guidance and are also included in the Negotiation Data Elements ICR.

50.2 Evidence About Therapeutic Alternatives for the Selected Drug

As noted above, section 1194(e)(2) of the Act directs CMS to consider evidence about alternative treatments to the selected drug, as available, including:

1. The extent to which the selected drug represents a therapeutic advance compared to existing therapeutic alternatives for the selected drug and the costs of such existing therapeutic alternatives;
2. FDA-approved prescribing information for the selected drug and its therapeutic alternatives;
3. Comparative effectiveness of the selected drug and its therapeutic alternatives, including the effects of the selected drug and its therapeutic alternatives on specific populations (including individuals with disabilities, the elderly, the terminally ill, children, and other patient populations, herein referred to as "specific populations"); and
4. The extent to which the selected drug and the therapeutic alternatives to the drug address unmet medical needs for a condition for which treatment or diagnosis is not addressed adequately by available therapy.

Section 1194(e)(2) of the Act additionally requires that CMS not use evidence from comparative clinical effectiveness research in a manner that treats extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill. Information submitted by members of the public, including manufacturers, Medicare beneficiaries, academic experts, clinicians, caregivers, and other interested parties, or other information found by CMS that treats extending the life of individuals in these populations as of lower value will not be used in the Negotiation Program.[57]

[57] Some uses of QALY treat extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill. CMS will not use any QALY in the Negotiation Program.

CMS will review cost-effectiveness measures used in studies relevant to a selected drug to determine whether the measure used is permitted in accordance with section 1194(e)(2), as well as with section 1182(e) of Title XI of the Act. CMS may use content in a study that uses a cost effectiveness-measure if it determines that the cost-effectiveness measure used is permitted in accordance with the law and does not treat extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill. In instances where some, but not all, content in a study is excluded (e.g., QALYs), CMS may still consider content that is relevant and allowable (e.g., clinical effectiveness, risks, harms) under section 1194(e)(2) of the Act and section 1182(e) of Title XI of the Act. CMS requires respondents submitting information to indicate whether their submission contains information from studies that use measures that treat extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill. CMS also requests that respondents submitting information under 1194(e)(2) provide a short description of any cost-effectiveness measures included in the research they are submitting, and how they believe the data avoids treating extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill.

The Primary Manufacturer and members of the public, including other manufacturers, Medicare beneficiaries, academic experts, clinicians, caregivers, and other interested parties, may submit information on selected drugs and their therapeutic alternatives (specifically pharmaceutical therapeutic alternatives, as described in detail in section 60.3.1 of this revised guidance), including information on whether the selected drug represents a therapeutic advance over its therapeutic alternative(s), prescribing information for the selected drug and its therapeutic alternative(s), comparative effectiveness data for the selected drug and its therapeutic alternative(s), information about the impact of the selected drug and its therapeutic alternative(s) on specific populations, information about patient experience, and/or information on whether the selected drug addresses unmet medical need, as described in section 1194(e)(2) of the Act. Outcomes such as changes to productivity, independence, and quality of life will also be considered when these outcomes correspond with a direct impact on the individuals taking the selected drug or therapeutic alternative and are appropriately measurable and quantifiable.

CMS will additionally review existing literature and real-world evidence, conduct internal analytics, and consult subject matter and clinical experts on these topics (described in section 60.3.1 of this revised guidance) when considering available evidence about alternative treatments to the selected drug. When reviewing the literature from the public and manufacturer submissions as well as literature from CMS' review, CMS will consider the source, rigor of the study methodology, current relevance to the selected drug and its therapeutic alternative(s), whether the study has been through peer review, study limitations, degree of certainty of conclusions, risk of bias, study time horizons, generalizability, study population, and relevance to the negotiation factors listed in section 1194(e)(2) of the Act to ensure the integrity of the contributing data within the negotiation process. CMS will prioritize research, including both observational research and research based on randomized samples, that is methodologically rigorous, appropriately powered (i.e., has sufficient sample size) to answer the primary question

of the research, and structured to avoid potential false positive findings due to multiple subgroup analyses.

CMS will consider research and real-world evidence relating to Medicare populations, including on individuals with disabilities, patients with end-stage renal disease (ESRD), and Medicare-aged populations, as particularly important. In considering impact on specific populations and patients with unmet medical needs, CMS will prioritize research specifically designed to focus on these populations over studies that include outcomes for these populations but for which these populations were not the primary focus.

All information on the factors described in section 1194(e)(2) of the Act related to drugs selected for initial price applicability year 2026 must be submitted to CMS by October 2, 2023.

Please see Appendix C of this revised guidance for a list of definitions that CMS adopted for the purposes of describing these data to be collected for use in the Negotiation Program.

60. Negotiation Process

In accordance with section 1194(b)(1) of the Act, CMS will develop and use a consistent methodology and process for negotiation with the aim of achieving agreement on "the lowest maximum fair price for each selected drug." This section 60 describes the negotiation process, including the development of the written initial offer, the process for making such offer and providing a concise justification to the Primary Manufacturer of a selected drug, the process and requirements for accepting an offer or providing a counteroffer, the potential for up to three negotiation meetings between CMS and the Primary Manufacturer, the conclusion of negotiation, the publication of the MFP, and explanation of the MFP.

60.1 Establishment of a Single MFP for Negotiation Purposes

In accordance with section 1191(c)(3) of the Act, MFP means, with respect to a year during a price applicability period and with respect to a selected drug, the price negotiated pursuant to section 1194 of the Act, and updated pursuant to section 1195(b), as applicable, for such drug and year. CMS interprets this language to refer to negotiation of a single price for a selected drug with respect to its price applicability period. Accordingly, CMS will identify a single price for use at each step in the negotiation process described in this section 60, meaning each offer and counteroffer, described in section 60.4 of this revised guidance, will include a single price, even for a selected drug with multiple dosage forms and strengths. Once the MFP has been agreed upon, section 1196(a)(2) of the Act directs CMS to establish procedures to compute and apply the MFP across different dosage forms and strengths of a selected drug.

For the purposes of determining a single price included in an initial offer (including evaluating clinical benefit compared to the therapeutic alternative(s), as described in section 60.3 of this revised guidance) and conducting the negotiation, CMS will base the single price on the cost of the selected drug per 30-day equivalent supply (rather than per unit – such as tablet, capsule, injection – or per volume or weight-based metric), weighted across dosage forms and strengths. This approach of negotiating a single price across all dosage forms and strengths aligns with the statutory requirement to negotiate an MFP for a selected drug. CMS believes this will also allow for a more direct comparison with the therapeutic alternative(s), which might have different

dosage forms, strengths, and treatment regimens (e.g., daily consumption of tablets versus monthly injections of solutions) than the selected drug.

Section 60.5 of this revised guidance describes the methodology CMS will use to translate the MFP once finalized (which, per above, will be an average price per 30-day equivalent supply for the selected drug) back into per unit (e.g., tablet) prices at the dosage form and strength level for the purposes of publishing per-unit MFPs for the different dosage forms and strengths of the selected drug at the NDC- 9 and NDC-11 levels, as contemplated under section 1196(a)(2). In addition to the description of that methodology included in this revised guidance, CMS will share the inputs behind that methodology specific to the selected drug with the Primary Manufacturer of the selected drug during the negotiation period such that the Primary Manufacturer will have visibility into the implied unit prices based on the MFP for each dosage form and strength throughout the negotiation process (i.e., any offer or counteroffer that identifies a single price would be clearly translatable to per unit prices at the dosage form and strength level). Please see section 60.5 of this revised guidance for details.

60.2 Limitations on Offer Amount

In accordance with section 1194(b)(2)(F)(i) of the Act, in negotiating the MFP of a selected drug, with respect to initial price applicability year 2026, CMS will not make an offer (or agree to a counteroffer) for an MFP that exceeds the ceiling specified in section 1194(c) of the Act. This section 60.2 of this revised guidance provides details on the determination of the ceiling for the MFP and comparison of the ceiling to the MFP.

60.2.1 Determination of the Ceiling for the MFP

In accordance with section 1194(c) of the Act, for initial price applicability year 2026, the ceiling for the MFP for a selected drug shall not exceed the lower of the following:

- As described in section 60.2.2 of this revised guidance, an amount equal to the sum of the plan-specific enrollment weighted amounts; or
- As described in section 60.2.3 of this revised guidance, an amount equal to the applicable percent, with respect to the selected drug, of the average non-FAMP as defined in section 1194(c)(6) of the Act for such drug for calendar year 2021 (or in the case that there is not an average non-FAMP for such drug for calendar year 2021, for the first full year following the market entry for such drug), increased by the percentage increase in the consumer price index for all urban consumers (all items; United States city average) from September 2021 (or December of such first full year following the market entry), as applicable, to September 2022.[58]

CMS interprets the language in section 1194(c)(1)(A) of the Act to mean it should calculate a single amount across all dosage forms and strengths of the selected drug for the sum of the plan-specific enrollment weighted amounts and for the applicable percent of the average non-FAMP in order to determine which one is lower and will serve as the ceiling for the MFP. To determine whether the sum of the plan-specific enrollment weighted amounts or the applicable percent of the average non-FAMP will be used to calculate the ceiling for the MFP, CMS will aggregate the

[58] The September 2021 CPI-U, not seasonally unadjusted, was 274.310; the September 2022 CPI-U, not seasonally adjusted, was 296.808. The percentage increase was 8.202 percent. Data retrieved from https://www.bls.gov/cpi/data.htm on May 16, 2023.

amounts determined for each NDC-11 for the selected drug to calculate a single amount – separately for each methodology – across dosage forms, strengths, and package sizes of the selected drug. These amounts can then be directly compared, and the ceiling for the single MFP of the selected drug (including all dosage forms and strengths) will be the lower amount.

CMS will calculate a single ceiling per 30-day equivalent supply (please see 42 C.F.R. § 423.104(d)(2)(iv)(A)(2) for details on 30-day equivalent supply methodology) across all dosage forms and strengths of the selected drug. Using the price per 30-day equivalent supply to calculate this amount facilitates aggregation across dosage forms and strengths of a selected drug where units (e.g., mg versus ml) and treatment regimens (e.g., daily consumption of tablets versus monthly injections of solutions) differ. Sections 60.2.2 and 60.2.3 of this revised guidance describe the process for calculating the sum of the plan-specific enrollment weighted amounts and for calculating the applicable percent of the average non-FAMP, respectively, and section 60.2.4 describes the selection of the ceiling for the single MFP.

For new NDCs included in the definition of the selected drug that are marketed before the ceiling is calculated, the new NDC will be included in the ceiling calculation (as described in this section) provided that CMS receives non-FAMP price data for at least one calendar quarter in calendar year 2021 (or for the first full calendar year following market entry) and observes PDE days supply, PDE quantity dispensed, and PDE gross expenditures for at least one quarter in calendar year 2022, and DIR amounts for calendar year 2022.

CMS will not include a new NDC in the ceiling calculation if any of the above PDE elements do not have at least one calendar quarter of data in calendar year 2022 or if there are no DIR amounts for calendar year 2022 or the Primary Manufacturer did not submit non-FAMP price data for at least one quarter of calendar year 2021 (or for the first full calendar year following market entry).

60.2.2 Sum of the Plan-Specific Enrollment Weighted Amounts

In accordance with section 1194(c)(1)(B)(i) of the Act, CMS will calculate for a selected drug an amount equal to the sum of the plan-specific enrollment weighted amounts determined using the methodology described in section 1194(c)(2) of the Act. Plan sponsors report Part D PDE data to CMS at the NDC-11 level. Sponsors also report Direct and Indirect Remuneration (DIR) data to CMS at the NDC-11 level in the annual Detailed DIR Report. CMS will use these reported data for plan year 2022, which is the most recent year for which data will be available, for the purpose of determining the sum of the plan-specific enrollment weighted amounts for a selected drug for initial price applicability year 2026.

CMS will include all Part D plans that have PDE data for dosage forms and strengths of the selected drug in this calculation. Because CMS will have no PDE data for Part D plans in the following circumstances, such Part D plans will, by definition, be excluded from the calculation of the plan-specific enrollment weighted amounts: (1) plans that have no utilization for the selected drug and (2) plans that have no enrollment for 2022.[59] CMS will also exclude any PDE

[59] CMS notes that employer sponsored plans that receive the retiree drug subsidy and health plans that offer creditable prescription drug coverage are not included because they are not Part D plans.

records for the selected drug for which the total gross covered prescription drug cost is equal to $0.

CMS will calculate the sum of the plan-specific enrollment weighted amounts in two stages. First, CMS will calculate the sum of the plan-specific enrollment weighted amounts for each NDC-9 associated with NDC-11s included on the list of NDC-11s of the selected drug in the CMS HPMS (see section 40.2 of this revised guidance). Second, CMS will calculate the sum of the plan-specific enrollment weighted amounts across these NDC-9s. The amounts calculated at each stage are for a 30-day equivalent supply (see 42 C.F.R. § 423.104(d)(2)(iv)(A)(2) for details on 30-day equivalent supply methodology).

To determine the sum of the plan-specific enrollment weighted amounts for each NDC-9 and across all NDC-9s of the selected drug, CMS will conduct the following steps.

Steps 1 through 8 will result in the sum of the plan-specific enrollment weighted amounts for each NDC-9 of the selected drug:

1. For each Part D plan, CMS will identify the PDE data for the selected drug for 2022 (that is, PDE records with dates of service during the period beginning on January 1, 2022 and ending on December 31, 2022).
2. For each Part D plan and each NDC-9, CMS will separately sum the negotiated price amounts (as defined in 42 C.F.R. § 423.100), the estimated rebate at point-of-sale amounts (ERPOSA), and units dispensed.
3. For each Part D plan and each NDC-9, CMS will sum the total DIR amounts found in the 2022 Detailed DIR Report and subtract the total ERPOSA calculated in step 2 to avoid double counting price concessions applied at the point of sale.
4. For each Part D plan and each NDC-9, CMS will subtract the total DIR minus ERPOSA amount calculated in step 3 from the total negotiated price amounts calculated in step 2 and then divide by the total units dispensed also determined in step 2. This calculation results in the NDC-9 price per unit, net of all price concessions received by such Part D plan or pharmacy benefit manager on behalf of such Part D plan.
5. Separately, CMS will identify the total number of individuals enrolled in all Part D plans in December 2022 and the total number of individuals enrolled in each Part D plan in that same month.[60] The Part D plans included in both calculations of step 5 will be restricted to Part D plans with at least one PDE record for the selected drug in calendar year 2022.
6. For each Part D plan and each NDC-9, CMS will divide the total number of Part D beneficiaries enrolled in the Part D plan during December 2022 as identified in step 5 by the total number of individuals enrolled in all Part D plans in December 2022 also as identified in step 5, and multiply this quotient by the price per unit, net of all price concessions received by such plan or pharmacy benefit manager on behalf of such Part D plan, calculated in step 4, to arrive at the plan-specific enrollment weighted amount.
7. For each NDC-9, CMS will then sum the amounts calculated in step 6 across all Part D plans to calculate the sum of the plan-specific enrollment weighted amounts.

[60] CMS conducted an analysis of monthly Part D plan enrollment changes during 2022 and determined that monthly enrollment changes were the lowest from November to December, so CMS chose December as the most stable month to identify enrollment. The choice of one month to identify enrollment also allows the weights calculated in step 6 to sum to one.

8. For each NDC-9, CMS will then multiply the sum of the plan-specific enrollment weighted amounts calculated in step 7, which are a per unit price, by the NDC-9 average number of units per 30-day equivalent supply calculated from PDE data for 2022 to yield the price of a 30-day equivalent supply.

Steps 9 through 10 result in the sum of the plan-specific enrollment weighted amounts across all NDC-9s of the selected drug:

9. For each NDC-9, CMS will divide the total 30-day equivalent supply for that NDC-9 by the total 30-day equivalent supply across all NDC-9s, both calculated from 2022 PDE data, and multiply this quotient by the sum of the plan-specific enrollment weighted amounts for a 30-day equivalent supply as calculated in step 8.
10. CMS will then sum amounts calculated in step 9 across all NDC-9s to generate the sum of the plan-specific enrollment weighted amounts for the selected drug for a 30-day equivalent supply.

60.2.3 Average Non-Federal Average Manufacturer Price

In accordance with section 1194(c)(1)(C)(i) of the Act, for initial price applicability year 2026, CMS will calculate an amount equal to the applicable percent, with respect to the selected drug, of the average non-FAMP in calendar year 2021 (or in the case that there is not an average non-FAMP for such drug for calendar year 2021, CMS will use the first full year following the market entry for such drug), increased by the percentage increase in the consumer price index for all urban consumers (all items; United States city average) (CPI-U) from September 2021 (or December of such first full year following the market entry), as applicable, to September 2022.[61]

For this calculation, CMS will use the non-FAMP price and unit volume data, as provided by the Primary Manufacturer, for each NDC-11 included on the list of NDC-11s of the selected drug in the CMS HPMS (see section 40.2 of this revised guidance), for each quarter of calendar year 2021 that is submitted to CMS by the Primary Manufacturer pursuant to section 1193(a)(4)(A) of the Act (as described in section 50.1 of this revised guidance) to calculate an annual average non-FAMP per unit. CMS will use 2022 PDE quantity dispensed and days supply data submitted to CMS at the NDC-11 level by Part D plan sponsors for the following: to calculate an annual average non-FAMP per unit for each NDC-9 of the selected drug, to calculate the annual average non-FAMP per 30-day equivalent supply for each NDC-9 of the selected drug, and to calculate the annual average non-FAMP per 30-day equivalent supply for the selected drug. In order to directly compare the amount calculated based on the applicable percent of average non-FAMP and the amount calculated based on the sum of the plan-specific enrollment weighted amounts (as described in section 60.2.2 above), CMS will base the average non-FAMP calculations on a 30-day equivalent supply and use the same 2022 PDE data for weighting both the sum of the plan-specific enrollment weighted amounts and the average non-FAMP across dosage forms and strengths to determine which amount is lower.

CMS will calculate the applicable percent of the average non-FAMP in two stages to determine the ceiling for the MFP. First, CMS will calculate the applicable percent of the average non-FAMP for each NDC-9 of the selected drug. Second, CMS will calculate the applicable percent

[61] The September 2021 CPI-U, not seasonally adjusted, was 274.310; the September 2022 CPI-U, not seasonally adjusted, was 296.808. The percentage increase was 8.202 percent. Data retrieved from https://www.bls.gov/cpi/data.htm on May 16, 2023.

of the average non-FAMP across NDC-9s of the selected drug. The amounts calculated in each stage are for a 30-day equivalent supply (see 42 C.F.R. § 423.104(d)(2)(iv)(A)(2) for details on 30-day equivalent supply methodology).

To determine the applicable percent of the average non-FAMP for each NDC-9 and across all NDC-9s of the selected drug, CMS will conduct the following steps.

Steps 1 through 9 will result in the average non-FAMP, adjusted for inflation and with the applicable percent applied, for each NDC-9 of the selected drug:

1. To calculate an average non-FAMP that is comparable to the sum of the plan-specific enrollment weighted amounts described in section 60.2.2 of this revised guidance, CMS will compare the non-FAMP unit type (e.g., tablet) to the PDE units (i.e., each, milliliter, and grams). In instances where the units are different, CMS will convert the non-FAMP unit type to the PDE units so that the two amounts (average non-FAMP and sum of the plan-specific enrollment weighted amounts) represent the same quantity of the selected drug.[62]
2. For each NDC-11 and for each quarter during calendar year 2021, CMS will calculate the non-FAMP per unit by dividing the non-FAMP per package by the total number of units per package.
    - Note: If the non-FAMP is missing for all NDC-11s of the selected drug for calendar year 2021 (as described in section 50.1.1 of this revised guidance), CMS will use the non-FAMP for the quarters of the first full calendar year following the market entry for such drug.
3. For each NDC-11 and for each quarter during calendar year 2021, CMS will divide the total unit volume (calculated as the product of the total number of packages sold by the number of units per package from manufacturer-reported non-FAMP data) in that quarter by the total unit volume across all four quarters during calendar year 2021 (also from manufacturer reported non-FAMP data), and multiply this quotient by the non-FAMP per unit calculated in step 2.
    - Note: If the non-FAMP is missing for all NDC-11s of the selected drug for calendar year 2021 (as described in section 50.1.1 of this revised guidance), CMS will use the non-FAMP and total unit volumes for the quarters of the first full calendar year following the market entry for such drug.
4. For each NDC-11, CMS will sum the amounts calculated in step 3 across quarters to calculate the average non-FAMP per unit for that NDC-11 for the calendar year CMS believes steps 3 and 4 are necessary to account for non-FAMP unit volume fluctuations that may occur across quarters.
5. For each NDC-11, CMS will divide the total quantity dispensed for that NDC-11 by the total quantity dispensed for all applicable NDC-11s of the same NDC-9 (both calculated from 2022 PDE data) and multiply this quotient by the average non-FAMP per unit for the calendar year calculated in step 4.
6. For each NDC-9, CMS will sum the amounts calculated in step 5 to calculate the average non-FAMP per unit for that NDC-9 for the calendar year. CMS believes steps 5 and 6 are

[62] PDE units are industry standard National Council for Prescription Drug (NCPDP) defined values of each, milliliter, and grams. See: https://standards.ncpdp.org/Billing-Unit-Request.aspx#:~:text=Billing%20Unit%20Requests,grams%22%20or%20%22milliliters.%22.

necessary to account for fluctuations in quantity dispensed that may occur across NDC-11s of an NDC-9 in the Medicare Part D population.

7. For each NDC-9, CMS will then increase the average non-FAMP per unit for calendar year 2021 calculated in step 6 by the percentage increase in CPI-U (all items; United States city average) from September 2021 until September 2022 as specified in section 1194(c)(1)(C)(i) of the Act.
    - Note: For initial price applicability year 2026, if the non-FAMP is missing for all NDC-11s of the selected drug for calendar year 2021(as described in section 50.1.1 of this revised guidance), and the non-FAMP is based on data from the first full calendar year following the market entry of the such drug, which can only be calendar year 2022, CMS will not apply the CPI-U adjustment.
8. For each NDC-9, after CMS has calculated the average non-FAMP per unit for the calendar year, adjusted for inflation, if applicable, CMS will then apply the applicable percent specified in section 1194(c)(3) of the Act for the monopoly type determined for the selected drug based on its initial approval date (described in section 30.1 of this revised guidance). Applying the applicable percent here, in step 8, results in the same step 11 amount as would result if CMS were to apply the applicable percent to the average non-FAMP per 30-day equivalent supply for the selected drug in step 11. The definition of each monopoly type and the applicable percentage are described below for initial price applicability year 2026. CMS notes that the "extended-monopoly" type is not discussed below because the definition of extended-monopoly drug under section 1194(c)(4)(B)(ii) of the Act expressly excludes a selected drug for which a manufacturer has entered into an Agreement with CMS with respect to an initial price applicability year that is before 2030. CMS interprets this to mean that no selected drug will be considered an extended-monopoly drug for purposes of calculating the ceiling prior to initial price applicability year 2030.

Figure 2: Monopoly Types and Applicable Percentage for Initial Price Applicability Year 2026

Monopoly Type	Definition	Applicable Percentage	Note
Short-monopoly drugs and vaccines (section 1194(c)(3)(A) of the Act)[63]	For initial price applicability year 2026, a selected drug that is not a long-monopoly drug or a selected drug that is a vaccine licensed under section 351(a) of the PHS Act and marketed pursuant to that section.	75%	The first approval date, under section 505(c) of the FD&C Act, associated with the initial FDA application number for the active moiety (or fixed combination drug) must be after January 1, 2010 and before September 1, 2016. The first licensure date, under section 351(a) of the PHS Act, associated with the initial FDA application number for the active ingredient (or fixed combination drug) must be after January 1, 2010 and before September 1, 2012.
Long-monopoly drug (section 1194(c)(5)(A) of the Act)	A selected drug for which at least 16 years have elapsed since the date of approval under section 505(c) of the FD&C Act or since the date of licensure under section 351(a) of the PHS Act, as applicable. The term 'long-monopoly drug' does not include a vaccine that is licensed under section 351(a) of the PHS Act and marketed pursuant to that section.	40%	The first approval date under section 505(c) of the FD&C Act or the first licensure date under section 351(a) of the PHS Act, as applicable, associated with the initial FDA application number for the active moiety / active ingredient (or fixed combination drug) must be on or before January 1, 2010.

9. For each NDC-9, CMS will then multiply the average non-FAMP per unit for the calendar year, adjusted for inflation, if applicable, and with the applicable percent applied as calculated in step 8 by the quotient of the total quantity dispensed divided by the total 30-day equivalent supply (i.e., this quotient represents the average units per 30-day supply equivalent for that NDC-9) calculated from 2022 PDE data to determine the

[63] Because the definition of extended-monopoly drug at section 1194(c)(4)(B)(ii) of the Act expressly excludes a selected drug for which a manufacturer has entered into an agreement with CMS with respect to an initial price applicability year before 2030, for initial price applicability year 2026, any drug, biological product, or vaccine that is not considered a long-monopoly drug will be considered a short monopoly drug.

average non-FAMP for a 30-day equivalent supply. As described above in section 60.2.1 of this revised guidance, CMS believes calculating the average non-FAMP for a 30-day equivalent supply is necessary to account for different units and treatment regimens across dosage forms and strengths.

Steps 10 and 11 will calculate the average non-FAMP per 30-day equivalent supply for the calendar year, adjusted for inflation, if applicable, and with applicable percent applied, across all NDC-9s of the selected drug:

10. For each NDC-9, CMS will divide the total 30-day equivalent supply for that NDC-9 by the total 30-day equivalent supply across all NDC-9s of the selected drug, both calculated from 2022 PDE data, and multiply this quotient by the average non-FAMP per 30-day equivalent supply for the calendar year, adjusted for inflation, if applicable, and with the applicable percent applied, calculated in step 9.
11. CMS will then sum amounts calculated in step 10 across all NDC-9s of the selected drug to calculate the average non-FAMP per 30-day equivalent supply for the calendar year, adjusted for inflation, if applicable, and with the applicable percent applied, for the selected drug.

60.2.4 Selection and Application of the Ceiling for the MFP

CMS will compare the values calculated in step 10 of section 60.2.2 of this revised guidance (sum of the plan-specific enrollment weighted amounts) and step 11 of section 60.2.3 of this revised guidance (applicable percent of the average non-FAMP) and select the lower value as the ceiling for the selected drug. Once CMS has identified whether the ceiling would be determined by the sum of the plan-specific enrollment weighted amounts or the applicable percent of the average non-FAMP, CMS will ensure that the MFP per 30-day equivalent supply, as negotiated through the process described in sections 60.3 and 60.4 of this revised guidance, is no greater than the lower ceiling.

60.3 Methodology for Developing an Initial Offer

Section 1194(e) of the Act directs CMS to consider certain factors related to manufacturer-specific data and available evidence about therapeutic alternative(s) as the basis for determining offers and counteroffers in the negotiation process. The statute requires CMS to provide the manufacturer of a selected drug with an initial offer and a concise justification based on the factors described in section 1194(e) that were used in developing the offer; however, CMS has the discretion to determine how and to what degree each factor should be considered.

As discussed in greater detail below, consistent with section 1194(e) of the Act, for the purposes of determining an initial offer, CMS will (1) identify therapeutic alternative(s), if any, for the selected drug as described in section 60.3.1 of this revised guidance; (2) use the Part D net price for the therapeutic alternative(s) that is covered under Part D and/or the Average Sales Price (ASP) for the therapeutic alternative(s) that is covered under Part B to determine a starting point for developing an initial offer as described in section 60.3.2 of this revised guidance; (3) evaluate the clinical benefit of the selected drug (including compared to its therapeutic alternative(s)) for the purposes of adjusting the starting point using the negotiation factors outlined in section 1194(e)(2) of the Act, including whether the selected drug meets an unmet medical need and the selected drug's impact on specific populations, as described in section 60.3.3 of this revised

guidance (resulting in the "preliminary price"); and (4) further adjust the preliminary price by the negotiation factors outlined in section 1194(e)(1) of the Act (described in section 60.3.4 of this revised guidance) to determine the initial offer price.

Pursuant to section 1194(b)(2)(F) of the Act, CMS will not make any offers or accept any counteroffers for the MFP that are above the statutorily defined ceiling.

60.3.1 Identifying Indications for the Selected Drug and Therapeutic Alternatives for Each Indication

For initial price applicability year 2026, CMS will identify the FDA-approved indication(s) not otherwise excluded from coverage or otherwise restricted under section 1860D-2(e)(2) of the Act for a selected drug, using prescribing information approved by the FDA for the selected drug, in accordance with section 1194(e)(2)(B) of the Act. CMS will consider off-label use when identifying indications if such use is included in nationally recognized, evidence-based guidelines and recognized in CMS-approved Part D compendia.[64]

For each indication of the selected drug, CMS will next identify a pharmaceutical therapeutic alternative(s). CMS considered evaluating non-pharmaceutical therapeutic alternatives; however, for initial price applicability year 2026, CMS will only consider therapeutic alternatives that are drugs or biologics covered under Part D or Part B. CMS believes that pharmaceutical therapeutic alternatives will be the most analogous alternatives to the selected drug when considering treatment effect and price differentials. For purposes of this revised guidance, the term "therapeutic alternative" may refer to one or more therapeutic alternative(s) or a subset of the most clinically comparable therapeutic alternatives.

To identify potential therapeutic alternatives for the indications of a selected drug, CMS will use data submitted by the Primary Manufacturer and the public, FDA-approved indications, drug classification systems commonly used in the public and commercial sector for formulary development, indications included in CMS-approved Part D compendia, widely accepted clinical guidelines, the CMS-led literature review, drug or drug class reviews, and peer-reviewed studies. In addition to brand name drugs and biologics, CMS will consider generic drugs and biosimilars when identifying a therapeutic alternative(s) to a selected drug. CMS will consider off-label use for therapeutic alternatives when identifying indications if such use is included in nationally recognized, evidence-based guidelines and recognized in CMS-approved Part D compendia.

CMS will begin by identifying therapeutic alternatives within the same drug class as the selected drug based on properties such as chemical class, therapeutic class, or mechanism of action before considering therapeutic alternatives in other drug classes. In cases where there are many potential therapeutic alternatives for a given indication of the selected drug, CMS may focus on the subset of therapeutic alternatives that are most clinically comparable to the selected drug for the purpose of developing the initial offer. CMS may consult with FDA to obtain information regarding other approved therapies for the same indication and may also consult with clinicians, patients or patient organizations, and/or academic experts, to ensure that appropriate therapeutic alternatives are identified. If a therapeutic alternative has not yet been incorporated into nationally recognized, evidence-based guidelines, CMS will consider clinical evidence available

[64] CMS-approved Part D compendia are described in Chapter 6, § 10.6 of the Prescription Drug Benefit Manual.

through a literature search and information submitted by the Primary Manufacturer and the public to inform the selection of a therapeutic alternative(s). In all cases, CMS will select therapeutic alternatives based on clinical appropriateness.

60.3.2 Developing a Starting Point for the Initial Offer

CMS considered several options for what price should be used as the starting point for developing the initial offer. Options considered included the use of the Part D net price(s) and/or the ASP(s) of therapeutic alternative(s), if any, to the selected drug, the unit cost of production and distribution for the selected drug, the ceiling for the selected drug (as described in section 60.2 of this revised guidance), a domestic reference price for the selected drug (e.g., the Federal Supply Schedule[65] (FSS) price), or a "fair profit" price for the selected drug based on whether R&D costs have been recouped and margin on unit cost of production and distribution. Under any of these options, the initial offer and final MFP would be capped at the statutory ceiling.

After considering these options and in accordance with section 1194(e)(2)(A) of the Act which directs CMS to consider the cost of therapeutic alternative(s), CMS will use the Part D net price(s) ("net price(s)") and/or ASP(s) of the therapeutic alternative(s) (or a subset of the most clinically comparable therapeutic alternatives) for the selected drug, as applicable, as the starting point for developing the initial offer unless this net price or ASP is greater than the statutory ceiling (described in section 60.2 of this revised guidance), and will then consider adjustments based on section 1194(e)(2) data and manufacturer-submitted data per section 1194(e)(1). CMS intends to identify the price of each therapeutic alternative that is covered under Part D net of all price concessions received by any Part D plan or pharmacy benefit manager on behalf of the Part D plan by using PDE data and detailed DIR report data. In taking this approach, CMS acknowledges that the therapeutic alternative(s) for a selected drug may not be priced to reflect its clinical benefit, however, using net prices and ASPs of therapeutic alternatives enables CMS to start developing the initial offer within the context of the cost and clinical benefit of one or more drugs that treat the same disease or condition. By using the price(s) of the selected drug's therapeutic alternative(s), CMS will be able to focus the initial offer on clinical benefit by adjusting this starting point relative to whether the selected drug offers more, less, or similar clinical benefit compared to its therapeutic alternative(s). The other options considered do not provide a starting point that reflects the cost of therapeutic alternatives in the current market, which is an important factor when considering the overall benefit that a treatment brings to Medicare beneficiaries relative to the other drug(s) available to treat the patient's disease or condition.

When comparing prices of therapeutic alternatives for purposes of informing a starting point for the initial offer, CMS may use an alternative methodology for calculating a 30-day equivalent supply as appropriate. For example, because Part B claims data do not contain a "days' supply" field similar to PDE data, CMS may use an alternative methodology to calculate the price per 30-day equivalent supply for therapeutic alternatives covered under Part B.

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[65] The Federal Supply Schedule (FSS) represents long-term government-wide contracts with commercial companies that provide access to millions of commercial products and services to the government. See: https://www.gsa.gov/buy-through-us/purchasing-programs/gsa-multiple-award-schedule/about-gsa-schedule#:~:text=The%20GSA%20Schedule%2C%20also%20known,reasonable%20prices%20to%20the%20government.

If there is one therapeutic alternative for the selected drug, CMS will use the net price or ASP, as applicable, of the therapeutic alternative (if it is lower than the ceiling) as the starting point to develop CMS' initial offer for the MFP. If there are multiple therapeutic alternatives, CMS will consider the range of net prices and/or ASPs, including the prices of generic and biosimilar therapeutic alternatives, as well as the utilization of each therapeutic alternative relative to the selected drug, to determine the starting point within that range. If the selected drug has no therapeutic alternative, if the prices of the therapeutic alternatives identified are above the statutory ceiling for the MFP (as described in section 60.2 of this revised guidance), or if there is a single therapeutic alternative with a price above the statutory ceiling for the MFP, then CMS will determine the starting point for the initial offer based on the FSS or "Big Four Agency"[66] price ("Big Four price"). If the FSS and Big Four prices are above the statutory ceiling, then CMS will use the statutory ceiling as the starting point for the initial offer. In all cases, this starting point will be subject to adjustments as described further below.

60.3.3 Adjusting the Starting Point Based on Clinical Benefit

To evaluate the clinical benefit conferred by the selected drug compared to its therapeutic alternative(s), as applicable, CMS will broadly evaluate the body of clinical evidence, including data received from the public and manufacturers as described in section 50.2 of this revised guidance, and data identified through a CMS-led literature review. CMS may also analyze Medicare claims or other datasets for utilization patterns of the selected drug versus its therapeutic alternative(s), clinical data, or other information relevant to the selected drug and its therapeutic alternative(s) and may consult with clinicians, patients or patient organizations, academic experts, and/or the FDA. As described in section 60.4 of this revised guidance, CMS will provide additional engagement opportunities for interested parties—specifically, meetings with manufacturers and patient-focused listening sessions—after the October 2, 2023 deadline for submission of section 1194(e)(2) data (further described in section 60.4 of this revised guidance).

This approach provides a pathway for CMS to consider the multitude of information expected from public input, including but not limited to peer-reviewed research, expert reports or whitepapers, clinician expertise, real-world evidence, and patient experience. This approach also provides flexibility for CMS to consider multiple perspectives on the clinical benefit of the selected drug and its therapeutic alternative(s), including potential risks, harms, or side effects, and any unique scenarios or considerations related to clinical benefit, safety, and patient experience.

Once the starting point for the initial offer has been established and evidence on clinical benefit has been considered, CMS will adjust the starting point for the initial offer based on the review of the clinical benefit. CMS will not, per section 1194(e)(2) of the Act, use evidence from comparative effectiveness research in a manner that treats extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual

[66] The Big Four price is the maximum price a drug manufacturer is allowed to charge the "Big Four" federal agencies, which are the Department of Veterans Affairs (VA), Department of Defense (DoD), the Public Health Service, and the Coast Guard. See section 8126 of title 38 of the U.S. Code. See: https://www.cbo.gov/publication/57007.

who is younger, non-disabled, or not terminally ill, and will not, per section 1182(e) of the Act, use QALYs. CMS considered employing both a qualitative approach (e.g., adjusting the starting point upward or downward relative to the clinical benefit offered by the selected drug compared to its therapeutic alternatives) and a more thoroughly pre-specified quantitative approach. CMS will use a qualitative approach to preserve flexibility in negotiation, including the ability to consider nuanced differences between different drugs, for example interactions with other treatments commonly prescribed simultaneously for a condition or disease, and other factors that might not be captured in a more thoroughly pre-specified quantitative approach.

60.3.3.1 Analysis for Selected Drugs with Therapeutic Alternative(s)

To consider comparative effectiveness between a selected drug and its therapeutic alternative(s), CMS will identify outcomes to evaluate for each indication of the selected drug. CMS will consider the identified outcomes, including patient-centered outcomes[67] and patient experience data, when reviewing the clinical benefit of the selected drug and its therapeutic alternative(s). When reviewing such information, as noted above, CMS will not, per section 1194(e)(2), use evidence in a manner that treats extending the life of an individual who is elderly, disabled, or terminally ill as lower value than extending the life of an individual who is younger, non-disabled, or not terminally ill, and will not, per section 1182(e) of the Act, use QALYs. Outcomes such as cure, survival, progression-free survival, or improved morbidity could be considered when comparing the selected drug to its therapeutic alternative(s). Outcomes such as changes in symptoms or other factors that are of importance to patients and patient-reported outcomes will also be identified and considered in determining clinical benefit, if available. Additional outcomes such as changes to productivity, independence, and quality of life will also be considered to the extent that these outcomes correspond with a direct impact on individuals taking the drug, including patient-centered outcomes when available. CMS may also consider the caregiver perspective to the extent that it reflects directly upon the experience or relevant outcomes of the patient taking the selected drug. Relevant outcomes will be identified using the CMS-led literature review and information submitted by manufacturers and the public, including patients and caregivers, through the Negotiation Data Elements ICR described in section 50 of this revised guidance, as well as in the patient-focused listening sessions described in section 60.4.

In all cases, CMS will consider applicable evidence and other input collectively, within the context of the course of care for the condition(s) or disease(s) that the selected drug is indicated to treat, and in accordance with section 50 of this revised guidance. As noted previously, this approach provides flexibility to consider multiple perspectives on the clinical benefit of the selected drug and its therapeutic alternative(s), including potential risks, harms, or side effects, and any unique scenarios or considerations related to clinical benefit, safety, and patient experience.

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[67] A patient-centered outcome is defined as: An outcome that is important to patients' survival, functioning, or feelings as identified or affirmed by patients themselves, or judged to be in patients' best interest by providers and/or caregivers when patients cannot report for themselves. (Source: ISPOR Plenary, Patrick (2013) via FDA's *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input – Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders*, June 2020.) See: https://www.fda.gov/media/139088/download.

CMS will also consider the effects of the selected drug and its therapeutic alternative(s) on specific populations as required by section 1194(e)(2)(C) of the Act. In doing so, CMS will evaluate access, equity, and health outcomes for specific populations. To do so, CMS will seek to identify studies focused on the impact of the selected drug and its therapeutic alternative(s) on individuals with disabilities, the elderly, individuals who are terminally ill, children, and other patient populations among Medicare beneficiaries. Specific populations may include underserved and underrepresented populations, as applicable. Further, CMS will consider whether the selected drug fills an unmet medical need, which CMS will define as treating a disease or condition in cases where no other treatment options exist or existing treatments do not adequately address the disease or condition. CMS will consider each selected drug and its therapeutic alternatives to determine whether the drug fills an unmet medical need at the indication level as of the time the section 1194(e)(2) data is submitted. CMS will consider the nonbinding recommendations in the FDA's "Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics,"[68] as well as any updates that may be issued by FDA in the future, when determining if a selected drug addresses an unmet medical need.

CMS will determine whether a selected drug represents a therapeutic advance by examining improvements in outcomes compared to its therapeutic alternative(s) (e.g., selected drug is curative versus a therapeutic alternative that delays progression). CMS understands that a selected drug can be first in class,[69] however, other drugs may have become available since the selected drug's initial approval. In accordance with section 1194(e)(2)(A) of the Act, CMS will review the analyses detailed above for each indication for the selected drug and its therapeutic alternative(s) and determine, based on the relevant information and evidence, what the difference in clinical benefit is between the selected drug and the therapeutic alternative(s).

As previously noted, CMS will take a qualitative approach to adjusting the starting point based on the unique characteristics of the drug and its therapeutic alternative(s) as well as the patient population(s) taking the selected drug. For each selected drug, the applicable starting point will first be adjusted (i.e., apply an upward or downward adjustment, or no adjustment) based on the totality of the relevant information and evidence submitted and gathered through CMS' analysis based on the clinical benefit the selected drug provides (and then subsequently it will be adjusted by the manufacturer-submitted data described in section 60.3.4). Because the extent of clinical benefit may vary across different indications, CMS may adjust the starting point based on the clinical benefit for an individual indication in cases where the clinical benefit of the selected drug is notably different than the therapeutic alternative(s) for that specific indication.

60.3.3.2 Analysis for Selected Drugs Without Therapeutic Alternatives

Similar to a selected drug with at least one therapeutic alternative, the starting point for a selected drug without a therapeutic alternative will be adjusted based on the totality of relevant information and evidence as detailed above, such as outcomes and impact on specific

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[68] FDA Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014. See: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics.

[69] First in class drugs are those that have a new mechanism of action, defined by the National Cancer Institute as "a term used to describe how a drug or other substance produces an effect in the body." See: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/mechanism-of-action.

populations, submitted through the Negotiation Data Elements ICR and gathered through CMS' analysis of the clinical benefit the selected drug provides.

CMS will consider whether the selected drug fills an unmet medical need separately for each indication. A selected drug will be considered to meet an unmet medical need for an indication included in the analysis when it is used to treat a disease or condition where no other treatment options exist or existing treatments do not adequately address the disease or condition. As noted previously, CMS will consider the nonbinding recommendations in the FDA "Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics," as well as any updates that may be issued by FDA in the future, when considering if a drug addresses an unmet medical need for the purpose of the Negotiation Program. A selected drug may be considered a therapeutic advance when a substantial improvement in outcomes is observed for an indication.

60.3.3.3 Preliminary Price

After the starting point has been adjusted, as appropriate, based on section 1194(e)(2) data submitted by manufacturers and the public through the Negotiation Data Elements ICR and gathered through CMS-led analyses and literature review, the resulting price is referred to as "the preliminary price." As described in section 60.3.4 of this revised guidance, the preliminary price will be adjusted, as appropriate, based on data submitted by the Primary Manufacturer in accordance with section 1194(e)(1) of the Act.

60.3.4 Adjusting the Preliminary Price Based on Consideration of Manufacturer-Specific Data

Under section 1194(e)(1) of the Act, CMS must also consider data reported by the Primary Manufacturer, as described in section 50.1 of this revised guidance. The adjustment to the preliminary price applied on the basis of these data, if any, may be upward or downward, as needed to account for these manufacturer-specific data elements. These data elements are: (1) R&D costs of the manufacturer for the drug and the extent to which the manufacturer has recouped R&D costs; (2) current unit costs of production and distribution of the drug; (3) prior Federal financial support for novel therapeutic discovery and development with respect to the drug; (4) data on pending and approved patent applications or exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the FD&C Act or section 351(a) of the PHS Act for the drug; and (5) market data and revenue and sales volume data for the drug in the United States.

CMS will consider the five elements outlined in section 1194(e)(1) of the Act in totality and apply an upward adjustment, downward adjustment, or no adjustment to the preliminary price. To do this, CMS may consider each factor in isolation or in combination with other factors. CMS provides illustrative examples for the manufacturer-specific data elements below. However, the overall adjustment, inclusive of all five elements taken together, may differ from the example adjustment for any single element viewed in isolation.

In considering element (1) above on R&D costs, CMS will consider the extent to which the Primary Manufacturer has recouped its R&D costs. CMS will compare the R&D costs with the global and U.S. total lifetime net revenue for the selected drug reported by the Primary Manufacturer to determine the extent to which the Primary Manufacturer has recouped its R&D costs. For example, if a Primary Manufacturer has not recouped its R&D costs, CMS may

consider adjusting the preliminary price upward. Conversely, if a Primary Manufacturer has recouped its R&D costs, CMS may consider adjusting the preliminary price downward or apply no adjustment. CMS may use the R&D costs reported by the Primary Manufacturer and the calculated recouped costs, including the assumptions and calculations in the accompanying narrative text, and/or other factors as described in the Negotiation Data Elements ICR and in Appendix C of this revised guidance to adjust the preliminary price.

In considering element (2) on current unit costs of production and distribution, CMS will consider the relationship between the preliminary price and the unit costs of production and distribution. For example, CMS may consider adjusting the preliminary price downward if the unit costs of production and distribution are lower than the preliminary price, or upward if the unit costs of production and distribution are greater than the preliminary price. Again, CMS may consider the assumptions and calculations in the accompanying narrative text submitted by the Primary Manufacturer of the selected drug to determine if an adjustment is appropriate.

In considering element (3) on prior Federal financial support, CMS will consider the extent to which the Primary Manufacturer benefited from Federal financial support with respect to the selected drug. For example, CMS may consider adjusting the preliminary price downward if funding for the discovery and development of the drug was received from Federal sources.

In considering element (4) on patent applications, exclusivities, and applications and approvals for the selected drug, CMS will review the patents and exclusivities reported as it develops its initial offer. CMS believes that this information will support CMS' consideration of the 1194(e)(1) and 1194(e)(2) factors described in section 50 of this revised guidance. For instance, patents and exclusivities may inform CMS' understanding of therapeutic alternatives and other available therapy for the purposes of adjusting for clinical benefit, including consideration of whether the selected drug represents a therapeutic advance or meets an unmet medical need. More specifically, in light of exclusivities, there may be no other available therapy aside from the selected drug that adequately addresses treatment or diagnosis of a disease or condition, and consideration of such information would be relevant to CMS' consideration of the extent to which the selected drug addresses an unmet medical need for that disease or condition.

Finally, in considering element (5) on market data and revenue and sales volume data for the U.S., CMS will consider how the data compare to the CMS preliminary price. For example, if the average commercial net price is lower than the preliminary price, CMS may consider adjusting the preliminary price downward. If the average commercial net price is greater than the preliminary price, CMS may consider adjusting the preliminary price upward.

Appendix C of this revised guidance includes a list of definitions that CMS adopts for the purposes of describing the data to be collected with respect to the data elements listed in section 1194(e)(1) of the Act.

After any adjustments to the preliminary price are made under this section 60.3.4 of this revised guidance, the result is the initial offer.

60.4 Negotiation Process

In accordance with sections 1191(b)(4)(A) and 1191(d)(2)(A) of the Act, and as described in section 40.1 of this revised guidance, the negotiation period begins on the earlier of the date that the Primary Manufacturer enters into an Agreement, or, for initial price applicability year 2026, October 1, 2023. CMS will implement the negotiation process consistent with the requirements of the statute, with the aim of achieving "the lowest maximum fair price for each selected drug" consistent with section 1194(b)(1) of the Act.

After the submission of the section 1194(e) data by manufacturers and other interested parties by October 2, 2023, CMS will host meetings with Primary Manufacturers of selected drugs that have submitted section 1194(e) data and other interested parties. CMS will invite the Primary Manufacturer for each selected drug to one meeting in Fall 2023 after the data submission deadline. The purpose of this meeting will be for the Primary Manufacturer to provide additional context on its data submission and share new section 1194(e)(2) data, if applicable, as CMS begins reviewing the data and developing an initial offer. Primary Manufacturers may bring materials to facilitate discussion and CMS may request any materials presented afterwards. Primary Manufacturers are limited to sharing 50 pages (or a combination of pages, slides, and/or charts and graphs totaling 50 pages) of material, in order to focus the discussion on issues that can reasonably be discussed within the scope of the meeting, anticipating that these materials may contain cross-references to other material, particularly other material already submitted to CMS. CMS will also host patient-focused listening sessions with interested parties. These meetings are intended to bring together patients, beneficiaries, caregivers, and consumer and patient organizations as well as other interested parties to share patient-focused feedback with CMS on therapeutic alternatives and other information as CMS reviews section 1194(e)(2) data submissions and develops an initial offer for each selected drug. More information about these listening sessions will be forthcoming.

CMS acknowledges that Primary Manufacturers may benefit from having access to the section 1194(e)(2) data submitted by other interested parties during the negotiation period. In addition to offering the meetings above, CMS will aim to share redacted section 1194(e)(2) data with the Primary Manufacturer of a selected drug during the negotiation process when feasible. The data will be redacted as per the confidentiality standards described in section 40.2 of this revised guidance and will not include proprietary information, PHI / PII, or information that is protected from disclosure under other applicable law.

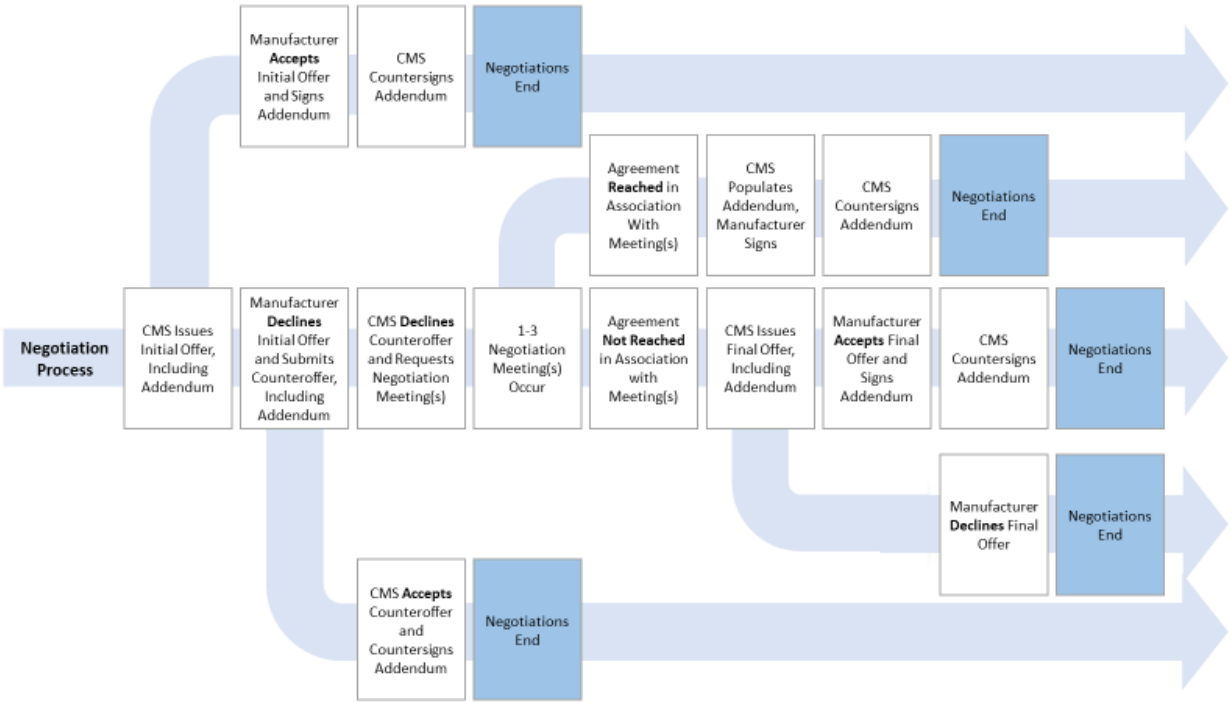
In accordance with sections 1191(d)(5)(B) and 1194(b)(2)(B) of the Act, CMS will make a written initial offer to the Primary Manufacturer with the proposal for the MFP for a selected drug for initial price applicability year 2026 no later than February 1, 2024. This written initial offer will be accompanied by an Addendum to the Agreement populated with the proposal for the MFP, in order for CMS and the Primary Manufacturer to effectuate agreement upon the MFP if such agreement is reached at this stage.

After the written initial offer from CMS is sent to the Primary Manufacturer, the negotiation process may include the following steps, depending on when and whether agreement on the MFP is reached and an offer is accepted:

(1) in accordance with section 1194(b)(2)(C) of the Act, an optional written counteroffer, including an Addendum populated with the counteroffer MFP as described in section 60.4.2 of this revised guidance, from the Primary Manufacturer (if CMS' written initial offer is not accepted by the Primary Manufacturer) that must be submitted no later than 30 days after the date of receipt of the written initial offer from CMS;
(2) in accordance with section 1194(b)(2)(D) of the Act, a written response from CMS to the optional written manufacturer counteroffer, which CMS will provide within 30 days;
(3) if the Primary Manufacturer's written counteroffer is not accepted by CMS, up to three possible in-person or virtual negotiation meetings between the Primary Manufacturer and CMS; and
(4) a final written offer, including an Addendum containing the final offer MFP as described in section 60.4.4 of this revised guidance, made by CMS to the Primary Manufacturer, if no agreement is reached before the end of the negotiation meetings.

Every offer and counteroffer will include an Addendum populated with the offered/counteroffered MFP. If an agreement is reached at any point during the negotiation process by the Primary Manufacturer accepting CMS' written initial offer or final offer (as described in section 60.4.4 of this revised guidance), CMS accepting the Primary Manufacturer's counteroffer, or an agreement being reached in association with the negotiation meetings, the Addendum to the Agreement, as described in section 40.3 of this revised guidance, will be executed by both parties and will constitute agreement on the MFP. Section 60.4.4 of this revised guidance describes how and when the Addendum will be created and signed. The MFP included in the executed Addendum will apply for the selected drug for initial price applicability year 2026 and will be updated according to section 1195(b)(1)(A) of the Act for subsequent years in the price applicability period, as applicable. The diagram below provides a non-exhaustive list of possible paths the negotiation process could take after CMS' initial offer, for a process taking place within the statutorily specified timelines.

Figure 3. Possible Negotiation Paths



During the entire negotiation process, CMS cannot offer or agree to any manufacturer counteroffer that exceeds the statutorily determined ceiling as defined in section 1194(c) of the Act and as described in section 60.2 of this revised guidance.

If the Primary Manufacturer is delayed in meeting one or more deadlines related to establishing the Agreement, submitting required data, and/or submitting the counteroffer, CMS will continue to engage in the negotiation process and will take the time to complete the established process as described in this section. During the period of time from when the Primary Manufacturer fails to meet a deadline until the date the Primary Manufacturer comes into compliance with the negotiation process, CMS will consider the Primary Manufacturer in violation of the Agreement and the Primary Manufacturer may be subject to civil monetary penalties as outlined in section 1197(c) of the Act. Section 90.3 and section 100 of this revised guidance further address possible actions to address noncompliance.

60.4.1 Provision of an Initial Offer and Justification

In accordance with section 1194(b)(2)(B) of the Act, the written initial offer from CMS, provided no later than February 1, 2024, must include a concise justification for the offer based on the data described in section 50 of this revised guidance. The justification will include a qualitative description of the factors from section 1194(e) (further described in sections 50 and 60.3 of this revised guidance) and a description of the methodology that CMS used to determine the initial offer. The information contained in the concise justification will provide the Primary Manufacturer with information on the range of evidence and other information considered pursuant to section 1194(e) that CMS found compelling during the development of the initial offer, thereby providing the Primary Manufacturer the necessary information to build a counteroffer if the Primary Manufacturer decides to reject the initial offer. The initial offer and

justification will not include information that CMS determines to be third-party proprietary pricing information, information that could lead to the calculation of a third party's proprietary information, PHI / PII, other information that is protected from disclosure under other applicable law, or the starting point.

No offer can exceed the statutorily determined ceiling as defined in section 1194(c) of the Act and described in section 60.2 of this revised guidance. As feasible, CMS will provide information on the calculation of the statutorily-determined ceiling and the computation of how CMS will apply a single MFP across dosage forms and strengths of the selected drug to the Primary Manufacturer within 60 days of the Primary Manufacturer's submission of data that complies with the requirements described in section 50.1 of this revised guidance. As described in section 40.2.3 of this revised guidance, CMS may reach out to the Primary Manufacturer for clarity on its data submission if CMS determines the information is not complete or accurate. In situations when additional outreach to the Primary Manufacturer is required to clarify the submitted data, CMS will aim to provide information on the calculation of the statutorily-determined ceiling and computation of how CMS will apply a single MFP across dosage forms and strengths of the selected drug to the Primary Manufacturer as close to 60 days from the initial data submission as feasible. As described in section 40.5 of this revised guidance, a Primary Manufacturer will have 30 days to submit a suggestion of error regarding the calculation of the ceiling and computation of how CMS will apply a single MFP across dosage forms and strengths for CMS' consideration.

60.4.2 Required Components of a Counteroffer

In accordance with section 1194(b)(2)(C) of the Act, the Primary Manufacturer will have no more than 30 days from receipt of the written initial offer from CMS to respond in writing by either accepting the initial offer for the selected drug or making a written counteroffer and providing a justification for such counteroffer based on the data described in section 50 of this revised guidance. Any counteroffer should also respond to the justification provided in CMS' written initial offer. The Primary Manufacturer's response should focus on the elements described in section 1194(e) and indicate the reasons the Primary Manufacturer believes that the information submitted by the Primary Manufacturer on the data in section 1194(e)(1) or (e)(2) of the Act, or other available data related to the selected drug and its therapeutic alternatives as described in section 1194(e)(2) of the Act, does not support the written initial offer made by CMS. Primary Manufacturers may also include in their counteroffer justification new information regarding the selected drug and its therapeutic alternative(s) as described in section 1194(e)(2) that supports the counteroffer MFP.

The Primary Manufacturer should provide a suggested MFP for the selected drug in its written counteroffer. As described in section 60.1 of this revised guidance, the counteroffer MFP should be made consistent with the manner that CMS' written initial offer was made; that is, a single price for the cost of the selected drug per 30-day equivalent supply, weighted across dosage forms and strengths. In accordance with section 1194(b)(2)(F) of the Act, CMS cannot accept a written counteroffer from a manufacturer that exceeds the statutorily determined ceiling as defined in section 1194(c) of the Act and described in section 60.2 of this revised guidance.

On April 18, 2023, CMS published the Drug Price Negotiation Process ICR for 60-day comment to capture information related to the counteroffer that Primary Manufacturers may submit after receiving CMS' initial offer.[70] The Drug Price Negotiation Process ICR includes instructions and a form for Primary Manufacturers to submit written counteroffers in the case where CMS' written initial offer of an MFP for a selected drug is not accepted. The comment period for the Drug Price Negotiation Process ICR closed on June 20, 2023. There will be an additional opportunity to submit comments for 30 days after revisions and re-publication in the Federal Register.

In order for a written counteroffer to be considered complete, a Primary Manufacturer must complete an Addendum in the CMS HPMS in addition to responding to the Drug Price Negotiation Process ICR, as described in section 40.3 of this revised guidance. A completed Addendum would include, but is not limited to, the MFP the Primary Manufacturer is counteroffering and a signature by an authorized representative.

60.4.3 Negotiation Process After Manufacturer Counteroffer

In accordance with section 1194(b)(2)(D) of the Act, CMS will respond in writing to a written counteroffer made by the Primary Manufacturer. Although the statute does not specify a timeframe for CMS' response to the counteroffer, negotiations for initial price applicability year 2026 must end prior to August 1, 2024, i.e., an agreement on MFP for the selected drug must be reached no later than July 31, 2024, to avoid potential excise tax liability under 26 U.S.C. § 5000D(b)(2).

In the case CMS' written initial offer is not accepted, and the Primary Manufacturer submits a written counteroffer, CMS will consider the counteroffer and either accept or reject it in writing within 30 days of receipt of the counteroffer. When considering a counteroffer, CMS will evaluate whether accepting the counteroffer is consistent with the statutory directive to aim to arrive at an agreement that achieves the lowest possible MFP for the selected drug. If CMS' written response to the counteroffer rejects the Primary Manufacturer's written counteroffer, CMS will extend an invitation to the Primary Manufacturer for a negotiation meeting. CMS will offer to hold a minimum of one meeting between CMS and the Primary Manufacturer to discuss CMS' written initial offer, the Primary Manufacturer's written counteroffer, and data considered. After this initial meeting, CMS will give each party (CMS and the Primary Manufacturer) the opportunity to request one additional meeting, resulting in a maximum of three meetings between CMS and the Primary Manufacturer.

The scope for these negotiation meetings will focus on the section 1194(e) data, including the therapeutic alternative(s) for the selected drug, and how they should inform the MFP. During these negotiation meetings, discussion of disputes and program policies regarding the negotiation process will be considered out of scope. CMS and the Primary Manufacturer will each be permitted to bring up to six meeting attendees, and both parties must share its participant lists ahead of each meeting. CMS arrived at this meeting attendee number after considering the roles from each party that would be critical to the conversation while ensuring that the meeting is sized appropriately to encourage active discussion. Additionally, a maximum of six attendees per side

[70] Drug Price Negotiation Process under Sections 11001 and 11002 of the Inflation Reduction Act (IRA). See: https://www.cms.gov/regulations-and-guidance/legislation/paperworkreductionactof1995/pra-listing/cms-10849.

is in line with requirements for similar meetings between government entities and manufacturers. Each meeting will last no more than two hours and may be conducted in-person at CMS or HHS headquarters. CMS believes two hours per negotiation meeting (of which there can be up to three meetings) is sufficient for a fruitful discussion and is appropriate considering time and scheduling constraints. If necessary, due to distance or scheduling challenges, meetings may be held virtually, or may be a "hybrid" arrangement where a portion of attendees are in-person and a portion of attendees are virtual. CMS' notes from negotiation meetings will be retained as part of the meeting record in compliance with applicable federal law including the Federal Managers Financial Integrity Act and the Federal Records Act and will be subject to the confidentiality policy described in section 40.2.1 of this revised guidance. Attendees on behalf of the Primary Manufacturer may take and keep notes of the meetings. Audio and/or video recording of negotiation meetings will not be permitted.

Correspondence regarding negotiation meetings will be conducted over email using the IRARebateandNegotiation@cms.hhs.gov mailbox. CMS will share a meeting agenda with the Primary Manufacturer via email approximately two weeks before the meeting. The Primary Manufacturer may request additions or edits to the agenda as long as they are in scope, as discussed in the paragraph above. Such requests must be submitted via email at least one week ahead of the meeting. CMS will circulate a final agenda two business days prior to the negotiation meeting. If a Primary Manufacturer would like to share materials at a negotiation meeting, such materials should be limited to 20 pages (or a combination of pages, slides, and/or charts and graphs totaling 20 pages), in order to focus the discussion on issues that can reasonably be discussed within the scope of the meeting, anticipating that these materials may contain cross-references to other material, particularly other material already submitted to CMS. Such materials must be submitted via email at least one week ahead of the meeting. Substantive discussion via email will not be permitted, in order for all attendees to benefit from such discussions as part of the negotiation meetings.

The meetings for initial price applicability year 2026 will occur between the time the Primary Manufacturer's written counteroffer is not accepted by CMS, which at the latest will be 30 days after the counteroffer is received, if applicable, and June 28, 2024. There would be about three months' time between CMS' rejection of the Primary Manufacturer's written counteroffer (approximately April 1, 2024) and the deadline for negotiation meetings to conclude (June 28, 2024). CMS requires that all negotiation meetings end no later than June 28, 2024, the last business day that is fifteen days prior to July 15, 2024, to allow CMS sufficient time to prepare a final offer (if an MFP was not reached in association with the negotiation meetings), send that final offer to the Primary Manufacturer by July 15, and to allow the Primary Manufacturer time to consider the final offer and accept or reject the final offer by July 31, 2024, as all negotiations must be concluded prior to August 1, 2024. These dates assume that a Primary Manufacturer is timely in entering into an Agreement, submitting information, and meeting deadlines related to the Negotiation Program.

CMS believes that the negotiation meeting process described above allows for a more efficient and effective approach than preparing and exchanging additional written offers and counteroffers. Negotiation meetings will also allow both parties to discuss any new information consistent with the data described in section 1194(e)(2) of the Act that may have become

available about the selected drug or its therapeutic alternative(s), and that may affect the determination of the MFP. Negotiation meetings will be attended solely by representatives of the Primary Manufacturer and of CMS. A written record will be developed and retained by CMS in compliance with applicable federal laws. The Primary Manufacturer can also develop and retain its own written record. As described in section 40.2.2 of this revised guidance, CMS will not publicly discuss ongoing negotiations with a Primary Manufacturer, including details of the negotiation meetings. Primary Manufacturers may publicly disclose information regarding ongoing negotiations with CMS at its discretion. If a Primary Manufacturer discloses information that is made public regarding any aspects of the negotiation process prior to the explanation of the MFP being released by CMS, CMS reserves the right to publicly discuss the specifics of the negotiation process regarding that Primary Manufacturer.

As described in section 60.6.1 of this revised guidance, in this public explanation, CMS will make public a narrative explanation of the negotiation process and the agreed-upon MFP and share redacted information regarding the section 1194(e) data received, the exchange of offers and counteroffers, and the negotiation meetings while abiding by the confidentiality policy described in section 40.2 of this revised guidance.

When developing this negotiation process, CMS considered using solely a written offer and counteroffer approach. That is, CMS considered providing one written offer and allowing a Primary Manufacturer to make a single written counteroffer, as described in the statute. CMS also contemplated allowing each party to make up to two written offers or counteroffers (i.e., CMS makes an initial offer, Primary Manufacturer possibly makes a counteroffer, CMS possibly makes a second offer, Primary Manufacturer possibly makes a second counteroffer). However, CMS believes that an offer/counteroffer process that includes in-person or virtual meetings (or a hybrid approach) will most effectively facilitate the negotiation process to arrive at an MFP and is more consistent with current industry practices for drug price negotiation.

60.4.4 Determination that Negotiations Have Finished

In accordance with sections 1194(b)(2)(E) and 1191(d)(2)(B) of the Act, all negotiations between CMS and the manufacturer of the selected drug must end prior to August 1, 2024, for initial price applicability year 2026 to avoid potential excise tax liability.

In the event that negotiation meetings occurred and an MFP was not agreed to in association with the negotiation meetings, CMS will send the Primary Manufacturer a "Notification of Final Maximum Fair Price Offer" and an Addendum with the final offer MFP by July 15, 2024. This will serve as the final offer to the Primary Manufacturer for the MFP for the selected drug. This final offer will only be sent if, by July 15, 2024, neither CMS nor the Primary Manufacturer has accepted the latest offer or counteroffer made in writing or agreed upon an MFP in association with the negotiation meetings. If a final offer is sent, the Primary Manufacturer must respond in writing to this final offer by either accepting or rejecting the final offer by July 31, 2024. The following table details CMS' timing for the negotiation process for initial price applicability year 2026:

Date[71]	**Milestone**
February 1, 2024	Statutory deadline for CMS to send written initial offer to the Primary Manufacturer
30 days after receipt of written initial offer from CMS (March 2nd if the offer is made by CMS on February 1, 2024)	Statutory deadline for the Primary Manufacturer to accept the initial offer or submit a written counteroffer to CMS
30 days after receipt of the manufacturer counteroffer (April 1st if the manufacturer counteroffer is made on March 2, 2024)	Date by which CMS will provide a written response accepting or rejecting the manufacturer counteroffer
Date that the Primary Manufacturer's written counteroffer is not accepted by CMS through June 28, 2024 (the last business day that is fifteen days prior to July 15, 2024)	Negotiation meetings (in-person, virtual, or hybrid, maximum of three possible meetings), if necessary
July 15, 2024	Date by which CMS will issue a "Notification of Final Maximum Fair Price Offer" to the Primary Manufacturer, if the written initial offer or Primary Manufacturer written counteroffer was not accepted and an MFP was not agreed upon in association with the negotiation meetings
July 31, 2024	Date by which the Primary Manufacturer must respond to (i.e., accept or reject) CMS' "Notification of Final Maximum Fair Price Offer," if applicable
July 31, 2024	Statutory deadline for all negotiations to end; CMS will notify the Primary Manufacturer of any failure to meet the deadline and the possible consequences thereof if agreement upon the MFP is not reached by July 31, 2024
August 1, 2024	Statutory end of negotiation period

To formalize agreement on an MFP, CMS and the Primary Manufacturer both sign an Addendum to the Agreement (described in sections 40.3 and 60.4 of this revised guidance) that sets forth the agreed-upon MFP. When CMS prepares a written offer, CMS also completes the Addendum with the offered MFP and sends the Addendum along with the written offer to the Primary Manufacturer via CMS HPMS. If the Primary Manufacturer accepts the written offer, they will sign the Addendum after which CMS will countersign the Addendum. Similarly, a

[71] These dates are contingent on CMS and the Primary Manufacturer meeting the deadlines described in this revised guidance and in statute. If the Primary Manufacturer is delayed in meeting one or more deadlines, CMS will continue to engage in the negotiation process and will take the time to complete the established process as described in this section. If a statutory deadline is missed, the Primary Manufacturer may be subject to a civil monetary penalty or excise tax.

Primary Manufacturer's written counteroffer is not considered complete unless the Primary Manufacturer submits a complete response to the Drug Price Negotiation Process ICR in CMS HPMS, submits an Addendum for the MFP consistent with the counteroffer amount in CMS HPMS, and signs that Addendum. If CMS accepts the written counteroffer, it will countersign the Addendum.[72]

If CMS and the Primary Manufacturer do not agree to an MFP by the statutory end of the negotiation period, the Primary Manufacturer will enter a period during which an excise tax potentially may be assessed. As described in 26 U.S.C. § 5000D(b)(2) and § 5000D(c), the Primary Manufacturer can end the period during which the excise tax may apply by agreeing to an MFP, as described in section 60.8 of this revised guidance, or can meet the statutory criteria for the suspension of tax or may terminate its Agreement in the manner described in section 40.6 of this revised guidance, which includes sending a notice terminating all of their applicable agreements under the Medicare and Medicaid programs and establishing that none of the Primary Manufacturer's drugs are covered by an agreement under section 1860D-14A or section 1860D-14C of the Act.

60.5 Application of the MFP Across Dosage Forms and Strengths

An MFP that is agreed upon as described in section 60.4 of this revised guidance establishes one price for the selected drug. In accordance with section 1196(a)(2) of the Act, CMS has the administrative duty to establish procedures to compute and apply the MFP across different dosage forms and strengths of the selected drug and not based on the specific formulation or package size or package type of such drug.

As described in section 60.1 of this revised guidance, the MFP will reflect a single price for the selected drug per 30-day equivalent supply. To ensure that the MFP is made available to MFP-eligible individuals at the point of sale (and to pharmacies, mail order services, or other dispensers, with respect to such MFP-eligible individuals), however, CMS will publish the MFP at the per-unit (e.g., tablet) level for each NDC-9 and NDC-11 associated with the selected drug.

The following methodology will be used to apply the single MFP across NDC-9s for a 30-day equivalent supply and to calculate an MFP per unit for each NDC-9 of the selected drug. CMS will use a methodology that scales the MFP per unit based on price differentials across different dosage forms and strengths. For initial price applicability year 2026, CMS will use the WAC of the selected drug in this calculation. CMS will first calculate an annual WAC per unit cost for each NDC-11 included on the list of NDC-11s of the selected drug in the CMS HPMS, inclusive of any NDC-11s added by the Primary Manufacturer (see section 40.2 of this revised guidance), from the manufacturer-submitted quarterly WAC per unit and unit volume data, to account for potential variation in unit volume across quarters. The annual WAC per unit for each NDC-11 will then be converted into an amount for a 30-day equivalent supply (using the methodology described in 42 C.F.R. § 423.104(d)(2)(iv)(A)(2)), so that the WAC will be comparable to the negotiated single MFP. CMS will then aggregate the WAC per 30-day equivalent supply for each NDC-11 into a WAC per 30-day supply for each NDC-9 of the selected drug. The WAC per 30-day equivalent supply for each NDC-9 will then be used to calculate a WAC price ratio

[72] In the event that this functionality is delayed in CMS HPMS, CMS will specify an alternative approach for sharing the Addendum in writing.

for each NDC-9 of the selected drug. The ratio derived from the WAC per 30-day equivalent supply for each NDC-9 will then be multiplied by the single MFP for the selected drug to calculate the MFP for a 30-day equivalent supply of each NDC-9 of the selected drug. Lastly, to determine the per unit MFP for an NDC-9, CMS will convert from an MFP for a 30-day equivalent supply to an MFP per unit based on the average number of units in a 30-day equivalent supply.

The following steps provide additional detail regarding the approach CMS will use:

1. For each NDC-11 and calendar quarter, CMS will divide the WAC quarterly units by the total WAC annual units (from- manufacturer submitted data) and multiply this quotient by the quarterly WAC per unit.
    - Note: CMS will use the WAC unit cost for the period beginning January 1, 2022 and ending December 31, 2022 for purposes of this calculation to align with the time period of data used to calculate the ceiling for the MFP.
2. For each NDC-11, CMS will then sum the amounts calculated in step 1 to calculate the annual WAC per unit.
3. For each NDC-11, CMS will divide the quantity dispensed by the total 30-day equivalent supply, both calculated from 2022 PDE data, to calculate the average number of units per 30-day equivalent supply.
4. For each NDC-11, CMS will multiply the WAC per unit calculated in step 2 by the average number of units per 30-day equivalent supply calculated in step 3 to calculate the WAC per 30-day equivalent day supply for that NDC-11.
5. For each NDC-11, CMS will divide the total 30-day equivalent supply for that NDC-11 by the total 30-day equivalent supply across all applicable NDC-11s within an NDC-9 and then multiply this quotient by the amount calculated in step 4.
6. For each NDC-9, CMS will then sum amounts calculated in step 5 across all NDC-11s to calculate the WAC per 30-day equivalent supply for that NDC-9.
7. For each NDC-9, CMS will divide the total 30-day equivalent supply for that NDC-9 by the total 30-day equivalent supply across all NDC-9s and then multiply this quotient by the amount calculated in step 6.
8. CMS will then sum amounts calculated in step 7 across all NDC-9s of the selected drug to calculate the WAC per 30-day equivalent supply for the selected drug.
9. For each NDC-9, CMS will then divide the WAC per 30-day equivalent day supply for that NDC-9 calculated in step 6 by the WAC per 30-day equivalent supply for the selected drug calculated in step 8 to calculate the WAC per 30-day equivalent supply ratio for that NDC-9.
10. For each NDC-9, CMS will multiply the single MFP for the selected drug by the relative WAC per 30-day equivalent supply ratio for that NDC-9 calculated in step 9 to calculate the MFP per 30-day equivalent supply for that NDC-9.
11. For each NDC-9, CMS will divide the MFP per 30-day equivalent supply for that NDC-9 calculated in step 10 by the quotient of the total number of units dispensed divided by the total 30-day equivalent supply to calculate the MFP per unit (e.g., tablet).

CMS will include the MFP per unit price for each NDC-9 of the selected drug, calculated in step 11 of this section 60.5 of this revised guidance, along with corresponding NDC-11 package prices (determined by multiplying the NDC-9 unit price by the number of units per NDC-11 package), in the publication of MFPs as described in section 60.6 of this revised guidance. CMS

recognizes there may be other ways to apply the MFP to dosage forms and strengths and will monitor whether this policy serves the intent of the Negotiation Program. As noted throughout this revised guidance, the policies described for the Negotiation Program are for initial price applicability year 2026, and CMS may consider additional policies for future years of the Negotiation Program.

60.5.1 Application of the MFP to New NDAs / BLAs or NDCs

Based on the definition of a qualifying single source drug described in section 30.1 of this revised guidance, if the Primary Manufacturer for a selected drug receives approval or licensure for a new NDA or BLA, as applicable, for the same active moiety / active ingredient after the drug has been selected, CMS requires that the MFP apply to drug or biological products marketed pursuant to the new NDA or BLA. Similarly, after the drug is selected, if the Primary Manufacturer for such drug receives approval or licensure for a new drug or biological product or NDC that is marketed pursuant to a supplement to an existing NDA or BLA, CMS requires that the MFP apply to such new drug or biological product. Additionally, an NDC that has been marketed pursuant to an applicable NDA or BLA prior to drug selection may lack sufficient PDE or WAC data in 2022 to apply the MFP across that dosage form and strength as described above. To apply the MFP to a new NDC that is marketed for the first time after the MFP is negotiated for a selected drug (including before or after the start of the initial price applicability year) or to an NDC that is marketed prior to MFP negotiation but which lacks either sufficient PDE unit data for calendar year 2022 or sufficient WAC data for calendar year 2022 for CMS to apply the MFP to that dosage form and strength as described above, CMS will determine whether there is an existing, comparable NDC to which the MFP for the selected drug has been applied. If a comparable NDC exists, CMS will impute the quotient of total quantity dispensed to 30-day equivalent supply based on the FDA-approved label associated with the new NDC and will use the same WAC ratio that was calculated for the existing NDC to apply the MFP to the new NDC.

If a comparable NDC does not exist, CMS will impute the quotient of total quantity dispensed to 30-day equivalent supply based on the FDA-approved label associated with the new NDC but will use a WAC ratio of 1.0 to apply the MFP to the new NDC.[73]

60.6 Publication of the MFP

In accordance with section 1191(d)(6) and section 1195(a)(1) of the Act, CMS will publish by September 1, 2024, the MFP for each drug selected for initial price applicability year 2026 for which CMS and the Primary Manufacturer have reached an agreement on an MFP. Related to this requirement, CMS will publish the following on the CMS website: the selected drug, the initial price applicability year, the MFP file, and the explanation for the MFP (published at a later date – see section 60.6.1 of this revised guidance). The MFP file will contain the single MFP for a 30-day equivalent supply of the selected drug, the NDC-9 per unit price, and NDC-11 per package price and will be updated annually to show the inflation-adjusted MFP for the selected drug. CMS will also publish on the CMS website when a drug is no longer a selected drug and

[73] While this guidance is focused on initial price applicability year 2026, CMS notes that in future years, renegotiation of the MFP might be appropriate in the event of certain new NDCs that represent material changes to the selected drug, such as where the new NDC is sought due to changes in the selected drug that result in the addition of a new indication. CMS will provide additional information in the future on renegotiation, which will be implemented for initial price applicability year 2028 and subsequent years, in accordance with the statute.

the reason for that change, and when an MFP between a Primary Manufacturer and CMS is not agreed upon.

60.6.1 Explanation for the MFP

Section 1195(a)(2) of the Act requires CMS to publish an explanation for the MFP no later than March 1 of the year prior to the initial price applicability year, which will be March 1, 2025 for initial price applicability year 2026. CMS will strive to publish these explanations earlier than March 1, 2025, if feasible. The explanation will focus on the section 1194(e) data that had the greatest impact in determining the MFP and include a discussion of the other section 1194(e) data, as applicable. It will also note any data or circumstances that may be unique to the selected drug. Alongside the narrative explanation, CMS will release redacted information regarding the section 1194(e) data received, exchange of offers and counteroffers, and the negotiation meetings, if applicable. CMS will develop and publish the public explanation of the MFP in accordance with the confidentiality policy described in section 40.2 of this revised guidance.

If an agreement for an MFP is not reached for a selected drug, neither an MFP nor a public explanation of the MFP will be published. Instead, CMS will indicate on the CMS website that an MFP has not been agreed upon between the Primary Manufacturer and CMS for the selected drug. In circumstances where an MFP is finalized after the statutory deadline for the conclusion of negotiations, the MFP and the public explanation of the MFP will be posted in accordance with section 60.8 of this revised guidance.

60.7 Exclusion from the Negotiation Process Based on Generic or Biosimilar Availability

In accordance with section 1192(c)(2) of the Act and subject to the timeline and situations discussed in section 70, a selected drug will no longer be subject to the negotiation process, with respect to its initial price applicability year, if CMS determines that at least one generic drug or biosimilar biological product satisfies the following criteria: (1) it is approved under section 505(j) of the FD&C Act with at least one dosage form and strength of the selected drug as the listed drug or licensed under section 351(k) of the PHS Act with at least one dosage form and strength of the selected drug as the reference product, and (2) it is marketed pursuant to such approval or licensure. The approach CMS will take to make this determination is described in section 70 of this revised guidance.

When the drug is no longer subject to the negotiation process based on the criteria in section 1192(c)(2) of the Act, the selected drug will continue to be considered a selected drug with respect to such initial price applicability year with respect to the number of negotiation-eligible drugs on the list published under section 1192(a) of the Act (see section 70 of this revised guidance for additional details).

60.8 Establishment of MFPs After the Negotiation Deadline

Sections 1194(b)(2) and 1191(d)(5)(C) of the Act contemplate that agreement upon an MFP must be reached for initial price applicability year 2026 by August 1, 2024 in order to avoid potential imposition of an excise tax. If negotiations have not ended by this date, the Primary Manufacturer may be subject to an excise tax. As a general matter, if the Primary Manufacturer is delayed in meeting one or more deadlines related to the negotiation process, CMS will continue to engage in the negotiation process described in section 60.4 of this revised guidance.

Certain actions or delays by the Primary Manufacturer may delay the process such that the MFP is established after the end of the negotiation period. If this occurs, in accordance with section 1194(b)(1) of the Act, CMS will follow timelines consistent with the negotiation process established in this revised guidance and take the time to complete the established process so described as appropriate for the selected drug. Likewise, certain actions by the Primary Manufacturer may delay the negotiation process to such an extent that a selected drug has a change in status that is material to CMS' statutory obligations under the negotiation process. If this occurs, in accordance with section 1194(b)(1), when CMS initiates or resumes the negotiation process, CMS will apply the consistent methodology and process with respect to the selected drug based on its status at the time the negotiation process occurs, including beginning in 2028 which may have potential implications with respect to the renegotiation process. Guidance about the renegotiation process will be forthcoming for future years of the Negotiation Program.

If the manufacturer and CMS have completed each step of the negotiation process as detailed in section 60.4 of this revised guidance, including CMS' issuance of a "Notification of Final Maximum Fair Price Offer" and then, after the statutory end of the negotiation period, the Primary Manufacturer of a selected drug wishes to agree to an MFP, the Primary Manufacturer must notify CMS in writing that it would like to accept the last offer of an MFP from CMS, as reflected in the "Notification of Final Maximum Fair Price Offer." In accordance with section 1195(b)(2) of the Act, in the case of a selected drug with respect to an initial price applicability year for which the MFP is determined after the MFPs are published for other selected drugs, CMS shall publish the MFP no later than 30 days after the date such MFP is so determined. In accordance with section 60.6 of this revised guidance, CMS will publish the MFP and the MFP explanation on the CMS website. CMS will follow timelines consistent with the established process for publishing the public explanation of the MFP and will not expedite its timeline due to late action from the Primary Manufacturer.

70. Removal from the Selected Drug List Before or During Negotiation, or After an MFP is in Effect

In accordance with section 1192(c) of the Act, a selected drug will no longer be subject to the negotiation process and will cease to be a selected drug, subject to the timeline and situations discussed below, if CMS determines (1) the FDA has approved a generic drug under section 505(j) of the FD&C Act that identifies as its reference-listed drug a product that is included in the selected drug, or the FDA has licensed a biosimilar biological product under section 351(k) of the PHS Act that identifies as its reference product a product that is included in the selected drug; and, (2) the generic drug or biosimilar biological product, as applicable, is marketed pursuant to such approval or licensure.

The approval (or licensure, as applicable) and marketing of an authorized generic drug (which includes authorized generic drugs and certain biological products as defined in section 1192(e)(2) of the Act) would not qualify as meeting the statutory requirement that a generic drug or a biosimilar biological product is being marketed. In accordance with section 1192(e)(2)(B)(i) of the Act, an authorized generic drug as defined in section 505(t)(3) of the FD&C Act is treated as the same qualifying single source drug as a qualifying single source drug that is the listed drug, for the purposes of the Negotiation Program. Likewise, section 1192(e)(2)(B)(ii) of the Act indicates that the same rule applies to a biological product that is approved under section 351(a)

of the PHS Act and is marketed, sold, or distributed directly or indirectly to the retail class of trade under different labeling or packaging (other than repackaging as the reference product in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trademark.

The determination whether a selected drug should not be subject to the negotiation process and ultimately removed from the selected drug list will be informed by CMS' review of PDE and AMP data for the generic drug or biosimilar biological product for which the selected drug is the listed drug or reference product on a monthly basis as described below. CMS will consider an approved generic drug or licensed biosimilar biological product to be marketed when the totality of the circumstances, including these data, reveals that the manufacturer of the generic drug or biosimilar biological product is engaging in bona fide marketing of that drug or product.

After the selected drug is removed from the selected drug list, CMS will monitor the manufacturers of such generic drugs or biosimilar biological products to ensure they continue to engage in bona fide marketing of the generic or biosimilar biological product based on the process described in section 90.4 of this revised guidance.

Starting in October 2023, and repeated each month thereafter, CMS will take the following approach in its review of data to inform its determination whether the statutory criteria in sections 1192(c)(1)(A) and 1192(c)(1)(B) of the Act for an approved generic drug or licensed biosimilar to be marketed pursuant to such approval or licensure are being met.

First, CMS will use FDA reference sources, including the Orange Book and Purple Book, to determine whether a generic drug or biosimilar biological product is approved or licensed for any strength(s) or dosage form(s) of a selected drug for initial price applicability year 2026.

Second, if CMS determines that a generic drug or biosimilar biological product has been approved or licensed, CMS will begin by reviewing the PDE and AMP data with dates of service during the most recent 12-month period available to determine if the manufacturer of the generic drug or biosimilar biological product has engaged in bona fide marketing of that drug or product. For example, when CMS performs this assessment in October of 2023, CMS will use PDE and AMP data with dates of service from October 2022 through September 2023. When CMS performs this assessment in November 2023, CMS will use PDE and AMP data for dates of service from November 2022 through October 2023.

The determination whether a generic drug or biosimilar is being bona fide marketed 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 biological product is regularly and consistently available for purchase through the pharmaceutical supply chain and whether any licenses or other agreements between a Primary Manufacturer and a generic drug or biosimilar manufacturer limit the availability or distribution of the selected drug, as articulated further in section 90.4.

Per section 1192(c)(2) of the Act, if CMS makes a determination regarding generic drug or biosimilar biological product availability on or after the selected drug publication date, and

before the end of or during the negotiation period for an initial price applicability year, the selected drug will not be subject to the negotiation process for the negotiation period, and an MFP will not be established. Accordingly, for initial price applicability year 2026, if CMS makes this determination between September 1, 2023, and August 1, 2024, the drug will remain a selected drug through 2026, but no MFP will apply and the drug will not be replaced with another selected drug.

In accordance with section 1192(c)(1) of the Act, a selected drug that is included on the list of selected drugs for an initial price applicability year will remain a selected drug for that year and each subsequent year beginning before the first year that begins at least nine months after the date on which CMS determines the statutory criteria in section 1192(c) are met. Accordingly, if CMS makes this determination between August 2, 2024, and March 31, 2026, for a drug selected for initial price applicability year 2026, then the drug will cease to be a selected drug on January 1, 2027, and the MFP will apply for 2026. If CMS makes this determination between April 1, 2026, and March 31, 2027, then the selected drug will cease to be a selected drug on January 1, 2028, and the MFP will apply for 2026 and 2027. These results are summarized in the following table:

Date on which CMS determines that a generic drug or biosimilar biological product is approved and marketed	**Result with respect to selected drug for the Negotiation Program**
September 1, 2023 through August 1, 2024 (which includes the Negotiation Period for the initial price applicability year 2026)	Selected drug remains a selected drug for initial price applicability year 2026, though MFP does not apply; selected drug ceases to be a selected drug on January 1, 2027.
August 2, 2024 through March 31, 2026	Selected drug remains a selected drug and MFP applies for initial price applicability year 2026; selected drug ceases to be a selected drug on January 1, 2027.
April 1, 2026 through March 31, 2027	Selected drug remains a selected drug and MFP applies for initial price applicability year 2026 and calendar year 2027; selected drug ceases to be a selected drug on January 1, 2028.

Without regard to whether the Primary Manufacturer decides to execute an Agreement as discussed in section 40.1 of this revised guidance, to terminate an Agreement as discussed in section 40.6, or to transfer ownership of the selected drug as discussed in section 40.7, a selected drug remains a selected drug until CMS determines otherwise under the criteria set forth in section 1192(c) of the Act.

In all cases, after CMS determines the statutory criteria in section 1192(c) for generic competition are met for a selected drug, CMS will publish such information on the CMS website.

80. MFP-Eligible Individuals

For initial price applicability year 2026, in accordance with section 1191(c)(2) of the Act, the term “maximum fair price eligible individual” means, with respect to a selected drug, the

following: in the case such drug is dispensed to the individual at a pharmacy, by a mail order service, or by another dispenser, an individual who is enrolled in a prescription drug plan under Medicare Part D or an MA–PD plan under Medicare Part C (including an Employer Group Waiver Plan), if Part D coverage is provided under such plan for such selected drug. The MFP is not required to be made available to a Medicare beneficiary who uses other sources of prescription drug coverage, such as a plan that receives the Retiree Drug Subsidy, prescription drug discount cards, or cash.[74] For initial price applicability year 2026, CMS does not expect manufacturers to provide access to the MFP of a selected drug to hospitals, physicians, and other providers of services and suppliers with respect to a drug furnished or administered to MFP eligible individuals enrolled under Part B, including an individual who is enrolled in an MA plan.

90. Manufacturer Compliance and Oversight

In accordance with section 1196(b) of the Act, CMS will monitor compliance by a Primary Manufacturer with the terms of the Agreement and establish a mechanism through which violations of such terms shall be reported.

90.1 Monitoring of Manufacturer Compliance

CMS will closely monitor the Primary Manufacturer's compliance with the terms of the Agreement and other aspects of the Negotiation Program. Following the publication of selected drugs for each initial price applicability year, CMS will provide information about the negotiation process to the Primary Manufacturer of each selected drug (see section 40 of this revised guidance for additional details). CMS anticipates this information will include operational and statutory timelines, procedural requirements, systems instructions, IRA resources, and contact information.

During the negotiation period, CMS will track and monitor progress during all steps of the process and engage in direct communications with each Primary Manufacturer. To facilitate successful Negotiation Program operations and support manufacturer compliance with Program requirements, CMS will issue reminder letters prior to manufacturer deadlines with warnings of potential applicability of excise taxes (see 26 U.S.C. § 5000D for additional information regarding the excise tax) or CMPs (see section 100 of this revised guidance), written requests for corrective action when applicable (see section 40.2.3 of this revised guidance), written notification that a Primary Manufacturer may be subject to enforcement action as applicable, and written confirmation that a Primary Manufacturer may no longer be subject to enforcement action as applicable.

Failure of a Primary Manufacturer to comply with certain Negotiation Program deadlines and other requirements of the Negotiation Program may result in potential excise tax liability (see 26 U.S.C. § 5000D). As described in section 100 of this revised guidance, failure of a Primary Manufacturer to comply with certain Negotiation Program deadlines and other requirements of the Negotiation Program could result in CMPs.

[74] CMS notes that employer sponsored plans that receive the retiree drug subsidy and health plans that offer creditable prescription drug coverage are not included because they are not Part D plans.

90.2 Monitoring of Access to the MFP

In accordance with section 1193(a)(3)(A) of the Act, under the Agreement with CMS with respect to a price applicability period, access to the MFP with respect to such a selected drug shall be provided by the Primary Manufacturer to MFP-eligible individuals at the pharmacy, mail order service, or other dispenser at the point of sale, and to the pharmacy, mail order service, or other dispenser with respect to such MFP-eligible individuals who are dispensed the selected drug.

Further, in accordance with section 1193(a)(5) of the Act, which requires that the manufacturer comply with requirements determined by the Secretary to be necessary for purposes of administering the program and monitoring compliance with the program, and section 40.4 of this revised guidance, CMS requires that the Primary Manufacturer establish safeguards to ensure the MFP is available to MFP-eligible individuals and to pharmacies, mail order services, and other dispensers on units of the selected drug for which there are Secondary Manufacturers. CMS reiterates that the requirement for the Primary Manufacturer to provide access to the MFP applies to all sales of the selected drug by a Secondary Manufacturer to MFP-eligible individuals and to pharmacies, mail order services, and other dispensers that are providing a selected drug to an MFP-eligible individual, as discussed in section 80 of this revised guidance.

As described in section 40.4 of this revised guidance, CMS is considering the potential to engage with an MTF to facilitate the exchange of data between supply chain entities to support the verification of MFP eligibility of an individual who is dispensed a selected drug. Each component of the pharmaceutical supply chain may have a role in making the MFP available to MFP-eligible individuals, but it is ultimately the Primary Manufacturer's responsibility to ensure access to the MFP. There are various methods by which dispensing entities and MFP-eligible individuals can determine whether they are accessing the MFP for a selected drug.

For example, under section 1195(a) of the Act, the MFP for a selected drug will be published by CMS, giving the public and other interested parties an opportunity to know the MFP for each selected drug, as well as the explanation for each MFP (see section 60.6 of this revised guidance for additional details). Under section 1191(d)(6), the MFPs for selected drugs for initial price applicability year 2026 must be published by September 1, 2024. In addition, CMS anticipates that pharmaceutical database compendia will publish the MFPs for selected drugs such that they would become more knowable and accessible to pharmaceutical purchasers. CMS believes such transparency of the MFPs for selected drugs will help dispensing entities and MFP-eligible individuals to know the MFP for a selected drug and determine whether they are able to access the MFP.

In accordance with section 1196(a)(3)(A) of the Act, as well as section 1196(b), which requires that the Secretary establish a mechanism by which violations of the terms of the Agreement shall be reported, CMS will establish procedures for reporting suspected violations related to access to the MFP with respect to MFP-eligible individuals who are enrolled in Medicare Part D plans and the pharmacies, mail order services, and other dispensers that provide selected drugs to MFP-eligible individuals. As part of this process, CMS may establish a toll-free phone line and email box where an individual or a dispenser could communicate information to CMS regarding an incident in which the MFP was not provided to an MFP-eligible individual or the applicable

pharmacy, mail order service, or other dispenser. CMS anticipates the submissions would likely include the name of the individual reporting the incident, the nature of the incident, the date the incident occurred, the name of the drug, the manufacturer of the drug, and contact information for follow-up.

Upon receipt of a report of a suspected violation, CMS will review the submissions, investigate reports of potential noncompliance, and if appropriate, impose CMPs on the Primary Manufacturer if CMS determines the Primary Manufacturer failed to provide an MFP-eligible individual or an eligible dispenser access to the MFP for the selected drug, including in cases where there are one or more Secondary Manufacturers of the selected drug. CMS would also expect manufacturers and other interested parties to report instances in which a dispenser was not passing through the MFP to an MFP-eligible individual, or a dispenser was extending the MFP to non-MFP-eligible individuals.

As described in section 40.4.1 of this revised guidance and consistent with section 1193(d) of the Act regarding the manufacturer's Agreement with CMS, a manufacturer with a Pharmaceutical Pricing Agreement (PPA) with the Secretary under the 340B program is not required to provide a 340B covered entity with access to the MFP of a selected drug with respect to an MFP-eligible individual who is eligible to be dispensed such selected drug at the covered entity if the 340B ceiling price is lower than the MFP for such selected drug.

CMS is also aware that it is conceptually possible for an entity that meets the statutory definition of a manufacturer, but that is not the Primary Manufacturer or a Secondary Manufacturer, to market one or more drug or biological products pursuant to one or more NDA(s) or BLA(s) included in the selected drug. For example, it is possible for an entity to purchase one or more drug or biological products included in the selected drug from a wholesaler, repackage or relabel such products, and then re-market them pursuant to one or more NDA(s) or BLA(s) included in the selected drug. CMS believes it would be appropriate for the MFP to be made available to all MFP-eligible individuals and to all pharmacies, mail order services, and other dispensers with respect to MFP-eligible individuals who are dispensed units of the selected drug. However, for initial price applicability year 2026, CMS is limiting the scope of Primary Manufacturer responsibility to provide access to the MFP for the selected drug to units of such drug sold by the Primary Manufacturer or a Secondary Manufacturer. CMS will monitor to determine if there are sales of selected drug to MFP-eligible individuals by manufacturers other than Primary Manufacturer and Secondary Manufacturers and consider whether other mechanisms are needed to promote access to MFP to Medicare-eligible individuals in these circumstances. CMS continues to seek feedback on how it might achieve this goal, interested parties can send feedback on this topic to IRARebateandNegotiation@cms.hhs.gov.

90.3 26 U.S.C. Section 5000D Excise Tax on Sale of Designated Drugs

The IRS will administer the excise tax. CMS understands that the Treasury Department will issue guidance relating to the excise tax in the coming weeks.

90.4 Monitoring for Bona Fide Marketing of Generic or Biosimilar Product

If CMS determines that either:

(1) a potential qualifying single source drug will not be considered a qualifying single source drug for initial price applicability year 2026 because 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 drugs or biosimilar biological products that CMS determined are approved or licensed and marketed based on the process described in section 30.1 of this revised guidance, or

(2) a selected drug is no longer subject to the negotiation process and ceases to be a selected drug because (a) the FDA has approved a generic drug under section 505(j) of the FD&C Act that identifies as its reference listed drug a product that is included in the selected drug, or the FDA has licensed a biosimilar biological product under section 351(k) of the PHS Act that identifies as its reference product a product that is included in the selected drug; and, (b) the generic drug or biosimilar biological product, as applicable, is marketed pursuant to such approval or licensure in accordance with section 1192(c) of the Act and under the process described in sections 60.7 and 70 of this revised guidance,

then CMS will monitor, after such an above determination is made, whether meaningful competition continues to exist in the market by ongoing assessments of whether the manufacturer of the generic drug or biosimilar is engaging in bona fide marketing. Such monitoring by CMS may include, but is not limited to, whether the generic drug or biosimilar biological product is regularly and consistently available for purchase through the pharmaceutical supply chain and whether any licenses or other agreements between a Primary Manufacturer and a generic drug or biosimilar manufacturer limit the availability or distribution of the selected drug.

CMS is aware that marketing or other agreements between the Primary Manufacturer and generic drug or biosimilar manufacturers may limit the availability of the generic drug or biosimilar for purchase through the pharmaceutical supply chain, and CMS will attempt to identify when such agreements exist as a factor in determining whether bona fide marketing exists, although such agreements would not by themselves be dispositive of that determination. CMS notes that any agreements limiting the availability of a selected drug may be subject to scrutiny and potential enforcement under antitrust laws (including laws prohibiting unfair methods of competition) as well as laws prohibiting unfair or deceptive acts or practices in or affecting commerce.

In addition, CMS will analyze the share of generic drug or biosimilar biological product units identified in PDE data as a percentage of total units of Part D expenditures, as well as whether manufacturers are reporting units of the selected drug as part of their AMP reporting responsibilities under section 1927(b)(3)(A) of the Act, and the trend in reporting of such AMP units. CMS reserves the right to also use other available data and informational sources on market share and relative market competition of the generic drug or biosimilar.

100. Civil Monetary Penalties

In accordance with section 1197 of the Act, Primary Manufacturers of selected drugs that enter into an Agreement may be subject to CMPs for (1) failure to ensure access to a price that is less than or equal to the MFP for MFP-eligible individuals and pharmacies, mail order services, and

other dispensers who dispense the selected drug with respect to MFP-eligible individuals, (2) failure to pay the rebate amount for a biological product for which inclusion on the selected drug list was delayed but has since undergone negotiation, as described in section 1192(f)(4) of the Act, (3) violation of certain terms of the Agreement, and (4) the provision of false information as described in section 1197(d) of the Act.

CMS' primary goal is to successfully administer all aspects of the Negotiation Program; CMS intends to exercise the authority to impose CMPs for instances of noncompliance that substantively obstruct negotiation processes and/or availability of the MFP Such instances may include, but are not limited to, failure to make the MFP available to MFP-eligible individuals; failure to provide timely, complete, and accurate information that is necessary to execute the negotiation process or other administrative or monitoring functions of the Negotiation Program; repeated violations of the Agreement or other Negotiation Program requirements; or egregious and/or knowing violations of Negotiation Program requirements.

Broadly, CMS is establishing a structure for enforcement actions that:

1. Is within CMS' statutory authority,
2. Is not punitive in response to immaterial or other instances of noncompliance that are not substantive,
3. Can be applied consistently across applicable instances of Primary Manufacturer noncompliance, and
4. Facilitates the ability to successfully engage in all components of the negotiation process within the established statutory timeframes.

This revised guidance addresses violations by a Primary Manufacturer for failure to ensure access to a price for a selected drug less than or equal to the MFP, violation of terms of the Agreement, and provision of false information as related to the aggregation rule of the Small Biotech Exception and the Biosimilar Delay Rule. This revised guidance does not address failure to pay a rebate for a biological product pursuant to section 1192(f)(4) of the Act, as this topic will be addressed in future guidance. CMS provides details about the process for CMP imposition in section 100.4 of this revised guidance.

100.1 Failure of Manufacturer to Ensure Access to a Price Less than or Equal to the MFP
In accordance with section 1197(a) of the Act, CMS may impose a CMP on a Primary Manufacturer of a selected drug that has entered into an Agreement with CMS upon failure to provide access to a price that is less than or equal to the MFP to MFP-eligible individuals dispensed the selected drug and to pharmacies, mail order services, or other dispensers with respect to MFP-eligible individuals who are dispensed the selected drug, including the failure to do so in connection with sales of the selected drug by a Secondary Manufacturer. CMS will be monitoring the WAC in relation to other pricing metrics. Upon discovery and confirmation of a failure to make the MFP available, CMS will send the Primary Manufacturer a Notice of Potential Noncompliance that will include information on the potential violation and an opportunity for corrective action. CMS will establish an informal process in which the Primary Manufacturer will have 10 business days to respond to the Notice of Potential Noncompliance to provide additional context, evidence refuting the violation, proof of mitigation of noncompliance, and/or other factors for CMS' consideration. CMS will consider the materials

provided by the Primary Manufacturer when determining the Primary Manufacturer's CMP liability.

If the Primary Manufacturer fails to ensure access to a price less than or equal to the MFP, the statute provides for a CMP equal to 10 times the amount equal to the product of the number of units of such drug so dispensed (during such year) and the difference between the price for such drug made available (for such year by such manufacturer) to MFP-eligible individuals and the MFP for such drug for such year. For the purposes of calculating this CMP, CMS will use the amount that is equal to the required pass through of the MFP described in section 40.4 of this revised guidance. As described in section 40.5 of this revised guidance, CMS will monitor for compliance and audit, as needed, to ensure that the MFP or a price lower than the MFP is being made available for the selected drug.

100.2 Violations of the Agreement

Pursuant to section 1197(c) of the Act, any Primary Manufacturer of a selected drug that has entered into an Agreement with CMS under section 1193 of the Act that fails to comply with requirements determined by CMS to be necessary for the purposes of administering the Negotiation Program and monitoring compliance with the Negotiation Program pursuant to section 1193(a)(5) or fails to provide the information required under section 1193(a)(4) may be subject to a CMP of $1,000,000 for each day of such violation. In applying CMPs for Primary Manufacturer violations of the Agreement, CMS intends to use discretion such that CMPs are reserved for instances of substantive noncompliance. Examples of such violations are shown in the table below. Note that these examples are not an exhaustive list of violations that could warrant CMPs. CMS reserves the authority to issue CMPs for other violations as required to effectively administer and monitor the Negotiation Program.

Category	Example of Substantive Violations
Manufacturer Information Submission	• Failure to submit data required under section 1194(e)(1) of the Act, including failure to engage in requested corrective action to mitigate such failures. • Omissions or inaccuracies of manufacturer-submitted information that is critical to the negotiation processes (e.g., non-FAMP data from the Primary Manufacturer, including non-FAMP data for a selected drug sold by any Secondary Manufacturer(s), required for ceiling calculation) or other efforts to administer or monitor the Negotiation Program (e.g., information requested during an audit), including failure to engage in requested corrective action to mitigate such omissions or inaccuracies. • Submission of false information that interferes with the negotiation process (e.g., submission of false data on unit costs of production). • Knowing submission of false information under the procedures to apply the aggregation rule in section 1192(d)(2)(B) for the Small Biotech Exception. • Knowing provision of false information under procedures to apply the aggregation rule in section 1192(f)(1)(C) of the Biosimilar Delay.
MFP Availability	• Failure to make the MFP available to MFP-eligible individuals, and to pharmacies, mail order services, or other dispensers (see section 100.1 of this revised guidance) • Failure to process timely and complete reimbursement under a retrospective reimbursement structure as described in section 40.4 of this revised guidance.

As an example of when CMS would impose a CMP, consider the following. As described in section 40.2 of this revised guidance, information on non-FAMP for each applicable quarter (as described in section 50.1.1 of this revised guidance) for each NDC-11 of the selected drug for the applicable period will be due to CMS as part of the Negotiation Data Elements ICR no later than October 2, 2023 for initial price applicability year 2026. If the Primary Manufacturer fails to timely submit the required non-FAMP information, including the non-FAMP information for each NDC-11 of a selected drug for which there is a Secondary Manufacturer, CMS will determine the number of days in which the Primary Manufacturer is in violation of the Agreement by counting the day after the applicable submission deadline (e.g., October 3, 2023 for initial price applicability year 2026) as the first day of violation with each additional day of violation thereafter counted until the day the Primary Manufacturer provides the required information to CMS, the selected drug ceases to be a selected drug, or the Primary Manufacturer terminates the Agreement. In the event a manufacturer never provides the required information, the daily CMP will continue to accrue until the end of the negotiation period (i.e., the final deadline for reaching an agreed upon MFP). Upon reaching that deadline, the manufacturer may also be subject to a potential excise tax for failing to reach an agreed upon MFP pursuant to 26 U.S.C. § 5000D(b)(2).

CMS may require additional information to administer or monitor compliance with the Negotiation Program in accordance with section 1193(a)(5) of the Act. When applicable, CMS will provide a written request to the Primary Manufacturer with details for such requests, including a date by which any requested information must be submitted. CMS is committed to providing Primary Manufacturers with reasonable timeframes to accommodate these information requests. CMS will consider written requests for deadline extension submitted no later than three calendar days prior to the initial deadline. Extension requests must include a reasonable basis for requiring the extension as determined by CMS. Only one extension, if applicable, will be granted for each request. Manufacturers that fail to comply with requests for information required to administer or monitor compliance with the Negotiation Program on or before the due date may be subject to a CMP.

In the event the manufacturer does not meet the final established deadline to provide the requested information and CMS determines a CMP is warranted, the CMP will begin to accrue beginning on the day after the due date. For example, if CMS requests information for monitoring purposes by November 15, 2027, day one of the violation would be November 16, 2027. Each additional day of violation thereafter will be counted until the day the Primary Manufacturer provides the required information to CMS, the selected drug ceases to be a selected drug, or the Primary Manufacturer terminates the Agreement. The CMP will not include the day the information is submitted. Because the day of data submission is not included in CMP calculation, should a Primary Manufacturer submit the requested information on the day after the deadline, no CMP will be imposed.

To facilitate program operations and support manufacturer compliance, CMS will provide the Primary Manufacturer with: (1) written reminders of impending submission deadlines, including warning of potential liability for a CMP for submission violations; and (2) Notification of Potential Noncompliance, if applicable, and the applicable next steps (see, for example, sections

40.2.3 and 100.1 of this revised guidance). If CMS determines a violation warrants a CMP, CMS will follow the procedures outlined in section 100.4 of this revised guidance to notify the Primary Manufacturer and initiate the CMP process.

A Primary Manufacturer that submits false Information that is required under the Agreement and interferes with the administration of the Negotiation Program will be out of compliance with the requirement to submit information and may be subject to this CMP. In instances of a Primary Manufacturer submitting false information that is required under the Agreement, CMS will determine the number of days in which the Primary Manufacturer is in violation of the Agreement by counting the day after the established deadline for submission of information under the Agreement as the first day of violation with each additional day of violation thereafter counted until the day the Primary Manufacturer provides a complete and accurate submission of the required information to CMS, the selected drug ceases to be a selected drug, or the Primary Manufacturer terminates the Agreement.

100.3 Provision of False Information Related to the Small Biotech Exception and the Biosimilar Delay Rule

In accordance with section 1197(d) of the Act, if CMS determines that any manufacturer knowingly provides false information under the procedures to apply the aggregation rule in section 1192(d)(2)(B) for the Small Biotech Exception, such manufacturer shall be subject to a CMP equal to $100,000,000 for each item of such false information. Likewise, if CMS determines that any Biosimilar Manufacturer knowingly provides false information under the procedures to apply the aggregation rule in section 1192(f)(1)(C) of the Biosimilar Delay, such manufacturer shall be subject to a CMP equal to $100,000,000 for each item of such false information.

CMS adopts a standard for "knowingly" that conforms with the Office of the Inspector General definition at 42 C.F.R. § 1003.110 in the application of other CMPs. Knowingly means that a manufacturer, for purposes of section 1197(d) of the Act for the Small Biotech Exception or a Biosimilar Manufacturer under section 1192(f)(1)(c) for the Biosimilar delay: (1) has actual knowledge of the information; (2) acts in deliberate ignorance of the truth or falsity of the information; or (3) acts in reckless disregard of the truth or falsity of the information. No proof of specific intent to defraud is required. Upon identifying instances of knowing submission of false information under either of these provisions, CMS will provide the Manufacturer with a CMP Notification detailing the final CMP amount and the basis for that amount, requesting payment, outlining the payment process, outlining the available appeals process, and establishing applicable deadlines for resolution.

100.4 Notice and Appeal Procedures

Where CMS makes a determination to impose a CMP, CMS will provide a written CMP Notification that the manufacturer has engaged in a substantive compliance violation and is subject to a CMP. As required by section 1128A of the Act, the CMP Notification will include the following:

- A description of the basis for the determination;
- The basis for the penalty;
- The Primary Manufacturer's right to a hearing (see below); and

- Information about where to file the request for a hearing.

In applicable cases (e.g., failure to provide required information), CMS will note the commencement date for a CMP accrual and alert the manufacturer that the daily CMP will continue to accrue until the period of noncompliance ends. CMS will send monthly noncompliance notices to the manufacturer during the noncompliance period to include the total amount of CMP accrued to date, the amount that will continue to accrue should the violation continue, and required actions on the part of the Primary Manufacturer to mitigate the noncompliance period (e.g., submission of required information), if applicable.

To operationalize the CMP appeal process in the Negotiation Program, CMS is adopting the existing procedures as codified in 42 C.F.R. section 423 subpart T: Appeal Procedures for Civil Money Penalties (see § 423.1000 through § 423.1094) that currently apply to Part D sponsors and to manufacturers under the Coverage Gap Discount Program. Pursuant to this appeals process, the manufacturer will have 60 calendar days from the date of receipt of the CMP Notification to request a hearing (§ 423.1020). The date of receipt is defined as the calendar day following the day on which the CMP Notification is issued. If the manufacturer requests a hearing, the procedures outlined in section 1128A of the Act and operationalized by 42 C.F.R. § 423 Subpart T will apply. As set forth in section 1128A(f), if the manufacturer does not pay the CMP timely, the CMP amount may be deducted from any sum then or later owing by the United States. CMP funds will be deposited in accordance with section 1128A(f).

The CMP amount will cease to accrue once the manufacturer has demonstrated compliance with the requirement(s) at issue in the relevant CMP Notification. Following the end of the noncompliance period, and at the conclusion of any appeals process initiated by the Primary Manufacturer within 60 days of the CMP Notification, CMS will issue the final CMP Notification. As required by section 1128A of the Act, the final notification will add the following to the information included in the initial CMP Notification and monthly noncompliance notices:

- The final amount of the penalty;
- The date the penalty is due; and
- Instructions for submitting the CMP payment.

110. Part D Formulary Inclusion of Selected Drugs

In accordance with section 1860D-4(b)(3)(I) of the Act, Medicare Part D plans shall include each covered Part D drug that is a selected drug under section 1192 of the Act on Part D formularies during contract year 2026 and all subsequent years for which the MFP of the selected drug is in effect during the price applicability period.[75] Because the selected drug includes all dosage forms and strengths to which the MFP applies for initial price applicability year 2026, the statute requires that all such dosage forms and strengths of the selected drug that constitute a covered Part D drug and for which the MFP is in effect be included on formulary. For contract year 2026, CMS will not implement explicit tier placement or utilization management requirements that

[75] As required by section 1860D-4(b)(3)(I)(ii) of the Act, nothing shall prohibit a Part D sponsor from removing a selected drug from a formulary if such removal would be permitted under 42 C.F.R. § 423.120(b)(5)(iv) (or any successor regulation).

apply uniformly across selected drugs in all formularies, but intends to apply the process described below.

While CMS understands that not all selected drugs and drug classes will present Part D sponsors and their Pharmacy & Therapeutics Committees with the same formulary considerations and might not warrant the same formulary placement in all situations, CMS is concerned that Part D sponsors may be incentivized in certain circumstances to disadvantage selected drugs by placing selected drugs on less favorable tiers compared to non-selected drugs, or by applying utilization management that is not based on medical appropriateness to steer Part D beneficiaries away from selected drugs in favor of non-selected drugs.

CMS reminds Part D sponsors of the existing statutory and regulatory restrictions on formulary design. Sections 1860D-2(b)(2)(B) and 1860D-4(c)(1)(A) of the Act permit Part D sponsors to use formularies and tiered cost sharing in their benefit design, subject to certain limitations, and requires them to have a cost-effective drug utilization management program that includes incentives to reduce costs when medically appropriate. Under section 1860D-11(e)(2)(D)(i) of the Act, CMS may approve a prescription drug plan only if the agency "does not find that the design of the plan and its benefits (including any formulary and tiered formulary structure) are likely to substantially discourage enrollment by certain part D eligible individuals under the plan." In addition, 42 C.F.R. § 423.272(b)(2)(i) states: "CMS does not approve a bid if it finds that the design of the plan and its benefits (including any formulary and tiered formulary structure) or its utilization management program are likely to substantially discourage enrollment by certain Part D eligible individuals under the plan." Furthermore, 42 C.F.R. § 423.120(b)(2)(iii) requires each Part D plan formulary to "include adequate coverage of the types of drugs most commonly needed by Part D enrollees, as recognized in national treatment guidelines." In addition, 42 C.F.R. § 423.120(b)(1)(v) requires that in making decisions about formulary design, the entity designing the formulary must "base clinical decisions on the strength of scientific evidence and standards of practice." CMS maintains a robust clinical formulary review process to ensure that all Medicare Part D plans meet these and other applicable requirements. CMS reviews all formularies annually to ensure that each formulary passes the agency's clinical review criteria, which includes comprehensive evaluation of tier placement and all utilization management restrictions and criteria.

Given CMS' statutory obligation to monitor Medicare Part D plans' compliance with all applicable formulary requirements, CMS will use its formulary review process to assess: (1) any instances where Part D sponsors place selected drugs on non-preferred tiers, (2) any instances where a selected drug is placed on a higher tier than non-selected drugs in the same class, (3) any instances where Part D sponsors require utilization of an alternative brand drug prior to a selected drug with an MFP (i.e., step therapy), or (4) any instances where Part D sponsors impose more restrictive utilization management (i.e., step therapy and/or prior authorization) for a selected drug compared to a non-selected drug in the same class.

For this review, CMS will consider class to mean the FDA Established Pharmacologic Class or other source that groups like drugs with similar mechanisms of action. Specifically, as part of the contract year 2026 Part D formulary review and approval process, CMS will expect Part D sponsors to provide a reasonable justification to support the submitted plan design that includes

any of the practices noted above during the annual bid review process. This justification should address applicable clinical factors, such as clinical superiority, non-inferiority, or equivalence of the selected and non-selected drugs, as well as the plan design's compliance with applicable statutory and regulatory requirements (e.g., the requirement to have a cost-effective drug utilization management program that bases decisions on the strength of the clinical evidence and standards of practice). CMS will evaluate these justifications for compliance with applicable statutory and regulatory requirements and will only approve a Part D plan bid submitted by a Part D sponsor if the plan benefit package complies with those requirements.

120. Application of Medicare Part B and Part D Prescription Drug Inflation Rebate Programs to Selected Drugs

This section of the guidance describes the application of Medicare Part B and Part D inflation rebates to selected drugs. As background, section 11101 of the IRA added a new section 1847A(i) to the Act to require that manufacturers of Part B rebatable drugs pay inflation rebates to Medicare for certain Part B rebatable drugs based on specific requirements and formulas. Likewise, section 11102 of the IRA added a new section 1860D-14B to the Act, which requires that manufacturers of Part D rebatable drugs pay inflation rebates to Medicare for certain Part D rebatable drugs based on specific requirements and formulas.[76]

Given that initial price applicability year 2026 is limited to drugs for which there is Part D utilization, this revised guidance describes the interaction between the Negotiation Program and the Part D inflation rebate program. CMS will address the application of Part B inflation rebates to selected drugs in future guidance for initial price applicability year 2028.

The Part D drug inflation rebate program is applicable to certain drugs that meet the definition of a Part D rebatable drug and are dispensed under Part D and covered and paid for by Part D plans for each 12-month applicable period, starting with the applicable period beginning October 1, 2022. These rebates are paid by manufacturers to the Medicare Prescription Drug Account in the Federal Supplementary Medical Insurance Trust Fund.

The Part B and Part D inflation rebate programs apply to selected drugs, regardless of the status of the drug as a selected drug. Alternatively said, whether a drug is a selected drug will have no bearing as to whether the drug is also subject to the Part B and Part D inflation rebate program, as applicable. However, when a selected drug is no longer considered to be a selected drug, certain components of the applicable rebate amount formula are recalculated as discussed further below.

[76] CMS published initial guidance on both Part B and Part D inflation rebates on February 9, 2023, which includes more specific details on the operation of the Part B and Part D inflation rebate programs. See: https://www.cms.gov/files/document/medicare-part-d-inflation-rebate-program-initial-guidance.pdf and https://www.cms.gov/files/document/medicare-part-b-inflation-rebate-program-initial-guidance.pdf.

The Part D inflation rebate calculation is based on changes in the AMP over time.[77] MFP is excluded from AMP and thus does not affect the rebate calculation.[78]

The statutory formula to determine the Part D drug inflation rebate amount owed by manufacturers for each Part D rebatable drug consists of various components, including the calculation of a benchmark period manufacturer price. This "benchmark period manufacturer price" is calculated based on a "payment amount benchmark period" for each Part D rebatable drug (established at section 1860D-14B(g)(3) of the Act for drugs first approved or licensed on or before October 1, 2021 and at section 1860D-14B(b)(5)(A) for drugs first approved or licensed after October 1, 2021), and a "benchmark period CPI-U"[79] for each Part D rebatable drug (established at section 1860D-14B(g)(4) of the Act for drugs first approved or licensed on or before October 1, 2021 and section 1860D-14B(b)(5)(A) for drugs first approved or licensed after October 1, 2021). The payment amount benchmark period is the basis for the calculation of the benchmark period manufacturer price. The benchmark period manufacturer price is based on a weighted AMP for the quarters in that period.

For the period of time before a Part D rebatable drug is a selected drug, and during the time it is a selected drug, CMS will calculate the Part D inflation rebate amount, if applicable, based on the Part D rebatable drug's applicable payment amount benchmark period and benchmark period CPI-U, which is determined based on when the drug is first approved or licensed, as noted above. However, the statute at section 1860D-14B(b)(5)(C) specifies a different "payment amount benchmark period" and "benchmark period CPI-U" for each Part D rebatable drug in the case such drug is no longer considered to be a selected drug under section 1192(c) of the Act, for each applicable period beginning after the price applicability period with respect to such drug. Accordingly, in such a case where a Part D rebatable drug is no longer a selected drug, the payment amount benchmark period will be reset as the last year that begins during such price applicability period for such selected drug, and the benchmark period CPI-U is established as the January of the last year beginning during such price applicability period.

[77] Section 1860D-14B(g)(6) of the Act defines AMP to have the meaning, with respect to a Part D rebatable drug of a manufacturer, given in section 1927(k)(1) with respect to a covered outpatient drug of a manufacturer for a rebate period under section 1927. Section 1927(k)(1) defines AMP, with respect to a covered outpatient drug of a manufacturer for a rebate period, to mean 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 directly from the manufacturer, subject to certain exclusions.

[78] Section 1927(k)(1)(B)(i)(VI), as amended by section 11001(b)(3) of the Inflation Reduction Act.

[79] CPI-U refers to the Consumer Price Index for all urban consumers (United States city average).

Appendix A: Email Template for Biosimilar Manufacturer to Indicate Intent to Submit an Initial Delay Request for Initial Price Applicability Year 2026

Email subject line:
Biosimilar Delay: Notice of Intent to Submit Initial Delay Request for Initial Price Applicability Year 2026

Body of email:
Dear CMS,

I, an authorized representative of [insert manufacturer name], am notifying CMS that my company is the manufacturer of a biosimilar biological product and we anticipate the reference product for our biosimilar biological product will be included in a negotiation-eligible drug with respect to initial price applicability year 2026 for the Medicare Drug Price Negotiation Program. My company reasonably believes the market entry of our biosimilar biological product meets the criteria for the special rule to delay selection and negotiation of the negotiation-eligible drug, described in section 1192(f) of the Social Security Act. Therefore, I am notifying CMS of my company's intent to request that CMS delay the inclusion of the negotiation-eligible drug that includes the reference product for our biosimilar biological product on the selected drug list for initial price applicability year 2026.

As part of this notification, I am providing the following information:

My job title:	[insert]
My email address:	[insert]
My phone number:	[insert]
My company's mailing address:	[insert]
My company's biosimilar biological product name:	[insert]
Product name of the reference product for my company's biosimilar biological product	[insert]

Signed,
[Insert name of authorized representative]

Appendix B: Template for the Initial Delay Request Form

Under the authority in sections 11001 and 11002 of the Inflation Reduction Act of 2022 (P.L. 117-169), the Centers for Medicare & Medicaid Services (CMS) is implementing the Medicare Drug Price Negotiation Program, codified in sections 1191 through 1198 of the Social Security Act (the Act), to negotiate maximum fair prices (MFPs)[80] for selected drugs. Under section 1192(f) of the Act (the "Biosimilar Delay"), the manufacturer of a biosimilar biological product ("Biosimilar Manufacturer" of a "Biosimilar") may submit a request, prior to the selected drug publication date, for CMS' consideration to delay the inclusion of a negotiation-eligible drug (as defined in section 1192(d) of the Act) that includes the reference product for the Biosimilar (such a negotiation-eligible drug is herein referred to as a "Reference Drug") on the selected drug list for a given initial price applicability year. The Biosimilar Manufacturer eligible to submit the request is the holder of the BLA for the Biosimilar or, if the Biosimilar has not yet been licensed, the sponsor of the BLA for the Biosimilar that has been submitted for review by FDA.

Please refer to the memo titled "Medicare Drug Price Negotiation Program: Initial Memorandum, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026, and Solicitation of Comments" (Initial Negotiation Program Guidance) for additional details regarding the implementation of the Biosimilar Delay for initial price applicability year 2026. This form serves as the template that a Biosimilar Manufacturer may complete to submit an Initial Delay Request with respect to initial price applicability year 2026.

Submission of the email described in that memo indicating the Biosimilar Manufacturer's intention to submit an Initial Delay Request for initial price applicability year 2026 and receipt of the fillable Initial Delay Request form template and request-specific Box folder should occur prior to completing this form.

Instructions

- Initial Delay Requests that are incomplete or not timely submitted will not be accepted. For an Initial Delay Request to be timely for initial price applicability year 2026, the Biosimilar Manufacturer must submit a complete Initial Delay Request to CMS no later than 11:59 pm PT on May 22, 2023. CMS will deem an Initial Delay Request to be complete if it includes a complete Initial Delay Request form using this fillable template and the following documentation:
    - All agreements related to the Biosimilar filed with the Federal Trade Commission or the Assistant Attorney General pursuant to subsections (a) and (c) of section 1112 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003;

[80] In accordance with section 1191(c)(3) of the Social Security Act ("the Act"), maximum fair price means, with respect to a year during a price applicability period and with respect to a selected drug (as defined in section 1192(c) of the Act) with respect to such period, the price negotiated pursuant to section 1194 of the Act, and updated pursuant to section 1195(b) of the Act, as applicable, for such drug and year.

  - The manufacturing schedule for the Biosimilar submitted to the FDA during its review of the application for licensure under section 351(k) of the PHS Act, to the extent available; and
  - Disclosures (in filings by the Biosimilar Manufacturer with the Securities and Exchange Commission required under section 12(b), 12(g), 13(a), or 15(d) of the Securities Exchange Act of 1934 about capital investment, revenue expectations, and actions taken by the manufacturer that are typical of the normal course of business in the year (or the 2 years, as applicable) before marketing of a biosimilar biological product) that pertain to the marketing of the Biosimilar, or comparable documentation that is distributed to the shareholders of privately held companies, to the extent available.
- The data entry component of this submission should be completed by an individual authorized by the Biosimilar Manufacturer.
- The certification of the Initial Delay Request should be executed by (1) the chief executive officer (CEO) of the Biosimilar Manufacturer, (2) the chief financial officer (CFO) of the Biosimilar Manufacturer, (3) an individual other than a CEO or CFO, who has authority equivalent to a CEO or a CFO, or (4) an individual with the directly delegated authority to perform the certification on behalf of one of the individuals mentioned in (1) through (3).

CMS is relying on the fullness, accuracy, and completeness of the Biosimilar Manufacturer's submission to determine whether to approve the Initial Delay Request for initial price applicability year 2026. If the Biosimilar Manufacturer submits an Initial Delay Request that is not timely, complete, and accurate, the submission may adversely affect the Negotiation Program, including the process for selecting drugs for negotiation for initial price applicability year 2026.

Section 1: Identifying information

Identifying information for Biosimilar Manufacturer

Q1. Complete the following table with identifying information for the Biosimilar Manufacturer.

Field	Response
Entity Type	☐ Biosimilar Manufacturer
Entity name	
Employer Identification Number (EIN(s))	
Address	
Unique Identifier Assigned by CMS (P-number)	
Labeler Code(s)	

Identifying information on Biosimilar

Q2. Complete the following table with identifying information for the Biosimilar.

Field	Response
Product Name	

Active Ingredient	
NDC-9(s) (if applicable)	[optional, only if available]

Q3. List all applications for licensure for the Biosimilar under 351(k) of the Public Health Service (PHS) Act regardless of status (i.e., including applications that are approved, accepted for review, and submitted but not yet accepted for review). Leave approval date blank if license has not been approved.

Add additional rows for each application

Application Number	Submission Number	Application status	Approval Date [if licensed]	Indication	Dosage Form and Strength	Licensure planned before September 1, 2025?	Marketing planned before September 1, 2025?
nnnnnn	nnn	[Approved, Accepted for Review, Submitted]	MM/DD/ YYYY	Text	Text	[Yes/No]	[Yes/No]

Identifying information on Reference Product

Q4. Complete the following table with identifying information for the reference product for the Biosimilar.

Field	**Response**
Product Name	
Active Ingredient	
NDC-9(s)	

Q5. List the Biologic License Application (BLA) approved by the Food and Drug Administration (FDA) under section 351(a) of the PHS Act for the reference product for the Biosimilar.

Application Number	Submission Number	Approval Date	Indication	Dosage Form and Strength	Sponsor
nnnnnn	nnn	MM/DD/ YYYY	Text	Text	Text

Identifying information on Reference Manufacturer

Q6. Complete the following table with identifying information for the Reference Manufacturer.

Field	**Response**
Entity Type	☐ Reference Manufacturer
Entity name	

Employer Identification Number (EIN)	*[Optional, only if known]*
Address	*[Optional, only if known]*
Unique Identifier Assigned by CMS (P-number)	*[Optional, only if known]*
Labeler Code(s)	*[Optional, only if known]*

Section 2: Attestations to Requirements for Granting an Initial Delay Request

In accordance with section 1192(f)(2)(D)(iv) of the Act, CMS will not delay inclusion of a biological product on the list of selected drugs if the Biosimilar Manufacturer meets any of the statutory criteria for an excluded manufacturer. Questions 7 through 9 address whether the Biosimilar Manufacturer is an excluded manufacturer.

Q7. Relationship between Biosimilar Manufacturer and Reference Manufacturer: In accordance with section 1192(f)(2)(D)(iv) of the Act, CMS will not approve an Initial Delay Request if the Biosimilar Manufacturer is the same as the Reference Manufacturer or is treated as being the same as the Reference Manufacturer based on the aggregation rule in section 1192(f)(1)(C) of the Act. This aggregation rule provides, "all persons treated as a single employer under subsection (a) or (b) of section 52 of the Internal Revenue Code of 1986, or in a partnership, shall be treated as one manufacturer" for purposes of the Biosimilar Delay. Further, section 1192(f)(1)(C) of the Act establishes that "the term 'partnership' means a syndicate, group, pool, joint venture, or other organization through or by means of which any business, financial operation, or venture is carried on" by two or more parties for the purposes of the Biosimilar Delay.

Read the following statement and check the box if accurate:

I confirm consistent with sections 1192(f)(1)(C) and 1192(f)(2)(D)(iv) of the Act that the Biosimilar Manufacturer submitting this request is not the same or is not treated as being the same as the Reference Manufacturer.	☐

Q8. Incentives: In accordance with section 1192(f)(2)(D)(iv)(II)(aa) of the Act, CMS will not approve any Initial Delay Request submitted by a Biosimilar Manufacturer that has entered into an agreement with the Reference Manufacturer that requires or incentivizes the Biosimilar Manufacturer to submit an Initial Delay Request.

Read the following statement and check the box if accurate:

I confirm consistent with section 1192(f)(2)(D)(iv)(II)(aa) of the Act that the Biosimilar Manufacturer submitting this request has not entered into an agreement with the Reference Manufacturer named in this request that requires or incentivizes the Biosimilar Manufacturer to submit this or any other Initial Delay Request.	☐

Q9. Quantity Restriction: In accordance with section 1192(f)(2)(D)(iv)(II)(bb) of the Act, CMS will not approve any Initial Delay Request submitted by a Biosimilar Manufacturer that has entered into an agreement with the Reference Manufacturer that restricts the quantity, either directly or indirectly, of the Biosimilar that may be sold in the United States over a specified period of time.

Read the following statement and check the box if accurate:

I confirm consistent with section 1192(f)(2)(D)(iv)(II)(bb) of the Act that the Biosimilar Manufacturer submitting this request has not entered into an agreement with the Reference Manufacturer named in this request that restricts the quantity, either directly or indirectly, of the Biosimilar that may be sold in the United States over a specified period of time.	☐

In accordance with section 1192(f)(1)(A) of the Act, CMS will only approve an Initial Delay Request for initial price applicability year 2026 if CMS determines there is a high likelihood that the Biosimilar will be licensed and marketed before September 1, 2025. Questions 10 and 11 are relevant for this determination.

Q10. Licensure: In accordance with section 1192(f)(1)(A) of the Act, CMS will only approve an Initial Delay Request for initial price applicability year 2026 if CMS determines there is a high likelihood that the Biosimilar will be licensed before September 1, 2025. For the purposes of this Initial Delay Request, 'licensed' means approved by the FDA under section 351(k) of the PHS Act.

Select the following option that best describes the current licensure status of the Biosimilar as of the submission of this Initial Delay Request:

(A) I confirm consistent with section 1192(f)(1)(A) of the Act that the Biosimilar Manufacturer has submitted an application for licensure of the Biosimilar under section 351(k) of the PHS Act and the Biosimilar has been licensed.	☐
(B) I confirm consistent with section 1192(f)(1)(A) of the Act that the Biosimilar Manufacturer has submitted an application for licensure of the Biosimilar under section 351(k) of the PHS Act and the FDA has accepted such application for review.	☐
(C) I confirm consistent with section 1192(f)(1)(A) of the Act that the Biosimilar Manufacturer has submitted an application for licensure of the Biosimilar under section 351(k) of the PHS Act and has not received a determination from FDA that such application has been accepted for review.	☐
(D) I confirm consistent with section 1192(f)(1)(A) of the Act that the Biosimilar Manufacturer has not submitted an application for licensure of the Biosimilar under section 351(k) of the PHS Act.	☐

Q11. Marketing: In accordance with section 1192(f)(1)(A) of the Act, CMS will only approve an Initial Delay Request for initial price applicability year 2026 if CMS determines there is a high likelihood that the Biosimilar will be marketed before September 1, 2025.
Select the following option that best describes the current marketing status of the Biosimilar as of the submission of this Initial Delay Request:

(A) I confirm consistent with section 1192(f)(1)(A) of the Act that the Biosimilar is currently marketed.	☐
(B) I confirm consistent with section 1192(f)(1)(A) of the Act that the Biosimilar has not yet been marketed but the Biosimilar Manufacturer expects it to be marketed by September 1, 2025.	☐

(C) I confirm consistent with section 1192(f)(1)(A) of the Act that the Biosimilar has not yet been marketed and the Biosimilar Manufacturer does not expect it to be marketed by September 1, 2025.	☐

Section 3: Supporting Documentation

Q12. Manufacturing schedule: In accordance with section 1192(f)(1)(B)(ii)(I) of the Act, an Initial Delay Request must include, to the extent available, the manufacturing schedule for the Biosimilar submitted to the FDA during its review of the Biosimilar's application for licensure. Further, in accordance with section 1192(f)(3)(B) of the Act, CMS will consider such information in determining whether there is clear and convincing evidence that the Biosimilar will be marketed.

Using the 'Supporting Documentation - Manufacturing schedule' subfolder within the Box folder that CMS shared for the purposes of this Initial Delay Request, upload the manufacturing schedule(s) for the Biosimilar submitted to the FDA for each application listed in Q3.

Read the following statements and check the boxes if accurate:

I confirm consistent with section 1192(f)(1)(B)(ii)(I) of the Act that the manufacturing schedule(s) for the Biosimilar submitted to the FDA during its review of the Biosimilar's application for licensure is available for submission.	☐
I confirm consistent with section 1192(f)(1)(B)(ii)(I) of the Act that I have submitted to CMS the manufacturing schedule(s) for the Biosimilar submitted to the FDA during its review of the Biosimilar's application for licensure.	☐

Q13. Disclosures: In accordance with section 1192(f)(1)(B)(ii)(I) of the Act, an Initial Delay Request must include, to the extent available, disclosures (in filings by the Biosimilar Manufacturer with the Securities and Exchange Commission required under section12(b), 12(g), 13(a), or 15(d) of the Securities Exchange Act of 1934 about capital investment, revenue expectations, and actions taken by the Biosimilar Manufacturer that are typical of the normal course of business before marketing of a biosimilar biological product) that pertain to the marketing of the Biosimilar, or comparable documentation that is distributed to the shareholders of privately held companies. Further, in accordance with section 1192(f)(3)(B) of the Act, CMS will consider such information in determining whether there is clear and convincing evidence that the Biosimilar will be marketed.

Using the 'Supporting Documentation – Disclosures' subfolder within the Box folder that CMS shared for the purposes of this Initial Delay Request, upload all such disclosures.
Read the following statements and check the boxes if accurate:

I confirm consistent with section 1192(f)(1)(B)(ii)(I) of the Act that disclosures (in filings by the Biosimilar Manufacturer with the Securities and Exchange Commission required under section12(b), 12(g), 13(a), or 15(d) of the Securities Exchange Act of 1934 about capital investment, revenue expectations, and actions taken by the Biosimilar Manufacturer that are typical of the normal course of business before marketing of a biosimilar biological product) that pertain to the marketing of the	☐

Biosimilar, or comparable documentation that is distributed to the shareholders of privately held companies, are available for submission.	
I confirm consistent with section 1192(f)(1)(B)(ii)(I) of the Act that I have submitted to CMS all such disclosures.	☐

Q14. Agreements:
In accordance with section 1192(f)(1)(B)(ii)(I) of the Act, an Initial Delay Request must include all agreements related to the Biosimilar filed with the Federal Trade Commission or the Assistant Attorney General pursuant to subsections (a) and (c) of section 1112 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. Further, in accordance with section 1192(f)(3)(B) of the Act, CMS will consider such information in determining whether there is clear and convincing evidence that the Biosimilar will be marketed.

Using the 'Supporting Documentation – Agreements' subfolder within the Box folder that CMS shared for the purposes of this Initial Delay Request, upload all such agreements.

Read the following statement and check the box if accurate:

I confirm consistent with section 1192(f)(1)(B)(ii)(I) of the Act that I have submitted to CMS all agreements related to the Biosimilar filed with the Federal Trade Commission or the Assistant Attorney General pursuant to subsections (a) and (c) of section 1112 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003.	☐

Section 4: Certification

I hereby certify, to the best of my knowledge, that the information being sent to CMS in this submission is complete and accurate, and the submission was prepared in good faith and after reasonable efforts. I reviewed the submission and made a reasonable inquiry regarding its content. I understand the information contained in this submission is being provided to and will be relied upon by CMS for Medicare reimbursement purposes, including to determine whether CMS should delay the selection of a biological product that would, absent this request, be included on the selected drug list for initial price applicability year 2026, as described in section 1192(f) of the Social Security Act. I also certify that I will timely notify CMS if I become aware that any of the information submitted in this form has changed. I also understand that any misrepresentations may also give rise to liability, including under the False Claims Act.

Yes []
No []

Contact Information

Field	Response
Name of the Person Responsible for the Submission	
Title	
Telephone	
Email	
Signature	
Date	

Appendix C: Definitions for Purposes of Collecting Manufacturer-Specific Data

For the purposes of describing the data at sections 1194(e)(1), 1194(e)(2), and 1193(a)(4)(A) of the Act to be collected for use in the Negotiation Program, as described in sections 40.2, 50.1, and 50.2 of this revised guidance and the Negotiation Data Elements Information Collection Request (ICR), CMS adopts the following definitions and standards.

General

- When calculating monetary values, assume at most an 8.1 percent annual cost of capital for purposes of applying an adjustment. If a Primary Manufacturer uses a cost of capital below 8.1 percent, that amount should be used.

Non-FAMP

- Non-FAMP: Section 1194(c)(6) of the Act defines "average non-Federal average manufacturer price" as the average of the non-FAMP (as defined in section 8126(h)(5) of title 38 of the U.S. Code) for the four calendar quarters of the year involved.[81] For initial price applicability year 2026, these are the quarters of 2021. When there are less than 30 days of commercial sales data for all NDC-11s of the selected drug in calendar year 2021, the applicable year will be the first full calendar year following market entry of such drug. When there are at least 30 days of commercial sales data but less than a calendar quarter of data to calculate the non-FAMP in calendar year 2021 (or the first full year following market entry of such drug, when applicable) for a given NDC-11 of such drug, the non-FAMP reported by the manufacturer to CMS should reflect the temporary non-FAMP predicated upon the first 30 days of commercial sales data. The temporary non-FAMP should be calculated following the same methodology used to calculate the temporary non-FAMP amount used to determine the Temporary Federal Ceiling Price, as described in the Department of Veterans Affairs (VA) 2023 Updated Guidance for Calculation of Federal Ceiling Prices (FCPs) for New Drugs subject to Public Law 102-585. Any restatements of the non-FAMP made in any manufacturer non-FAMP submissions to the VA must be reflected in the non-FAMP submitted to CMS.
- Non-FAMP unit: Non-FAMP unit is the package unit as described in 38 U.S.C. § 8126(h)(6).
- Non-FAMP dosage form unit: The non-FAMP dosage form unit is the dosage form of the NDC that is reported in the "Dose form" field of the Excel workbook used by the Office of Pharmacy Benefits Management Services at the VA to collect non-FAMP information.

Research and Development (R&D) Costs

R&D costs mean a combination of costs incurred by the Primary Manufacturer for all FDA-approved indications of a drug falling into the five categories below, and excluding (a) prior Federal financial support, (b) costs associated with applying for and receiving foreign approvals,

[81] The term "non-Federal average manufacturer price" means, with respect to a covered drug and a period of time (as determined by the Secretary), the weighted average price of a single form and dosage unit of the drug that is paid by wholesalers in the United States to the manufacturer, taking into account any cash discounts or similar price reductions during that period, but not taking into account— (A) any prices paid by the Federal Government; or (B) any prices found by the Secretary to be merely nominal in amount. 38 U.S.C. § 8126(h)(5).

and (c) costs associated with *ongoing* basic pre-clinical research, clinical trials, and pending approvals:

1. R&D: Acquisition Costs
2. R&D: Basic Pre-Clinical Research Costs
3. R&D: Post-Investigational New Drug (IND) Application Costs
4. R&D: Abandoned and Failed Drug Costs
5. R&D: All Other R&D Direct Costs

CMS is calculating recoupment of R&D costs using both the global and U.S. total lifetime net revenue for the selected drug:

6. Recoupment: Global and U.S. Total Lifetime Net Revenue for the Selected Drug

The definitions and associated time periods for these terms are included below.

Definitions for 1. R&D: Acquisition Costs

- For the sole purpose of data collection under section 1194(e)(1)(A) of the Act, acquisition costs are defined as costs associated with the Primary Manufacturer's purchase from another entity of the rights to hold previously approved or future NDA(s) / BLA(s) of the selected drug.

Definitions for 2. R&D: Basic Pre-Clinical Research Costs

- Basic pre-clinical research costs are defined as all discovery and pre-clinical developmental costs incurred by the Primary Manufacturer with respect to the selected drug during the basic pre-clinical research period and are the sum of (1) direct research expenses and (2) the appropriate proportion of indirect research expenses (defined below).
- For each indication of the selected drug, the basic pre-clinical research period is defined as the date of initial discovery *or* the date the Primary Manufacturer acquired the right to hold the potential NDA(s) / BLA(s) or NDA(s) / BLA(s) of the selected drug (whichever is later) to the day before the last IND application for that indication of the selected drug went into effect.[82, 83] The basic pre-clinical research period may include both the initial research on the discovery of the selected drug and basic pre-clinical research related to new applications of the selected drug. If the length of the basic pre-clinical research period for the selected drug cannot be calculated, use 52 months ending the day before the first IND application went into effect. For example, if the selected drug had five IND applications that went into effect, use the date of the first IND application that went into effect as the end date for the 52-month period.[84]

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[82] CMS acknowledges that the exact date of initial discovery might not be known, but manufacturers should use their best estimate.

[83] For the purposes of identifying the date the Primary Manufacturer acquired the right to hold the potential NDA(s) / BLA(s) or NDA(s) / BLA(s) of the selected drug, use the earliest date of acquisition for any NDA / BLA of the selected drug.

[84] CMS believes that 52 months represents a solid average across studies. For example, one study reported that the pre-clinical phase takes 52 months on average. See DiMasi, J, Hansen, R, Grabowski, H. The price of innovation: new estimates of drug development costs. *Journal of Health Economics*, 2003, https://fds.duke.edu/db?attachment-

- Direct basic pre-clinical research costs are costs that can be specifically attributed to the discovery and pre-clinical development of the selected drug. Direct research expenses could include personnel (compensation for investigators and staff) researching the selected drug, materials for conducting basic pre-clinical research, and the costs of in vivo and in vitro studies on the selected drug before an IND application went into effect.
- Indirect basic pre-clinical research costs and relevant general and administrative costs are operating costs for basic pre-clinical research beyond the basic pre-clinical research costs for the selected drug, including administrative personnel and overhead costs (expenses for clinical facilities and equipment) that are shared across multiple potential drugs or biologics. To calculate the proportion of indirect costs, the Primary Manufacturer must use proportional allocation, whereby the same proportion of spending allocated for direct research on the selected drug is used to estimate the proportional spending for indirect research.[85, 86] For example, if the *direct* pre-clinical research costs spent on the selected drug were approximately 10 percent of a Primary Manufacturer's total *direct* basic pre-clinical research costs, then *indirect* costs should be allocated proportionally, thus for the selected drug they should be 10 percent of the total spending on *indirect* pre-clinical research costs during that time period.

Definitions for 3. R&D: Post-Investigational New Drug (IND) Application Costs

- Post-IND costs are defined as all direct costs associated with dosing and preparing the selected drug for clinical trials and the selected drug's Phase I, Phase II, and Phase III clinical trials for each FDA-approved indication. Post-IND costs also include all direct costs associated with completed FDA-required, post-marketing trials that are conducted after the FDA has approved a product. Post-IND costs exclude FDA-required, post-marketing trials that were not completed.
- Direct post-IND costs are defined as Institutional Review Board (IRB) review and amendment costs, user fees, patient recruitment, per-patient costs, research and data collection costs, personnel, and facility costs that are directly related to conducting the dosing and Phase I, Phase II, and Phase III clinical trials during the post-IND period. Direct post-IND costs also include patient recruitment, per-patient costs, research and data collection costs, personnel, and facility costs that are directly related to conducting the completed FDA-required, post-marketing trial.

25--1301-view-168. Another study estimated that the pre-clinical phase can take 31 months on average. See DiMasi, J, Grabowski, H, Hansen, R. Innovation in the pharmaceutical industry: New estimates of R&D costs, *Journal of Health Economics*, 2016, as cited by the Congressional Budget Office (CBO) in Research and Development in the Pharmaceutical Industry, April 2021, https://www.cbo.gov/publication/57126. Other estimates have found that the pre-clinical phase ranges from three to six years. See PhRMA, "Biopharmaceutical Research & Development: The Process Behind New Medicines," 2015, http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf.

[85] Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA.* 2020;323(9):844–853. doi:10.1001/jama.2020.1166

[86] Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programme*. 3rd ed. Oxford, UK: Oxford University Press; 2005, https://pure.york.ac.uk/portal/en/publications/methods-for-the-economic-evaluation-of-health-care-programme-third-edition(e43f24cd-099a-4d56-97e6-6524afaa37d1)/export.html.

- The post-IND period begins on the day the IND went into effect for the first FDA-approved indication for the selected drug through the date when the last FDA-required post-marketing trial was completed for the selected drug.

Definitions for 4. R&D: Abandoned and Failed Drug Costs

- Failed or abandoned product costs include a sum of the portion of direct *basic pre-clinical research* costs on drugs with the same active moiety / active ingredient or mechanism of action as the selected drug that did not make it to clinical trials and a portion of direct *post-IND costs* for drugs in the same therapeutic class as the selected drug that did not achieve FDA approval.
- Failed or abandoned product costs include a portion of direct *basic pre-clinical research* costs on drugs with the same active moiety / active ingredient or mechanism of action as the selected drug that did not make it to clinical trials.
    - Direct research expenses are costs that can specifically be attributed to the discovery and pre-clinical development of the drug.
    - Direct research expenses include personnel (compensation for investigators and staff) researching the drug, materials for conducting basic pre-clinical research, and in vivo and in vitro studies on the drug.
- Failed or abandoned product costs include a portion of direct *post-IND costs* for drugs in the same therapeutic class as the selected drug that did not achieve FDA approval.
    - Direct post-IND costs are costs that can specifically be attributed to the dosing and clinical trials for the drug.
    - Direct post-IND costs include IRB review and amendment costs, user fees, patient recruitment, per-patient costs, research and data collection costs, personnel, and facility costs that are directly related to conducting dosing and clinical trials for the drug.

Definitions for 5. R&D: All Other R&D Direct Costs

- All other R&D direct costs are any other allowable costs that do not align with R&D definitions 1-4. For example, other R&D direct costs may include direct costs associated with conducting FDA-required post-marketing trials that were not completed. No additional definitions adopted.

Definitions for 6. Global and U.S. Total Lifetime Net Revenue for the Selected Drug

CMS will use both the Primary Manufacturer's global and U.S. total lifetime net revenue for the selected drug to determine the extent to which the Primary Manufacturer has recouped R&D costs for the selected drug.

Definitions for 6a. Global, including U.S., Total Lifetime Net Revenue for the Selected Drug

- Global, total lifetime net revenue for the selected drug is defined as the direct sales and payments from all other entities, minus the discounts, chargebacks, rebates, cash discounts, free goods contingent on a purchase agreement, up-front payments, coupons, goods in kind, free or reduced-price services, grants, other price concessions or similar benefits offered to any purchasers or any royalty payments or percentage payments in purchase contracts.

- Global, total lifetime net revenue period is defined as the date the drug or biologic was first sold anywhere globally through the date of the publication of the selected drug list that includes the drug as a selected drug for an initial price applicability year.
- If global, total lifetime net revenue for the selected drug is not available through the date of the publication of the selected drug list that includes the drug as a selected drug for an initial price applicability year, calculate net revenue through the most recent quarter for which such data are available.

Definitions for 6b. U.S. Lifetime Net Revenue for the Selected Drug

- U.S. lifetime net revenue for the selected drug is defined as the direct sales and payments from U.S. entities, minus the discounts, chargebacks, rebates, cash discounts, free goods contingent on a purchase agreement, up-front payments, coupons, goods in kind, free or reduced-price services, grants, other price concessions or similar benefits offered to any purchasers or any royalty payments or percentage payments in purchase contracts.
- U.S. lifetime net revenue period is defined as the date the drug or biologic was first sold in the U.S. through the date of the publication of the selected drug list that includes the drug as a selected drug for an initial price applicability year.
- If U.S. lifetime net revenue for the selected drug is not available through the date of the publication of the selected drug list that includes the drug as a selected drug for an initial price applicability year, calculate net revenue through the most recent quarter for which such data are available.

Current Unit Costs of Production and Distribution

- In accordance with section 1191(c)(6) of the Act, the term "unit" means, with respect to a drug or biological product, the lowest identifiable amount (such as a capsule or tablet, milligram of molecules, or grams) of the drug or biological product that is dispensed or furnished.
- Units must be reported in one of the three National Council for Prescription Drug Programs (NCPDP) Billing Unit Standards (BUS)[87]: each (EA), milliliter (ML), or gram (GM). The unit reported must be specified for each of the NDC-11s of the selected drug. Selections of EA, ML or GM must be made as follows:
    - "EA" is used when the product is dispensed in discrete units. These products are not measured by volume or weight. The Billing Unit of "EA" is also used to address exceptions where "GM" and "ML" are not applicable. Examples of products defined as "EA" include, but are not limited to:
        - Tablets;
        - Capsules;
        - Suppositories;
        - Transdermal patches;
        - Non-filled syringes;
        - Tapes;
        - Devices/Digital Therapies;

[87] See: https://standards.ncpdp.org/Billing-Unit-Request.aspx#:~:text=Billing%20Unit%20Requests,grams%22%20or%20%22milliliters.%22.

        - Blister packs;
        - Oral powder packets;
        - Powder filled vials for injection;
        - Kits;[88] and
        - Unit-of-use packages of products other than injectables with a quantity less than one milliliter or gram should be billed as "one each," for example, ointment in packets of less than 1 gram or eye drops in dropperettes that contain less than 1 ML.
    - "ML" is used when a product is measured by its liquid volume. Examples of products defined as "ML" include, but are not limited to:
        - Liquid non-injectable products of 1 ML or greater;
        - Liquid injectable products in vials/ampules/syringes;
        - Reconstitutable non-injectable products at the final volume after reconstitution except when they are in powder packets; and
        - Inhalers (when labeled as milliliters on the product).
    - "GM" is used when a product is measured by its weight. Examples of products defined as "GM" include, but are not limited to:
        - Creams (of 1 GM or greater);
        - Ointments (of 1 GM or greater); and
        - Inhalers (when labeled as GM on the product).[89]
- Costs of <u>production</u> are defined as all (direct and allocation of indirect) costs related to:
    - Purchase of raw ingredients, including intermediates, active pharmaceutical ingredients, excipients, and other bulk chemicals;
    - Formulation and preparation of the finished drug product;
    - Quality control and testing of the drug; and
    - Operating costs for personnel, facilities, transportation, importation (if any), and other expenses related to the preparation of the finished drug product for the selected drug.
- Costs of <u>distribution</u> are defined as all (direct and allocation of indirect) costs related to:
    - Packaging and packaging materials;
    - Labeling (e.g., the mechanical aspects of printing and affixing the approved label);
    - Shipping to any entity (e.g., distributor, wholesaler, retail or specialty pharmacy, physician office or hospital, etc.) that acquires the drug from the Primary Manufacturer or any Secondary Manufacturer; and
    - Operating costs for facilities, transportation, and other expenses related to packaging, labeling, and shipping to any entity that acquires the drug from the Primary Manufacturer or any Secondary Manufacturer.
- Current unit costs of production and distribution of the selected drug are defined to include:

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[88] Kits are defined as products that contain one of the following: (1) at least two distinct items with different billing units; (2) one product packaged with medicated or unmedicated swabs, wipes and/or cotton swabs/balls; or (3) meters packaged with test strips.

[89] See: https://standards.ncpdp.org/Standards/media/pdf/BUS_fact_sheet.pdf. *Permission is hereby granted to any organization to copy and distribute this material as long as this copyright statement is included, the contents are not changed, and the copies are not sold.*

  - Units (and associated costs) marketed by the Primary Manufacturer and any Secondary Manufacturer(s);
  - Average unit costs during the 12-month period ending May 31, 2023 (for selected drugs for initial price applicability year);
  - Only units (and associated costs) produced and distributed for U.S. sales; costs incurred outside of the U.S. are included, provided that they are incurred for the production or distribution of units produced and distributed for use in the U.S.;
  - Only costs incurred by the Primary Manufacturer and any Secondary Manufacturers; such costs may include payments to third parties (e.g., contractors) performing activities that qualify as production or distribution, as specified above; and
  - Allocated shared operating and other indirect costs (such as capitalized production facility costs, benefits, generalized and administrative costs, and overhead expenses) specific to each NDC-11 based on unit volume.
- Current unit costs of production and distribution of the selected drug are defined not to include:
  - R&D costs; and
  - Marketing costs.
- "Marketing costs" are defined as expenditures incurred in the introduction or delivery for introduction into interstate commerce of a drug product, specifically including media advertisements, direct-to-consumer promotional incentives including patient assistance programs, promotion of the drug to health professionals, and other paid promotion.

Prior Federal Financial Support

For the purposes of describing prior federal financial support for novel therapeutic discovery and development to be collected for use in the Negotiation Program with respect to the selected drug, as described in section 1194(e)(1) of the Act and section 50.1 of this revised guidance, CMS adopts the definitions described in this subsection.

- "Federal financial support for novel therapeutic discovery and development" refers to tax credits, direct financial support, grants or contracts, and any other funds provided by the federal government that support discovery, research, and/or development related to the selected drug.
- "*Prior* Federal financial support" refers to Federal financial support for novel therapeutic discovery and development (as defined above) issued during the time period from when initial research began (as defined above in the R&D Costs subsection), or when the drug was acquired by the Primary Manufacturer, whichever is later, to the day through the date the most recent NDA / BLA was approved for the selected drug.

Patents, Exclusivities, and Approvals

- CMS considers relevant patents, both expired and unexpired, and relevant patent applications to include:
  - All patents issued by the United States Patent and Trademark Office (USPTO), as of September 1, 2023, both expired and unexpired, for which a claim of patent infringement could reasonably be, or has been, asserted against a person or manufacturer engaged in the unlicensed manufacture, use, or sale of the selected

drug in any form or any person or manufacturer seeking FDA approval of a product that references the selected drug.
    - All patents related to the selected drug, both expired and unexpired, where the Primary Manufacturer is not listed as the assignee/applicant (for example, for a joint venture product or if any patents related to the selected drug are held by a federal agency).
    - All patent applications related to the selected drug that are pending issuance by the USPTO.
    - Patents and patent applications related to the selected drug include, but are not limited to, any patents that are, have been, or may be listed for the selected drug in the FDA Orange Book or Purple Book[90]; utility patents that claim the drug product (formulation or composition), drug substance (active ingredient), metabolites or intermediaries of a selected drug, method(s) of using the drug, or method(s) of manufacturing the drug; and design patents that, for example, claim a design on the packaging of the selected drug.
- Exclusivity periods under the FD&C Act or the PHS Act refer to certain delays and prohibitions on the approval of competitor drug products. An NDA or BLA holder is eligible for exclusivity if statutory requirements are met. Exclusivities include:
    - Orphan Drug Exclusivity (ODE);[91]
    - New Chemical Entity Exclusivity (NCE);[92]
    - Generating Antibiotic Incentives Now (GAIN) Exclusivity for Qualified Infectious Disease Products (QIDP);[93]
    - New Clinical Investigation Exclusivity (NCI);[94]
    - Pediatric Exclusivity (PED);[95] and
    - Reference Product Exclusivity for Biological Products.[96]
- Active and pending FDA applications and approvals includes all applications for approval under section 505(c) of the FD&C Act or sections 351(a) of the PHS Act, including those not yet decided.

Market Data and Revenue and Sales Volume Data

- Wholesale Acquisition Cost (WAC) unit price: The manufacturer's list price for the drug or biological product to wholesalers or direct purchasers in the United States, not including prompt pay or other discounts, rebates or reductions in price, for the most recent month for which the information is available, as reported in wholesale price guides or other publications of drug or biological product pricing data (as defined in section 1847A(c)(6)(B) of the Act). The WAC unit price is reported at the NDC-11 level.

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[90] FDA serves a ministerial role with regard to the listing of patent information in the Orange Book and Purple Book.
[91] Section 527 of the Federal Food, Drug and Cosmetic (FD&C) Act.
[92] Section 505(c)(3)(E)(ii) and Section 505(j)(5)(F)(ii) of the FD&C Act.
[93] Section 505E(a) of the FD&C Act.
[94] Section 505(c)(3)(E)(iii) & (iv) and Section 505(j)(5)(F)(iii) & (iv) of the FD&C Act.
[95] Section 505A(b) & (c) of the FD&C Act.
[96] Section 351(k)(7) of the PHS Act.

- National Council of Prescription Drug Programs (NCPDP) Billing Unit Standards: The three NCPDP Billing Unit Standards (BUS)[97] are: each (EA), milliliter (ML), and gram (GM). For certain volume data of the selected drug, CMS is requesting units be reported using the NCPDP BUS to facilitate comparison with the amounts in the quantity dispensed field found in PDE data, which also uses the NCPDP BUS.
- Medicaid best price: The Medicaid best price is defined in 42 C.F.R. § 447.505(a). The Medicaid best price is reported at the NDC-9 level.
- Average manufacturer price (AMP) unit: The unit type used by the manufacturer to calculate AMP (42 C.F.R. § 447.504) and best price (42 C.F.R. § 447.505) for purposes of the Medicaid Drug Rebate Program (MDRP): injectable anti-hemophilic factor, capsule, suppository, gram, milliliter, tablet, transdermal patch, each, millicurie, microcurie. Such units are reported by the manufacturer on a monthly basis at the NDC-9 level.
- Federal supply schedule (FSS) price: The price offered by the VA in its FSS program, by delegated authority of the General Services Administration.[98] The FSS price is reported at the NDC-11 level.
- Big Four price: The Big Four price is described in 38 U.S.C. § 8126. The Big Four price is reported at the NDC-11 level.
- U.S. commercial average net unit price: For the sole purpose of data collection under section 1194(e)(1)(E) of the Act, the average net unit price of the selected drug for group or individual commercial plans on- and off-Exchange, excluding Medicare fee-for-service (Parts A and B), Medicare Advantage, Medicare Part D, Medicaid fee-for-service, and Medicaid managed care. The average net unit price must be net of discounts, chargebacks or rebates, cash discounts, free goods contingent on a purchase agreement, up-front payments, coupons, goods in kind, free or reduced-price services, grants, or other price concessions or similar benefits offered by the Primary Manufacturer and any Secondary Manufacturer(s) to any purchasers. The U.S. commercial average net unit price is reported at the NDC-11 level.
- U.S. commercial average net unit price─ without patient assistance program: For the sole purpose of data collection under section 1194(e)(1)(E) of the Act, the U.S. commercial average net unit price net of manufacturer-run patient assistance programs that provide financial assistance such as coupons and co-payment assistance or free drug products to patients offered by the Primary Manufacturer and any Secondary Manufacturer(s). The U.S. commercial average net unit price─ without patient assistance program is reported at the NDC-11 level.
- U.S. commercial average net unit price─ best: For the sole purpose of data collection under section 1194(e)(1)(E) of the Act, the lowest U.S. commercial average net unit price offered by the Primary Manufacturer and any Secondary Manufacturer(s) to any commercial payer in the U.S. The average net unit price must be net of discounts, chargebacks or rebates, cash discounts, free goods contingent on a purchase agreement, up-front payments, coupons, goods in kind, free or reduced-price services, grants, or other price concessions or similar benefits offered by the Primary Manufacturer or any

[97] See: https://standards.ncpdp.org/Billing-Unit-Request.aspx#:~:text=Billing%20Unit%20Requests,grams%22%20or%20%22milliliters.%22.
[98] See: https://www.fss.va.gov/index.asp.

Secondary Manufacturer(s) to any purchasers. The U.S. commercial average net unit price─ best is reported at the NDC-11 level.

Evidence About Alternative Treatments

- Therapeutic Alternative: A therapeutic alternative must be a pharmaceutical product that is clinically comparable to the selected drug. CMS will consider different therapeutic alternatives for each indication, as applicable. Therapeutic alternatives may be a brand name drug or biological product, generic drug, or biosimilar and may be on-label or off-label to treat a given indication. CMS will begin by identifying therapeutic alternatives within the same drug class as the selected drug based on properties such as chemical class, therapeutic class, or mechanism of action before considering therapeutic alternatives in other drug classes. In cases where there are many potential therapeutic alternatives for a given indication of the selected drug, CMS may focus on the subset of therapeutic alternatives that are most clinically comparable to the selected drug.
- Outcomes: Outcomes may be clinical or related to the functioning, symptoms, quality of life, or other aspects of a patient's life. Outcomes such as cure, survival, progression-free survival, or improved morbidity could be considered when comparing the selected drug to its therapeutic alternative(s). Outcomes such as changes in symptoms or other factors that are of importance to patients, and patient-reported outcomes will also be identified and considered in determining clinical benefit, if available. Additional outcomes such as changes to productivity, independence, and quality of life will also be considered, including patient-centered outcomes when available, to the extent that these outcomes correspond with a direct impact on individuals taking the drug. The caregiver perspective will be considered when there is a direct impact on the individuals taking the selected drug or therapeutic alternative.
- Patient-centered outcome: An outcome that is important to patients' survival, functioning, or feelings as identified or affirmed by patients themselves, or judged to be in patients' best interest by providers and/or caregivers when patients cannot report for themselves.[99]
- Specific populations: Specific populations include individuals with disabilities, the elderly, individuals who are terminally ill, children, and other patient populations among Medicare beneficiaries including those that may experience disparities in access to care, health outcomes, or other factors when taking the selected drug that impact health equity.
- Health equity: The attainment of the highest level of health for all people, where everyone has a fair and just opportunity to attain their optimal health regardless of race, ethnicity, disability, sexual orientation, gender identity, socioeconomic status, geography, preferred language, or other factors that affect access to care and health outcomes.[100]
- Unmet medical need: A drug or biological product may be considered to meet an unmet medical need if the drug or biological product treats a disease or condition in cases where no other treatment options exist or existing treatments do not adequately address the

[99] Source: ISPOR Plenary, Patrick (2013) via FDA's "Patient-Focused Drug Development: Collecting Comprehensive and Representative Input – Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders" (June 2020). See: https://www.fda.gov/media/139088/download.

[100] See: https://www.cms.gov/pillar/health-equity.

disease or condition.[101] Unmet medical need is determined at the time of submission of this information.

[101] CMS will consider the nonbinding recommendations in the FDA "Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics" (May 2014) when considering if a drug addresses an unmet medical need for the purpose of the Negotiation Program.

EXHIBIT G

Congressional Research Service
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Tax Provisions in the Inflation Reduction Act of 2022 (H.R. 5376)

Updated August 10, 2022

Congressional Research Service
https://crsreports.congress.gov
R47202

CRS REPORT
Prepared for Members and
Committees of Congress

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On July 27, 2022, Senate Majority Leader Chuck Schumer and Senator Joe Manchin released legislative text for budget reconciliation legislation, also known as the "Inflation Reduction Act of 2022."[1] On August 7, 2022, the Senate passed a modified version of the Inflation Reduction Act of 2022.[2] This text will replace the legislative text of the House-passed Build Back Better Act (BBBA; H.R. 5376) as a substitute amendment.[3]

This report summarizes the tax provisions in the Inflation Reduction Act of 2022, which include

- establishing a corporate minimum tax;
- imposing an excise tax on corporate stock repurchases;
- establishing an excise tax on drug manufacturers, producers, and importers who fail to enter into drug pricing agreements;
- extending the health insurance premium tax credit modifications made in the American Rescue Plan Act of 2021 (ARPA; P.L. 117-2) through 2025; and
- modifications to the tax treatment of the energy sector that would generally reduce revenues; including
  - extension and modification of the credit for electricity produced from certain renewable resources;
  - extension and modification of the energy credit; and
  - extension of excise tax credits for alternative fuels, biodiesel, and renewable diesel.

All tax provisions in the Inflation Reduction Act of 2022 text are summarized in a series of tables below. References to relevant CRS reports are included where applicable.

- **Table 1** includes the provisions in Subtitle A, Deficit Reduction;
- **Table 2** includes the provisions in Subtitle B, Prescription Drug Pricing Reform;
- **Table 3** includes the provisions in Subtitle C, Affordable Care Act Subsidies; and
- **Table 4** includes the provisions in Subtitle D, Energy Security.

Provisions in Subtitle A, as passed on August 7, 2022, were modified from what was introduced on July 27. Specifically, the July 27 version included changes to the tax treatment of carried interest. This provision was not included in the Senate-passed version. The Senate-passed version instead included an excise tax on corporate stock repurchases and an extension of loss limits for pass-through businesses. Additionally, the Senate-passed version made some modifications to the corporate minimum tax. **Table 1** includes information on the provisions in the Senate-passed version of the IRA, while **Table A-1** includes the provisions that were in Subtitle A in the July 27

[1] Legislative text for the Inflation Reduction Act of 2022 is available at https://www.democrats.senate.gov/inflation-reduction-act-of-2022.

[2] The text as passed by the Senate on August 7, 2022, can be found on the House Rules Committee website at https://rules.house.gov/bill/117/hr-5376-sa. The updated text for the Inflation Reduction Act of 2022 was originally introduced in the Senate as an amendment in the nature of a substitute (S.Amdt. 5194). Two other amendments were agreed to during Senate consideration (S.Amdt. 5472 and S.Amdt. 5488). The text of these amendments can be found at https://ats.senate.gov/Index.aspx?view=11010001&type=2&bill=H.R.5376.

[3] For information on the provisions in the Build Back Better Act, see CRS Report R46998, *Senate Finance Committee Tax Provisions in the Build Back Better Act*, coordinated by Molly F. Sherlock; CRS Report R46960, *Tax Provisions in the Build Back Better Act: Rules Committee Print 117-18*, coordinated by Molly F. Sherlock; and CRS Report R46923, *Tax Provisions in the "Build Back Better Act:" The House Ways and Means Committee's Legislative Recommendations*, coordinated by Molly F. Sherlock.

version of the IRA. **Table A-2** also includes the provisions that were in subtitle B in the July 27 version of the IRA that were modified in the Senate-passed version. **Table 4** also includes the provisions that were newly added as the IRA was being considered in the Senate.

The Joint Committee on Taxation (JCT) has estimated that the Senate-passed version of the IRA would increase federal tax revenue by $90.7 billion over the 10-year FY2022 through FY2031 budget window.[4] The revenue provisions in Subtitle A would generate additional federal tax revenue of an estimated $295.9 billion over this period. The mostly energy-related provisions in Subtitle D would reduce federal tax revenue by an estimated $205.2 billion over the 10-year period (additional non-energy-related revenues of $53.8 billion would come from extending the limits on excess business losses for noncorporate taxpayers by two years, after 2026). The JCT revenue estimate is presented in **Table 5**. JCT's preliminary revenue estimate of the IRA before Senate consideration can be found in **Table A-3**.

Table 1. Subtitle A—Deficit Reduction

Section Title	Description	CRS Resources
Part 1—Corporate Tax Reform		
Corporate Alternative Minimum Tax Section 10101	This provision would impose a new alternative minimum tax of 15% on corporations based on financial income. It would apply to corporations with $1 billion or more in average annual earnings in the previous three years. In the case of U.S. corporations that have foreign parents, it would apply only to income earned in the United States of $100 million or more of average annual earnings in the previous three years (and apply when the international financial reporting group has income of $1 billion or more). It would apply to a new corporation in existence for less than three years based on the earnings in the years of existence. The provision would exclude Subchapter S corporations, regulated investment companies (RICs), and real estate investment trusts (REITs). The tax would apply would to large private equity firms organized as partnerships, but excludes portfolio companies owned by these firms (due to a modification made by Section 13904 of the bill). Firms that file consolidated returns would include income allocable to the firm from related firms including controlled foreign corporations (and any disregarded entities); for other related firms, dividends would be included. The provision would allow special deductions for cooperatives and Alaska Native Corporations. It would make adjustments to conform financial accounting to tax accounting for certain defined benefit pension plans. It would apply with respect to items under the unrelated business income tax for tax-exempt entities. Financial income would be adjusted to allow depreciation deductions based on tax rules. It would also be adjusted to	For background, see • CRS In Focus IF12179, *The Corporate Minimum Tax Proposal*, by Jane G. Gravelle. • CRS Report R46887, *Minimum Taxes on Business Income: Background and Policy Options*, by Molly F. Sherlock and Jane G. Gravelle. • CRS Insight IN11646, *A Look at Book-Tax Differences for Large Corporations Using Aggregate Internal Revenue Service (IRS) Data*, by Molly F. Sherlock and Jane G. Gravelle.

[4] Joint Committee on Taxation, *Estimated Budgetary Effect of the Revenue Provisions of Title I -Committee on Finance, of an Amendment in the Nature of a Substitute to H.R. 5376, "An Act to Provide for Reconciliation Pursuant to Title II of S. Con. Res. 14," as Passed by the Senate on August 7, 2022, and Scheduled for Consideration by the House of Representatives on August 12, 2022,"* JCX-18-22, August 9, 2022, https://www.jct.gov/publications/2022/jcx-18-22/.

Section Title	Description	CRS Resources
	allow recovery of wireless spectrum rights as allowed under tax rules (recovered over 15 years). The additional tax would equal the amount of the minimum tax in excess of the regular income tax plus the additional tax from the Base Erosion and Anti-Abuse tax. Income would be increased by federal and foreign income taxes to place income on a pretax basis. Losses would be allowed in the same manner as with the regular tax, with loss carryovers limited to 80% of taxable income. Domestic credits under the general business tax (such as the R&D credit) would be allowed to offset up to 75% of the combined regular and minimum tax. Foreign tax credits would be allowed based on the allowance for foreign taxes paid in a corporation's financial statement. A credit for additional minimum tax could be carried over to future years to offset regular tax when that tax is higher. This tax would apply to taxable years beginning after December 31, 2022.	
Part 2—Excise Tax on Repurchase of Corporate Stock		
Excise Tax on Repurchase of Corporate Stock Section 10201	This provision would impose a 1% excise tax on the repurchase of stock by a publicly traded corporation. The amount subject to tax would be reduced by any new issues to the public or stock issued to employees. The tax would not apply if repurchases are less than $1 million or are contributed to an employee pension or similar plan. The tax would not apply if the repurchases are treated as a dividend. It also would not apply to repurchases by regulated investment companies (RICs) or real estate investment trusts (REITs). Further, it would not apply to repurchases that are treated as dividends or to purchases by a dealer in securities in the ordinary course of business. The excise tax would apply to purchases of corporation stock by a subsidiary of the corporation (a corporation or partnership that is more than 50% owned). The tax would also apply to purchases by a U.S. subsidiary of a foreign-parented firm. It would apply to newly inverted (after September 20, 2021) or surrogate firms (firms that merged to create a foreign parent with the former U.S. shareholders owning more than 60% of shares). The tax would not be deductible. The tax would apply to repurchases after December 31, 2022.	For background, see • CRS In Focus IF11960, *An Excise Tax on Stock Repurchases and Tax Advantages of Buybacks over Dividends*, by Jane G. Gravelle. • CRS Legal Sidebar LSB10266, *Stock Buybacks: Background and Reform Proposals*, by Jay B. Sykes. • CRS In Focus IF11393, *Stock Buybacks: Concerns over Debt-Financing and Long-Term Investing*, by Gary Shorter. • CRS In Focus IF11506, *Stock Buybacks and Company Executives' Profits*, by Gary Shorter.

Source: CRS analysis of the legislative text of the Senate amendment to H.R. 5376, "Inflation Reduction Act of 2022," as posted on the House Rule Committee Website at https://rules.house.gov/bill/117/hr-5376-sa.

Notes: The changes that would be made by these provisions are permanent. Part 3 of Subtitle A would provide additional appropriations of $79.6 billion over the next 10 years to enhance IRS service and enforcement activities. For background on IRS appropriations, see CRS Insight IN11977, *IRS-Related Funding in the Inflation Reduction Act*, by Brendan McDermott; and CRS In Focus IF12098, *Internal Revenue Service Appropriations, FY2023*, by Gary Guenther.

Table 2. Subtitle B—Prescription Drug Reform

Section Title	Description	CRS Resources
Part 1—Lowering Prices Through Drug Price Negotiations		
Selected Drug Manufacturer Excise Tax Imposed During Noncompliance Period Section 11003	This provision would impose a new excise tax on drug manufacturers, producers, and importers who fail to enter into drug pricing agreements under Section 1193 of the Social Security Act, as added by the bill on selected drugs (i.e., are noncompliant with Section 1193). This excise tax would be found under the new Internal Revenue Code (IRC) Section 5000D. The excise tax rate would range from 185.71% to 1,900% of the selected drug's price depending on the duration of noncompliance. The provision does not specify these rates explicitly, but instead defines an applicable percentage which equals the share of the post-tax sale price attributable to the excise tax. Specifically, the applicable percentage as defined in the statute equals tax/(tax+price) which simplifies to tax rate/(tax rate+1) with the applicable percentages being 65% for the sales of selected drugs during the first 90 days of noncompliance, 75% for sales during the 91st to 180th days of noncompliance, 85% for sales during the 181st to 270th days of noncompliance, and 95% for sales after the 270th day of noncompliance. Hence, the corresponding tax rates would be calculated as (applicable percentage)/(1-applicable percentage) and equal 185.71%, 300%, 566.67% and 1,900% respectively, depending on the duration of noncompliance. For example, if a selected drug was subject to the top tax rate of 1,900% and cost $10 pre-tax, it would cost $200 post-tax with $190 of the $200 cost (or 95%, the applicable percentage) being attributable to the excise tax. Selected drugs would be those defined in Section 1192(a) of the Social Security Act, as enacted under this bill, which are manufactured or produced in the United States or enter into the United States for consumption, use, or warehousing. The excise tax would not apply to drugs sold for export, and the provision addresses the refund or credit process if tax is paid. Noncompliance periods as defined in the bill would generally begin after the deadline to enter into an agreement to negotiate or renegotiate, or to agree upon a maximum price, had passed. Such periods would end when such agreement has been reached. The noncompliance period would also end if a generic version of the selected drug becomes available. The earliest potential noncompliance period would begin on October 2, 2023. The excise tax would be suspended during any period in which none of the drugs made by a selected drug's manufacturer are covered by a Medicaid Drug Rebate Program agreement, a Medicare Part D Coverage Gap Discount agreement, or a Medicare Part D Manufacturer Discount Program agreement.	For background, see • CRS Report R47056, *Build Back Better Act (BBBA) Health Coverage Provisions: House-Passed and Senate-Released Language*, coordinated by Vanessa C. Forsberg and Ryan J. Rosso.

Section Title	Description	CRS Resources
	For sales that were timed to avoid the excise tax, the Secretary of the Treasury could treat the sale as occurring during a day in a noncompliance period. Manufacturers would be prohibited from deducting excise tax payments from their federal income taxes.	

Source: CRS analysis of the legislative text of the Senate amendment to H.R. 5376, "Inflation Reduction Act of 2022," as posted on the House Rule Committee Website at https://rules.house.gov/bill/117/hr-5376-sa.

Notes: This provision would apply after the date of enactment to the sale of drugs during a noncompliance period. The first noncompliance period could begin on October 2, 2023. Within the description, "Section" citations refer to the section within the Internal Revenue Code (IRC), 26 U.S.C., unless otherwise noted.

Table 3. Subtitle C—Affordable Care Act Subsidies

Section Title	Description	CRS Resources
Improve Affordability and Reduce Costs of Health Insurance for Consumers Section 12001	Under current law, income eligibility for and calculation of the premium tax credit (PTC) incorporates temporary changes enacted under the American Rescue Plan Act of 2021 (ARPA; P.L. 117-2). For 2021 and 2022, ARPA expanded income eligibility by eliminating the phaseout for households with annual incomes above 400% of the federal poverty level (FPL). For those same years, ARPA also increased credit amounts by adjusting the percentage of annual income that eligible households may be required to contribute toward the premium. The percentages currently range from 0.0% to 8.5% of household income, with higher-income groups subject to larger percentages, as specified. This provision would extend these ARPA changes to 2023, 2024, and 2025.	For background, see • CRS Report R44425, *Health Insurance Premium Tax Credit and Cost-Sharing Reductions*, by Bernadette Fernandez.

Source: CRS analysis of the legislative text of the Senate amendment to H.R. 5376, "Inflation Reduction Act of 2022," as posted on the House Rule Committee Website at https://rules.house.gov/bill/117/hr-5376-sa.

Notes: The provision in this table is effective for taxable years beginning after December 31, 2022.

Table 4. Subtitle D—Energy Security

Section Title	Description	CRS Resources
Part 1—Clean Electricity and Reducing Carbon Emissions		
Extension and Modification of Credit for Electricity Produced from Certain Renewable Resources Section 13101	Current law provides a production tax credit (PTC), at a rate of 2.5 cents or 1.3 cents per kilowatt hour (kWh) depending on the technology used, for the first 10 years of production at qualifying renewable electricity production facilities that began construction before 2022. The credit amount is adjusted annually for inflation from a statutory rate of 1.5 cents per kWh, with some technologies qualifying for a half-credit amount. This provision would extend the PTC for wind, biomass, geothermal, solar (which previously expired at the end of 2005), landfill gas, trash, qualified hydropower, and marine and hydrokinetic resources through 2024. The base credit amount for the PTC would be set in statute at 0.3 cents per kWh (0.5 cents per kWh in 2021, or 0.3 cents for half-credit technologies, after being adjusted for inflation). Facilities that pay prevailing wages during the construction phase and first 10 years of	For background, see • CRS Report R43453, *The Renewable Electricity Production Tax Credit: In Brief*, by Molly F. Sherlock. • CRS Report R46865, *Energy Tax Provisions: Overview and Budgetary Cost*, by Molly F. Sherlock. • CRS Report R46451, *Energy Tax Provisions Expiring in 2020, 2021, 2022, and 2023 ("Tax Extenders")*, by Molly F.

Section Title	Description	CRS Resources
	operation and meet registered apprenticeship requirements are eligible for a PTC that is five times the base amount, or 2.5 cents or 1.3 cents per kWh in 2021 after being adjusted for inflation. Facilities with a maximum net output of less than one megawatt are also eligible for the five times base credit amount (e.g., 2021 rates of 2.5 cents or 1.3 cents per kWh), as are facilities that begin construction before 60 days after the Secretary of the Treasury publishes guidance on the wage and registered apprenticeship requirements. Qualifying hydropower and marine and hydrokinetic renewable energy projects, which are half-credit technologies under current law, would be allowed the full PTC. A "bonus credit" amount would be provided for projects that meet domestic content requirements to certify that certain steel, iron, and manufactured products used in the facility were domestically produced. The bonus credit amount would be 10% of the credit amount. In 2024, the amount of the credit that could be received as direct pay would be limited to 90% for large facilities not meeting domestic content requirements (see "Elective Payment for Energy Property and Electricity Produced from Certain Renewable Resources, Etc." below). This limit would be waived if materials are not available domestically or if including domestic materials would increase the facility's construction cost by more than 25%. The credit amount could be increased by 10% for facilities located in an energy community. An energy community is defined as being a brownfield site; an area which has or had certain amounts of direct employment or local tax revenue related to oil, gas, or coal activities and has an unemployment rate at or above the national average; or a census tract or any adjoining tract in which a coal mine closed after December 31, 1999, or in which a coal-fired electric power plant was retired after December 31, 2009. The provision provides that for facilities financed with tax-exempt bonds, the credit amount would be reduced by the lesser of (1) 15%; or (2) the fraction of the proceeds of a tax-exempt obligation used to finance the project over the aggregate amount of the project's financing costs. The proposal also extends the option to claim the energy investment tax credit (ITC) in lieu of the PTC.	Sherlock, Margot L. Crandall-Hollick, and Donald J. Marples. • CRS Report R45171, *Registered Apprenticeship: Federal Role and Recent Federal Efforts*, by Benjamin Collins. • CRS In Focus IF11927, *Federally Funded Construction and the Payment of Locally Prevailing Wages*, by David H. Bradley and Jon O. Shimabukuro. • CRS Insight IN11983, *Proposed Tax Preference for Domestic Content in Energy Infrastructure*, by Christopher D. Watson and Molly F. Sherlock.
Extension and Modification of Energy Credit Section 13102	Current law provides a temporary investment tax credit (ITC) for investments in certain energy property. This provision would extend and modify the ITC, with the credit generally extended through the end of 2024. The ITC would be extended through 2024 at a base rate of 6% for solar, fuel cells, waste energy recovery, combined heat and power, and small wind property, and 2% for microturbine property. These amounts would be increased to 30% and 10%, respectively, if projects pay prevailing wages during the construction phase and during the first five years of operation and meet registered apprenticeship requirements. The higher credit rates	For background, see • CRS In Focus IF10479, *The Energy Credit or Energy Investment Tax Credit (ITC)*, by Molly F. Sherlock. • CRS Report R46865, *Energy Tax Provisions: Overview and Budgetary Cost*, by Molly F. Sherlock.

Section Title	Description	CRS Resources
	would also be available to any project with a maximum net output of less than one megawatt of electrical or thermal energy and for facilities that begin construction before 60 days after the Secretary of the Treasury publishes guidance on the wage and registered apprenticeship requirements. The ITC for geothermal heat pumps would be extended through 2034 with a 6% base credit rate with the 30% credit rate allowed for projects meeting wage and workforce requirements or for projects below the maximum net output threshold. The credit would phase down after 2032, with the rates being 5.2% and 26% in 2033 and 4.4% and 22% in 2034, with no credit allowed for property beginning construction after 2035. This list of qualifying property would be expanded to include energy storage technology (including thermal energy storage property), qualified biogas property, electrochromic glass, and microgrid controllers at the 6% or 30% rate. Linear generator assemblies would be added to the definition of qualifying fuel cells. The credit would also be available for interconnection property. Public utilities, under certain circumstances, would be able to elect out of normalization requirements for investments in energy storage technologies. A "bonus credit" amount would be provided for projects that meet domestic content requirements to certify that certain steel, iron, and manufactured products used in the facility were domestically produced. The bonus credit amount would be 2 percentage points, or 10 percentage points for projects that meet wage and workforce requirements. In 2024, the amount of the credit that could be received as direct pay would be limited to 90% for large facilities not meeting domestic content requirements (discussed below). This limit would be waived if materials are not available domestically or if including domestic materials would increase the facility's construction cost by more than 25%. The provision provides that for facilities financed with tax-exempt bonds, the credit amount would be reduced by the lesser of (1) 15%; or (2) the fraction of the proceeds of a tax-exempt obligation used to finance the project over the aggregate amount of the project's financing costs. An increased credit amount would be available to projects in an energy community, with the credit increase being 10 percentage points for projects meeting wage and workforce requirements or 2 percentage points otherwise. An energy community is defined as being a brownfield site; an area which has or had certain amounts of direct employment or local tax revenue related to oil, gas, or coal activities and has an unemployment rate at or above the national average; or a census tract or any adjoining tract in which a coal mine closed after December 31, 1999, or in which a coal-fired electric power plant was retired after December 31, 2009.	• CRS Report R46451, *Energy Tax Provisions Expiring in 2020, 2021, 2022, and 2023 ("Tax Extenders")*, by Molly F. Sherlock, Margot L. Crandall-Hollick, and Donald J. Marples. • CRS Report R45171, *Registered Apprenticeship: Federal Role and Recent Federal Efforts*, by Benjamin Collins. • CRS In Focus IF11927, *Federally Funded Construction and the Payment of Locally Prevailing Wages*, by David H. Bradley and Jon O. Shimabukuro. • CRS Insight IN11983, *Proposed Tax Preference for Domestic Content in Energy Infrastructure*, by Christopher D. Watson and Molly F. Sherlock.

Section Title	Description	CRS Resources
Increase in Energy Credit for Solar and Wind Facilities Placed in Service in Connection with Low-Income Communities Section 13103	This provision would allow for the allocation of 1.8 gigawatts for "environmental justice solar and wind capacity" credits in each of calendar year 2023 and 2024. Taxpayers receiving a capacity allocation may be entitled to tax credits in addition to otherwise allowed ITCs. Specifically, projects receiving an allocation that are located in a low-income community or on Indian land would be eligible for a bonus investment tax credit of 10 percentage points, while projects that are part of a low-income residential building project or qualified low-income economic benefit project would be eligible for a 20 percentage point bonus investment credit. Qualifying solar and wind facilities would include those with a nameplate capacity of 5 megawatts or less, and qualifying property would include energy storage property installed in connection with the solar property and interconnection property. Facilities receiving an allocation would be required to have the facility placed in service within four years.	For background on the ITC, see • CRS In Focus IF10479, *The Energy Credit or Energy Investment Tax Credit (ITC)*, by Molly F. Sherlock. For background on housing assistance programs, see • CRS Report RL34591, *Overview of Federal Housing Assistance Programs and Policy*, by Maggie McCarty, Libby Perl, and Katie Jones.
Extension and Modification of Credit for Carbon Oxide Sequestration Section 13104	Under current law, industrial carbon capture or direct air capture (DAC) facilities that begin construction by December 31, 2025, can qualify for the Section 45Q tax credit for carbon oxide sequestration. This tax credit can be claimed for carbon oxide captured during the 12-year period following a qualifying facility's being placed in service. Currently, the per metric ton tax credit for geologically sequestered carbon oxide is set to increase to $50 per ton by 2026 ($35 per ton for carbon oxide that is reused, such as for enhanced oil recovery) and adjusted for inflation thereafter. This provision would extend the start of construction deadline to December 31, 2032. The amount of carbon oxide that must be captured at a qualifying facility would be reduced to 1,000 metric tons annually for a DAC facility, 18,750 metric tons annually for an electricity generating facility (and be designed to capture not less than 75% of the baseline carbon oxide production), and 12,500 metric tons for any other facility. Base credit amounts would be $17 per metric ton for carbon oxide that is captured and geologically sequestered and $12 per metric ton for carbon oxide that is reused. Increased credit amounts of $85 per ton and $60 per ton, respectively, would be available for facilities that pay prevailing wages during the construction phase and during the first 12 years of operation and meet registered apprenticeship requirements. The credit amount for carbon oxide captured using DAC and geologically sequestered would be increased to a base rate of $36 per metric ton, with a credit of $180 per metric ton for projects that meet wage and workforce requirements. These amounts would be $26 and $130 per metric ton for carbon oxide captured using DAC that is utilized in a qualified manner. Projects financed with tax-exempt bonds would have the credit amount reduced by the lesser of (1) 15%; or (2) the fraction of the proceeds of a tax-exempt obligation used	For background, see • CRS In Focus IF11455, *The Tax Credit for Carbon Sequestration (Section 45Q)*, by Angela C. Jones and Molly F. Sherlock. • CRS Insight IN11710, *Carbon Capture and Sequestration Tax Credit ("Section 45Q") Legislation in the 117th Congress*, by Molly F. Sherlock and Angela C. Jones. • CRS Report R46451, *Energy Tax Provisions Expiring in 2020, 2021, 2022, and 2023 ("Tax Extenders")*, by Molly F. Sherlock, Margot L. Crandall-Hollick, and Donald J. Marples. • CRS Report R45171, *Registered Apprenticeship: Federal Role and Recent Federal Efforts*, by Benjamin Collins. • CRS In Focus IF11927, *Federally Funded Construction and the Payment of Locally Prevailing Wages*, by David H. Bradley and Jon O. Shimabukuro.

Section Title	Description	CRS Resources
	to finance the project over the aggregate amount of the project's financing costs. The provision would also provide flexibility with respect to the period in which credits can be claimed for projects affected by federally declared disasters.	
Zero-Emission Nuclear Power Production Credit Section 13105	This provision would create a new tax credit for qualifying zero-emission nuclear power produced and sold after December 31, 2023. Qualified nuclear power facilities are taxpayer-owned facilities that use nuclear power to generate electricity that did not receive an advanced nuclear production tax credit allocation under Section 45J, and are placed in service before the date of enactment (i.e., are existing nuclear power plants). The PTC amount would be 0.3 cents per kWh. The credit would be reduced when the price of electricity increases. Credits would be reduced by a "reduction amount," which is 16% of the excess of gross receipts from electricity produced by the facility and sold over the product of 2.5 cents times the amount of electricity sold during the taxable year. Thus, the credit would phase down as annual average prices exceed 2.5 cents per kWh. Taxpayers that satisfy prevailing wage and registered apprenticeship requirements would be eligible for a tax credit of five times the base amount per kWh (i.e., up to 1.5 cents per kWh). Credit amounts and amounts in the reduction amount formula would be adjusted for inflation. The credit would terminate on December 31, 2032.	For background, see • CRS Report R42853, *Nuclear Energy: Overview of Congressional Issues*, by Mark Holt. • CRS Insight IN10725, *The Advanced Nuclear Production Tax Credit*, by Molly F. Sherlock and Mark Holt. • CRS Report R45171, *Registered Apprenticeship: Federal Role and Recent Federal Efforts*, by Benjamin Collins. • CRS In Focus IF11927, *Federally Funded Construction and the Payment of Locally Prevailing Wages*, by David H. Bradley and Jon O. Shimabukuro.
Part 2—Clean Fuels		
Extension of Incentives for Biodiesel, Renewable Diesel, and Alternative Fuels Section 13201	Current law provides a 50-cents-per-gallon tax credit for alternative fuels and alternative fuel mixtures through 2021 and a $1.00-per-gallon tax credit for biodiesel and renewable diesel (with an additional $0.10-per-gallon tax credit for agri-biodiesel) through 2022. The biodiesel and renewable diesel mixtures tax credit may be claimed as an immediate excise tax credit against the blender's motor and aviation fuels excise taxes. Credits in excess of excise tax liability may be refunded. The biodiesel and small agri-biodiesel credits may be claimed as income tax credits. The alternative fuels credit can be claimed as an excise tax credit or received as an outlay. The alternative fuels mixture credit is an excise tax credit. This provision would extend the existing tax credits for alternative fuels and alternative fuel mixtures and biodiesel and renewable diesel through December 31, 2024. This provision would establish a special rule for paying claims for tax credits during the period of retroactive eligibility. The biodiesel and renewable diesel credit, alternative fuel credit, alternative fuel mixture credit, and payments for alternative fuels expired at the end of 2021. This provision would allow those credits for all of 2022. The IRS would need to create a process within 30 days of enactment for one-time claims for these tax credits. Taxpayers would have 180 days to submit a claim, which	For background, see • CRS Report R46865, *Energy Tax Provisions: Overview and Budgetary Cost*, by Molly F. Sherlock. • CRS Report R46451, *Energy Tax Provisions Expiring in 2020, 2021, 2022, and 2023 ("Tax Extenders")*, by Molly F. Sherlock, Margot L. Crandall-Hollick, and Donald J. Marples.

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	would need to be paid within 60 days of receipt (interest would be paid on any payment made after that date).	
Extension of Second Generation Biofuel Incentives Section 13202	Current law provides a $1.01-per-gallon income tax credit for second-generation biofuel production through 2021. This provision would extend the second-generation biofuel producer tax credit through December 31, 2024.	For background, see • CRS Report R46865, *Energy Tax Provisions: Overview and Budgetary Cost*, by Molly F. Sherlock. • CRS Report R46451, *Energy Tax Provisions Expiring in 2020, 2021, 2022, and 2023 ("Tax Extenders")*, by Molly F. Sherlock, Margot L. Crandall-Hollick, and Donald J. Marples.
Sustainable Aviation Fuel Credit Section 13203	This provision would create a new tax credit for the sale or mixture of sustainable aviation fuel starting in 2023. The tax credit would have a base amount of $1.25 per gallon, with a supplemental credit amount of $0.01 per gallon for each percentage point by which the lifecycle greenhouse gas emissions reduction percentage for the fuel exceeds 50% (with a maximum supplemental credit of $0.50 per gallon, making the maximum potential per gallon credit $1.75). Sustainable aviation fuel is defined as liquid fuel that (1) meets the requirements of either ASTM International Standard D7566 or the Fischer Tropsch provisions of ASTM International Standard D1655, Annex AI; (2) is not derived from coprocessing an applicable material with a feedstock which is not biomass; (3) is not derived from palm fatty acid distillates or petroleum; and (4) has been certified to achieve at least a 50% lifecycle greenhouse gas reduction percentage as defined according to the most recent Carbon Offsetting and Reduction Scheme for International Aviation adopted by the International Civil Aviation Organization and agreed to by the United States (or a similar methodology which satisfies criteria in the Clean Air Act Section 211(o)(1)(H)), as compared with petroleum-based jet fuel. The sustainable aviation fuel credit would require claimants to be registered with the Secretary of the Treasury, and could be used to offset fuel excise tax liability or, in the case of insufficient fuel excise tax liability, be received as a payment. Like the tax credit for biodiesel and renewable diesel, there would be a coordinated income tax credit. Credit amounts would be included in a taxpayer's gross income for income tax purposes. The $1.00 per gallon tax credit for aviation fuel produced from biodiesel (under Section 40A) would terminate after December 31, 2022. The credit would expire after December 31, 2024.	For background, see: • CRS Report R47171, *Sustainable Aviation Fuel (SAF): In Brief*, by Kelsi Bracmort and Molly F. Sherlock.
Clean Hydrogen Section 13204	This provision would create a new credit for the qualified production of clean hydrogen. The credit would be available for qualified clean hydrogen produced at a	For background, see • CRS Report R45171, *Registered*

Section Title	Description	CRS Resources
	qualifying facility during the facility's first 10 years of operation. The base credit amount would be $0.60 per kilogram (kg) times the applicable percentage. Credit amounts would be indexed for inflation. The applicable percentage would be determined by the lifecycle greenhouse gas emissions rate achieved in producing clean hydrogen. The applicable percentage would be 100% for hydrogen achieving a lifecycle greenhouse gas emissions rate of less than 0.45 kilograms of carbon dioxide equivalent (CO_2e) per kg. The applicable percentage would be 33.4% for hydrogen achieving a lifecycle greenhouse gas emission rate of less than 1.5 kilograms of CO_2e per kg (but not less than 0.45 kilograms). For hydrogen with a lifecycle greenhouse gas emission rate of less than 2.5 kgs of CO_2e per kg (but not less than 1.5), the applicable percentage would be 25%, and for hydrogen with a lifecycle greenhouse gas emissions rate of less than 4 kgs of CO_2e per kg (but not less than 2.5), the applicable percentage would be 20%. The credit would be five times the base credit amount (i.e., up to $3.00 per kg) if the clean hydrogen is produced at a facility that meets prevailing wage and registered apprenticeship requirements. The provision provides that for facilities financed with tax-exempt bonds, the credit amount would be reduced by the lesser of (1) 15%; or (2) the fraction of the proceeds of a tax-exempt obligation used to finance the project over the aggregate amount of the project's financing costs. To qualify for the credit, new facilities must begin construction before January 1, 2033. Facilities existing before January 1, 2023, would be able to qualify based on the date that modifications to their facility required to produce clean hydrogen are placed into service. Taxpayers may claim the PTC for electricity produced from renewable resources by the taxpayer if the electricity is used at a qualified clean hydrogen facility to produce qualified clean hydrogen. Taxpayers could elect to claim the energy investment tax credit (ITC) in lieu of the clean hydrogen production credit. Taxpayers could not claim credits for clean hydrogen produced at facilities that claimed credits for carbon capture under Section 45Q. The provision would terminate the alternative fuel excise tax credit for hydrogen.	*Apprenticeship: Federal Role and Recent Federal Efforts*, by Benjamin Collins. • CRS In Focus IF11927, *Federally Funded Construction and the Payment of Locally Prevailing Wages*, by David H. Bradley and Jon O. Shimabukuro.
Part 3—Clean Energy and Efficiency Incentives for Individuals		
Extension, Increase, and Modifications of Nonbusiness Energy Property Credit Section 13301	Current law provides a 10% tax credit for qualified energy-efficiency improvements and expenditures for residential energy property on a taxpayer's primary residence through 2021. The credit is subject to a $500 per taxpayer lifetime limit. This provision would extend the tax credit through December 31, 2032, and make additional modifications. The proposed modifications would increase the credit rate to 30% with an annual per-taxpayer limit of $1,200 and a $600 per-item limit. For geothermal and air source	For background, see • CRS Report R42089, *Residential Energy Tax Credits: Overview and Analysis*, by Margot L. Crandall-Hollick and Molly F. Sherlock. • CRS Report R46451, *Energy Tax Provisions*

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	heat pumps and biomass stoves, there would be an annual credit limit of $2,000. Limits for expenditures on windows and doors would also be increased. Biomass stoves would be made eligible for tax credits. Required energy-efficiency standards would be modified, and changed to update over time without additional legislative action. Qualifying building envelope components would no longer include roofs, but would include air sealing insulation. Improvements to or replacements of panelboards, sub-panelboards, branch circuits, or feeders used with qualifying property would also be credit-eligible costs. The credit would be allowed for expenditures made on any dwelling unit used by the taxpayer (not limited to primary residences). A 30% credit, up to $150, would be allowed for home energy audits. Treasury would be given the authority to treat errors related to this section as mathematical or clerical errors. Starting in 2025, taxpayers would be required to submit a product identification number to claim the tax credit. The credit would be renamed the energy efficient home improvement credit.	*Expiring in 2020, 2021, 2022, and 2023 ("Tax Extenders")*, by Molly F. Sherlock, Margot L. Crandall-Hollick, and Donald J. Marples.
Residential Clean Energy Credit Section 13302	Current law provides a tax credit for the purchase of solar electric property, solar water heating property, fuel cells, geothermal heat pump property, small wind energy property, and qualified biomass fuel property. The credit rate is 26% through 2022 (it was 30% through 2019), and is scheduled to be reduced to 22% in 2023 before expiring at the end of that year. This provision would extend the credit through December 31, 2034, restoring the 30% credit rate through 2032, and then reducing the credit rate to 26% in 2033 and 22% in 2034. Qualified battery storage technology would be added to the list of eligible property. The credit would be renamed the residential clean energy credit.	For background, see • CRS Report R42089, *Residential Energy Tax Credits: Overview and Analysis*, by Margot L. Crandall-Hollick and Molly F. Sherlock. • CRS Report R46451, *Energy Tax Provisions Expiring in 2020, 2021, 2022, and 2023 ("Tax Extenders")*, by Molly F. Sherlock, Margot L. Crandall-Hollick, and Donald J. Marples.
Energy Efficient Commercial Buildings Deduction Section 13303	Under current law, a permanent deduction of up to $1.80 per square foot is allowed for certain energy-saving commercial building property installed as part of (1) the interior lighting system; (2) the heating, cooling, ventilation, or hot water system; or (3) the building envelope. This provision would update efficiency requirements, providing that a qualifying building must increase its efficiency relative to a reference building by 25%. The deduction would be set at $0.50 per square foot, and increased by $0.02 for each percentage point by which the certified efficiency improvements reduce energy and power costs, with a maximum amount of $1.00 per square foot. For projects that meet prevailing wage and registered apprenticeship requirements, the base amount is $2.50, which would be increased by $0.10 for each percentage point increase in energy efficiency, with a maximum amount of $5.00 per square foot. The maximum deduction amount would be the total deduction	For background, see • CRS Committee Print CP10004, *Tax Expenditures: Compendium of Background Material on Individual Provisions — A Committee Print Prepared for the Senate Committee on the Budget, 2020*, by Jane G. Gravelle et al. (pp. 99-104). • CRS Report R45171, *Registered Apprenticeship: Federal Role and Recent Federal*

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	a building can claim less deductions claimed with respect to the building in the preceding three years. Taxpayers making energy-efficiency retrofits that are part of a qualified retrofit plan on a building that is at least five years old would be able to deduct their adjusted basis in the retrofit property (so long as that amount does not exceed a per-square foot value determined on the basis of energy usage intensity). To qualify, retrofit plans must be expected to reduce a building's energy use intensity by at least 25%. Any tax-exempt entity would be allowed to allocate the deduction to the designer of the building or retrofit plan.	*Efforts*, by Benjamin Collins. • CRS In Focus IF11927, *Federally Funded Construction and the Payment of Locally Prevailing Wages*, by David H. Bradley and Jon O. Shimabukuro.
Extension, Increase, and Modifications of New Energy Efficient Home Credit Section 13304	Under current law, through 2021, a tax credit is available for eligible contractors for building and selling qualifying energy-efficient new homes. The credit is equal to $2,000, with certain manufactured homes qualifying for a $1,000 credit. This provision would extend the energy-efficient new home credit through December 31, 2032, and increase and modify the credit amount. For homes acquired after 2021, a $2,500 credit would be available for new homes that meet certain Energy Star efficiency standards, and a $5,000 credit would be available for new homes that are certified as zero-energy ready homes. Multifamily dwellings that meet certain Energy Star efficiency standards would be eligible for a $500 credit per unit, with a $1,000 per unit credit available for eligible zero-energy ready multifamily dwellings. The credits for multifamily dwelling units would be increased to $2,500 and $5,000, respectively, if the taxpayer ensures that the laborers and mechanics employed by contractors and subcontractors in the construction of the residence are paid prevailing wages. Taxpayers claiming the low-income housing tax credit would not have to reduce their basis for credits claimed under this section.	For background, see • CRS Report R46451, *Energy Tax Provisions Expiring in 2020, 2021, 2022, and 2023 ("Tax Extenders")*, by Molly F. Sherlock, Margot L. Crandall-Hollick, and Donald J. Marples. • CRS In Focus IF11927, *Federally Funded Construction and the Payment of Locally Prevailing Wages*, by David H. Bradley and Jon O. Shimabukuro.
Part 4—Clean Vehicles		
Clean Vehicle Credit Section 13401	Buyers of qualifying plug-in electric vehicles (EVs) may be able to claim a nonrefundable tax credit of up to $7,500 under current law. The tax credit phases out once a vehicle manufacturer has sold 200,000 qualifying vehicles. Current law also allows, through 2021, a tax credit of up to $8,000 for fuel cell vehicles (the base credit amount is $4,000, with up to an additional $4,000 available based on fuel economy). Heavier fuel cell vehicles qualify for up to a $40,000 credit. This provision would modify the tax credit for plug-in electric vehicles, allowing certain clean vehicles to qualify and eliminating the current per manufacturer limit. The credit would be renamed the clean vehicle credit. The modified credit for clean vehicles would be $3,750 for any vehicle meeting the critical minerals requirement, and $3,750 for any vehicle meeting the battery components requirement. The maximum credit per vehicle would be $7,500. Clean vehicles would include plug-in electric vehicles with a battery capacity of at least	For background, see • CRS In Focus IF11017, *The Plug-In Electric Vehicle Tax Credit*, by Molly F. Sherlock. • CRS Report R46864, *Alternative Fuels and Vehicles: Legislative Proposals*, by Melissa N. Diaz. • CRS Report R46231, *Electric Vehicles: A Primer on Technology and Selected Policy Issues*, by Melissa N. Diaz.

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	7 kilowatt hours and fuel cell vehicles. Qualifying vehicles would include those that had final assembly occur in North America. Sellers would be required to provide taxpayer and vehicle information to the Treasury for tax credit eligible vehicles. Only vehicles made by qualified manufacturers, who have written agreements with and provide periodic reports to the Treasury, could qualify. For vehicles placed in service after 2023, qualifying vehicles would not include any vehicle with battery components that were manufactured or assembled by a foreign entity of concern (as defined in 42 U.S.C. §18741). For vehicles placed in service after 2024, qualifying vehicles would not include any vehicle in which applicable critical minerals in the vehicle's battery were from a foreign entity of concern. Taxpayers would be required to include the vehicle identification number (VIN) on their tax return to claim a tax credit. To receive the $3,750 critical minerals portion of the credit, the vehicle's battery must contain a threshold percentage (in value) of critical minerals that were extracted or processed in a country with which the United States has a free trade agreement, or recycled in North America. The threshold percentage would be 40% through 2023, increasing to 50% in 2024, 60% in 2025, 70% in 2026, and 80% after 2026. To receive the $3,750 battery components portion of the credit, the percentage of the battery's components manufactured or assembled in North America would have to meet threshold amounts. For vehicles placed in service through 2023, the percentage would be 50%. The percentage increases to 60% for 2024 and 2025, 70% for 2026, 80% for 2027, 90% for 2028, and 100% after 2028. The credit would be disallowed for certain higher-income taxpayers. Specifically, no credit would be allowed if the current year or preceding year's modified AGI exceeds $300,000 for married taxpayers ($225,000 in the case of head of household filers; $150,000 in the case of other filers). Credits would only be allowed for vehicles that have a manufacturer's suggested retail price of no more than $80,000 for vans, SUVs, or pickup trucks, and $55,000 for other vehicles. Taxpayers would be allowed to claim the credit for one vehicle per year. Starting in 2024, taxpayers purchasing eligible vehicles could elect to transfer the tax credit to the dealer, so long as the dealer meets registration, disclosure, and other requirements. The Secretary of the Treasury is directed to establish a program to make advance payments to dealers for transferred credits. Amounts provided as direct spending would be grossed-up (increased) by 6.0445%. The credit would not apply to vehicles acquired after December 31, 2032.	
Credit for Previously-Owned Clean Vehicles	This provision would create a new tax credit for buyers of previously owned qualified clean (plug-in electric and	For background, see • CRS In Focus IF11017, *The Plug-In Electric*

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Section 13402	fuel cell) vehicles. The credit would be up to $4,000 limited to 30% of the vehicle purchase price. The credit would be disallowed for taxpayers above modified AGI thresholds. Married taxpayers filing a joint return could not claim the credit if their modified AGI was above $150,000 ($112,500 in the case of head of household filers; $75,000 in the case of other filers). The taxpayer's modified AGI would be the lesser of modified AGI in the taxable year or prior year. Credits would only be allowed for vehicles with a sale price of $25,000 or less with a model year that is at least two years earlier than the calendar year in which the vehicle is sold. This credit could only be claimed for vehicles sold by a dealer and on the first transfer of a qualifying vehicle. Taxpayers could only claim this credit once every three years and would be required to include the VIN on their tax return to claim a tax credit. Starting in 2024, taxpayers purchasing eligible vehicles could elect to transfer the tax credit to the dealer, so long as the dealer meets registration, disclosure, and other requirements. Amounts provided as direct spending would be grossed-up (increased) by 6.0445%. The credit would not apply to vehicles acquired after December 31, 2032.	*Vehicle Tax Credit*, by Molly F. Sherlock. • CRS Report R46864, *Alternative Fuels and Vehicles: Legislative Proposals*, by Melissa N. Diaz. • CRS Report R46231, *Electric Vehicles: A Primer on Technology and Selected Policy Issues*, by Melissa N. Diaz.
Qualified Commercial Clean Vehicles Section 13403	This provision would create a new tax credit for qualified commercial clean vehicles placed in service by the taxpayer during the year. The credit would be the lesser of (1) 15% of the vehicle's cost (30% for vehicles not powered by a gasoline or diesel internal combustion engine); or (2) the incremental cost of the vehicle relative to a comparable vehicle. Credit amounts cannot exceed $7,500 for vehicles weighing less than 14,000 pounds, or $40,000 otherwise. Eligible vehicles would have a battery capacity of not less than 15 kilowatt hours (7 kilowatt hours in the case of vehicles weighing less than 14,000 pounds) and be charged by an external source of electricity. Mobile machinery and qualified commercial fuel cell vehicles would also be eligible for this credit. Qualifying vehicles must be depreciable property. Only vehicles made by qualified manufacturers, who have written agreements with and provide periodic reports to the Treasury, could qualify. Taxpayers would be required to include the VIN on their tax return to claim a tax credit. Tax-exempt entities would have the option of electing to receive direct payments. The credit would not apply to vehicles acquired after December 31, 2032.	
Alternative Fuel Refueling Property Credit Section 13404	Current law allows, through 2021, a tax credit for the cost of any qualified alternative fuel vehicle refueling property installed by a business or at a taxpayer's principal residence. The credit is equal to 30% of these costs, limited to $30,000 for businesses at each separate location with qualifying property, and $1,000 for residences. This provision would extend the credit	For background, see • CRS Report R46451, *Energy Tax Provisions Expiring in 2020, 2021, 2022, and 2023 ("Tax Extenders")*, by Molly F. Sherlock, Margot L.

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	through December 31, 2032, and make additional modifications. For business property (property subject to depreciation), the credit would be extended at a rate of 6% (30% if prevailing wage and registered apprenticeship requirements were met), with the credit limit increased to $100,000. The definition of qualifying property would be modified to include bidirectional charging equipment. The credit could also be claimed for electric charging stations for two- and three-wheeled vehicles that are intended for use on public roads. Starting in 2023, charging or refueling property would only be eligible if it is placed in service within a low-income or rural census tract.	Crandall-Hollick, and Donald J. Marples. • CRS Report R46864, *Alternative Fuels and Vehicles: Legislative Proposals*, by Melissa N. Diaz. • CRS Report R46231, *Electric Vehicles: A Primer on Technology and Selected Policy Issues*, by Melissa N. Diaz. • CRS Report R45171, *Registered Apprenticeship: Federal Role and Recent Federal Efforts*, by Benjamin Collins. • CRS In Focus IF11927, *Federally Funded Construction and the Payment of Locally Prevailing Wages*, by David H. Bradley and Jon O. Shimabukuro.
Part 5—Investment in Clean Energy Manufacturing and Energy Security		
Extension of the Advanced Energy Project Credit Section 13501	This provision would provide additional allocations of the qualified advanced energy manufacturing tax credit, which is a 30% tax credit for investments in projects that reequip, expand, or establish certain energy manufacturing facilities. The American Recovery and Reinvestment Act (P.L. 111-5) provided $2.3 billion in allocations, which have been fully allocated. An additional $10 billion in allocations would be provided with at least $4 billion to be allocated to energy communities (as defined in the extended PTC, Section 13101) or projects not located in census tracts in which projects having received prior allocations under Section 48C are located. The definition of qualifying advanced energy projects would be amended such that it would include projects that reequip, expand, or establish a manufacturing or industrial facility for the production or recycling of renewable energy property; energy storage systems and components; grid modernization equipment and components; property designed to remove, use, or sequester carbon oxide emissions; equipment designed to refine, electrolyze, or blend any fuel, chemical, or product which is renewable or low-carbon and low-emission; property designed to produce energy conservation technologies; electric or fuel-cell vehicles, including technologies, components, or materials for such vehicles and the associated charging infrastructure; hybrid vehicles weighing less than 14,000 pounds, including technologies, components, or materials for such vehicles; which reequips an industrial manufacturing facility with	For background, see • CRS Committee Print CP10004, *Tax Expenditures: Compendium of Background Material on Individual Provisions — A Committee Print Prepared for the Senate Committee on the Budget, 2020*, by Jane G. Gravelle et al. (pp. 221-224). • CRS Report R45171, *Registered Apprenticeship: Federal Role and Recent Federal Efforts*, by Benjamin Collins. • CRS In Focus IF11927, *Federally Funded Construction and the Payment of Locally Prevailing Wages*, by David H. Bradley and Jon O. Shimabukuro.

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	equipment designed to reduce greenhouse gas emissions by at least 20%; or which reequips, expands, or establishes an industrial facility for the processing, refining or recycling of critical materials. The base rate for the credit would be 6%, with the 30% credit rate allowed for projects meeting prevailing wage and registered apprenticeship requirements. The Secretary of the Treasury would be directed to establish a program to award credits to qualifying advanced energy project sponsors. Applicants accepting certifications for credits would have two years to provide evidence that the requirements of the certification have been met and to place property in service.	
Advanced Manufacturing Production Credit Section 13502	This provision would create a new production tax credit that could be claimed for the domestic production and sale of qualifying solar and wind components. Credits for solar components would include (1) for a thin film photovoltaic cell or crystalline photovoltaic cell, 4 cents per direct current watt of capacity; (2) for photovoltaic wafers, $12 per square meter; (3) for solar grade polysilicon, $3 per kilogram; (4) for polymeric backsheet, 40 cents per square meter; and (5) for solar modules, 7 cents per direct current watt of capacity. For wind energy components, if the component is an offshore wind vessel, the credit amount would be 10% of the sales price. Otherwise, credits for wind components would be computed as an applicable amount times the total rated capacity of the completed wind turbine for which the component was designed. The applicable amount would be 2 cents for blades, 5 cents for nacelles, 3 cents for towers, 2 cents for fixed platform offshore wind foundations, and 4 cents for floating platform offshore wind foundations. The credit for torque tubes and longitudinal purlin would be $0.87 per kg, and the credit for structural fasteners would be $2.28 per kg. The credit for inverters would be based on the inverter's capacity, with different types of inverters eligible for specified credit amounts ranging from 1.5 cents to 11 cents per watt. For electrode active materials, the credit would be 10% of the production cost. Battery cells could qualify for a credit of $35 per kilowatt hour of capacity, and battery modules could qualify for a credit of $10 per kilowatt hour of capacity (or $45 in the case of a battery module which does not use battery cells). A credit of 10% would also be available for the production of critical minerals. The credit would phase out for components sold after December 31, 2029. Components sold in 2030 would be eligible for 75% of the full credit amount. Components sold in 2031 and 2032 would be eligible for 50% and 25% of the full credit amount, respectively. No credit would be available for components sold after December 31, 2032. The phaseout would not apply to the production of critical minerals.	For background, see • CRS Insight IN11980, *Offshore Wind Provisions in the Inflation Reduction Act*, by Laura B. Comay, Corrie E. Clark, and Molly F. Sherlock.

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	The credit could not be claimed for components produced at a facility for which a credit was claimed under Section 48C.	
Part 6—Superfund		
Reinstatement of Superfund Section 13601	This provision would permanently reinstate the Hazardous Substance Superfund financing rate for certain excise taxes, but would not reauthorize the Superfund special environmental tax on corporate income that also once financed this trust fund. This provision would permanently reinstate Superfund excise taxes on domestic crude oil and imported petroleum products at the rate of 16.4 cents per barrel in 2023, with adjustments for inflation annually thereafter. The previous tax rate was 9.7 cents per barrel when this tax last expired at the end of 1995. Generally, the tax is paid by refineries that receive crude oil or by the person using or importing a petroleum product. The Infrastructure Investment and Jobs Act (P.L. 117-58) separately renewed other excise taxes that contribute to the Superfund. P.L. 117-58 increased the tax rate on domestically produced chemical feedstocks and imported chemical derivatives and renewed those taxes from July 1, 2022, through December 31, 2031. P.L. 117-58 also removed the statutory link between the dates of applicability of the crude oil and chemical products taxes. Revenues from the excise tax finance the Hazardous Substance Superfund Trust Fund. Borrowing would be authorized through repayable advances from the General Fund of the U.S. Treasury until the end of 2032.	For background, see • CRS In Focus IF11982, *Superfund Tax Legislation in the 117th Congress*, by Anthony A. Cilluffo and David M. Bearden. • CRS Report R41039, *Comprehensive Environmental Response, Compensation, and Liability Act: A Summary of Superfund Cleanup Authorities and Related Provisions of the Act*, by David M. Bearden.
Part 7—Incentives for Clean Electricity and Clean Transportation		
Clean Electricity Production Credit Section 13701	This provision would create a new clean electricity production tax credit (PTC). This new PTC would be for the sale of domestically produced electricity with a greenhouse gas emissions rate not greater than zero. To qualify for a tax credit, electricity would need to be produced at a qualifying facility placed in service after December 31, 2024. The base PTC amount would be 0.3 cents per kWh, with the tax credit amount increased to 1.5 cents per kWh for facilities that pay prevailing wages and meet registered apprenticeship requirements (0.5 cents and 2.5 cents, respectively, in 2021, applying the inflation adjustment factor; the amounts would be adjusted for inflation annually). Facilities with a maximum net output of less than 1 megawatt and that begin before 60 days after the Secretary of the Treasury publishes guidance on the wage and registered apprenticeship requirements would also qualify for the full 1.5 cents per kWh amount. The PTC would be available for electricity produced during the facility's first 10 years of operation. The credit amount would be increased by 10% for electricity produced in energy communities (as defined for	For background, see • CRS Report R45171, *Registered Apprenticeship: Federal Role and Recent Federal Efforts*, by Benjamin Collins. • CRS In Focus IF11927, *Federally Funded Construction and the Payment of Locally Prevailing Wages*, by David H. Bradley and Jon O. Shimabukuro. • CRS Insight IN11983, *Proposed Tax Preference for Domestic Content in Energy Infrastructure*, by Christopher D. Watson and Molly F. Sherlock.

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	the purposes of the increased credit amount under the PTC and ITC). The provision would provide that for facilities financed with tax-exempt bonds, the credit amount is reduced by the lesser of (1) 15%; or (2) the fraction of the proceeds of a tax-exempt obligation used to finance the project over the aggregate amount of the project's financing costs. A 10% domestic content bonus would be available for electricity produced at facilities that certify that certain steel, iron, and manufactured products used in the facility were domestically produced. The ability to claim the credit as direct pay would be subject to meeting domestic content requirements. Taxpayers would not be able to claim the clean electricity production credit if the facility or electricity produced from the facility claimed certain other energy-related investment or production tax credits. Taxpayers would choose between the clean electricity PTC and ITC, and could not claim both. The tax credit would phase out when emissions reduction target levels are achieved or after 2032 (the later of the two). The emissions target phaseout would begin after the calendar year in which greenhouse gas emissions from the electric power sector are equal to or less than 25% of 2022 electric power sector emissions. Once phaseout begins, the full credit amount would remain available for facilities that begin construction the following year. The credit amount for facilities beginning construction in the second year would be 75% of the full credit amount. This would be reduced to 50% for facilities beginning construction in the third year, and zero afterward.	
Clean Electricity Investment Credit Section 13702	This provision would create a new clean electricity investment tax credit (ITC). This new ITC would be for investment in qualifying zero-emissions electricity generation facilities or energy storage technology. Costs of interconnection property would be eligible for clean electricity projects smaller than 5 megawatts. This credit would be available for facilities and property placed in service after December 31, 2024. The base ITC amount would be 6%, with the tax credit rate increased to 30% for facilities that pay prevailing wages and meet registered apprenticeship requirements. Facilities with a maximum net output of less than 1 megawatt and that begin before 60 days after the Secretary of the Treasury publishes guidance on the wage and registered apprenticeship requirements would also qualify for the full 30% amount. The clean electricity ITC is increased by one-third (2 percentage points or 10 percentage points) for property placed in service in an energy community (as defined above for the purposes of the clean electricity PTC). Similarly, a 10 percentage point domestic content bonus also applies for the clean electricity ITC. The ability to claim the credit as direct pay would be subject to meeting domestic content requirements.	For background, see • CRS Report R45171, *Registered Apprenticeship: Federal Role and Recent Federal Efforts*, by Benjamin Collins. • CRS In Focus IF11927, *Federally Funded Construction and the Payment of Locally Prevailing Wages*, by David H. Bradley and Jon O. Shimabukuro. • CRS Insight IN11983, *Proposed Tax Preference for Domestic Content in Energy Infrastructure*, by Christopher D. Watson and Molly F. Sherlock.

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	The provision would provide that for facilities financed with tax-exempt bonds, the credit amount is reduced by the lesser of (1) 15%; or (2) the fraction of the proceeds of a tax-exempt obligation used to finance the project over the aggregate amount of the project's financing costs. Taxpayers would not be able to claim the clean electricity production credit if the facility or electricity produced from the facility claimed certain other energy-related investment or production tax credits. Taxpayers would choose between the clean electricity PTC and ITC, and could not claim both. This provision would also allow for the annual allocation of 1.8 gigawatts for "environmental justice solar and wind capacity" credits. Taxpayers receiving a capacity allocation may be entitled to tax credits in addition to otherwise allowed clean electricity ITCs. Specifically, projects receiving an allocation that are located in a low-income community or on Indian land would be eligible for a 10 percentage point bonus investment tax credit, while projects that are part of a low-income residential building project or qualified low-income economic benefit project would be eligible for a 20 percentage point bonus investment credit. Qualifying clean electricity projects would include those with a nameplate capacity of 5 megawatts or less (other than facilities producing electricity through combustion or gasification). Facilities receiving an allocation would be required to have the facility placed in service within four years. The clean electricity ITC would phase out according to the same schedule as would apply to the clean electricity PTC.	
Cost Recovery for Qualified Facilities, Qualified Property, and Energy Storage Technology Section 13703	This provision would provide that any facility qualifying for the clean electricity PTC or any facility or property qualifying for the clean electricity ITC would be treated as 5-year property under the modified accelerated cost recovery system (MACRS), making it so that cost recovery for renewable energy investments would be generally similar to current law. This provision would apply to facilities and property placed in service after December 31, 2024.	
Clean Fuel Production Credit Section 13704	This provision would create a tax credit for domestic clean fuel production starting in 2025. The tax credit per gallon of transportation fuel would be calculated as the applicable amount multiplied by the emissions factor of the fuel. To qualify, the fuel must be produced by the taxpayer at a qualified facility (excluding facilities that receive credits for producing clean hydrogen or carbon oxide sequestration, or the investment credit for energy produced in clean hydrogen facilities) and sold by the taxpayer. Qualified producers must be registered with the IRS. The "applicable amount" would be determined by the type of fuel and the producer's labor practices. The base credit amount for zero-emissions fuels would be $0.20 for nonaviation fuel and $0.35 for aviation fuel. If the	For background, see • CRS Report R47171, *Sustainable Aviation Fuel (SAF): In Brief*, by Kelsi Bracmort and Molly F. Sherlock. • CRS Report R45171, *Registered Apprenticeship: Federal Role and Recent Federal Efforts*, by Benjamin Collins. • CRS In Focus IF11927, *Federally Funded*

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	producer meets prevailing wage and registered apprenticeship requirements, then the applicable amount would be $1.00 for nonaviation fuel and $1.75 for aviation fuel. These amounts would be adjusted annually for inflation. The "emissions factor" would be calculated according to the following formula: [(50 kilograms of CO2-equivalent (CO2e) global warming potential per metric million British Thermal Units (mmBTU) – emissions rate of fuel produced) / 50 kilograms of CO2e per mmBTU]. The Treasury Secretary would publish tables of emissions rates for various fuel types that would be used in the calculation. Qualifying transportation fuel would be fuel with an emissions rate not greater than 50 kilograms of CO2e per mmBTU. The credit would not be available for transportation fuel sold after December 31, 2027.	*Construction and the Payment of Locally Prevailing Wages*, by David H. Bradley and Jon O. Shimabukuro.
Part 8—Credit Monetization and Appropriations		
Elective Payment for Energy Property and Electricity Produced from Certain Renewable Resources, Etc. Section 13801	This provision would allow certain organizations, generally tax-exempt entities including state and local governments and Indian tribal governments, to treat certain tax credit amounts as payments of tax. Payments in excess of tax liability can be refunded to these organizations, allowing the credits to be received as "direct pay." This direct payment would be allowed for the Section 30C credit for alternative fuel refueling property, the Section 45 renewable electricity production credit, the Section 45Q carbon oxide sequestration credit, the new Section 45U zero-emission nuclear power production credit; the new Section 45V clean hydrogen production credit; in the case of certain tax-exempt entities, the new Section 45W credit for qualified commercial vehicles; the new Section 45X advanced manufacturing production credit; the new Section 45Y clean electricity production credit; the new Section 45Z clean fuel production credit; the Section 48 energy investment tax credit, and the Section 48C qualifying advanced energy project credit; and the new Section 48D clean electricity investment credit. Taxpayers who are not tax-exempt entities would be allowed to elect direct pay for the clean hydrogen, carbon oxide sequestration, and advanced manufacturing production credits for the first five years starting with the year a facility is placed in service. This election cannot be made after December 31, 2032. This provision would not apply to territories with mirror-code tax systems. Taxpayers who are not tax-exempt entities would be allowed a one-time transfer of these tax credits. Any payments received in exchange for the transfer of credits would be excluded from income, and any amounts paid to obtain a transferred credit could not be deducted from income. Credits that could be transferred would also be given extended carryback and carryforward periods. The carryback period for these credits would be extended from 1 to 3 years, and the carryforward period extended from 20 to 22 years.	For background, see • CRS Report R45693, *Tax Equity Financing: An Introduction and Policy Considerations*, by Mark P. Keightley, Donald J. Marples, and Molly F. Sherlock. • CRS Insight IN11983, *Proposed Tax Preference for Domestic Content in Energy Infrastructure*, by Christopher D. Watson and Molly F. Sherlock.

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Part 9—Other Provisions		
Permanent Extension of Tax Rate to Fund Black Lung Disability Trust Funds Section 13901	Under current law, an excise tax is imposed on coal from mines in the United States. The tax rate depends on how the coal is mined. The current rates are $0.50 per ton for coal from underground mines and $0.25 per ton for coal from surface mines, with both limited to 2% of the sales price. The Black Lung excise tax is intended to fund benefits for U.S. coal miners who develop Black Lung disease as a result of working in coal mines. Temporary, higher rates of $1.10 per ton of coal from underground mines and $0.55 per ton of coal from surface mines, limited to 4.4% of the sales price, have applied for much of the time since 1986. They most recently applied from the beginning of 2020 through the end of 2021. This provision would permanently extend the higher rates.	For background, see • CRS Report R45261, *The Black Lung Program, the Black Lung Disability Trust Fund, and the Excise Tax on Coal: Background and Policy Options*, by Scott D. Szymendera and Molly F. Sherlock.
Increase in Research Credit Against Payroll Tax for Small Business Section 13902	Under current law, businesses are allowed a credit against income tax that is based on their qualified research expenses. The credit is calculated as the amount of qualified research expenses above a base amount that is meant to represent the amount of research expenditures in the absence of the credit. Some small businesses may not have a large enough income tax liability to take advantage of their research credit. Current law allows a small business, defined as a business with less than $5 million in gross receipts and that is under five years old, to apply up to $250,000 of the research credit toward its Social Security payroll tax liability. This provision would allow an additional credit of up to $250,000 against Medicare Hospital Insurance tax for taxable years beginning after December 31, 2022. The credit could not exceed the tax imposed for any calendar quarter, with unused amounts of the credit carried forward.	For background, see • CRS Report RL31181, *Federal Research Tax Credit: Current Law and Policy Issues*, by Gary Guenther. • CRS Report R47062, *Payroll Taxes: An Overview of Taxes Imposed and Past Payroll Tax Relief*, by Anthony A. Cilluffo and Molly F. Sherlock.
Reinstatement of Limitation Rules for Deduction for State and Local, etc., Taxes; Extension of Limitation on Excess Business Losses of Noncorporate Taxpayers Section 13903	This provision would reinstate the current-law expiration date of the state and local tax (SALT) limitation enacted in Section 13904 of the bill. In other words, the expiration date would remain 2025, as under current law. The provision would also extend the limitation on excess business losses of noncorporate taxpayers. Businesses are generally permitted to carry over a net operating loss (NOL) to certain past and future years. Under the passive loss rules, individuals and certain other taxpayers are limited in their ability to claim deductions and credits from passive trade and business activities, although unused deductions and credits may generally be carried forward to the next year. Similarly, certain farm losses may not be deducted in the current year, but can be carried forward to the next year. For taxpayers other than C corporations, a deduction in the current year for excess business losses is temporarily disallowed (through 2026) and such losses are treated as a NOL carryover to the following year. An excess	For background, see • CRS Insight IN11296, *Tax Treatment of Net Operating Losses (NOLs) in the Coronavirus Aid, Relief, and Economic Security (CARES) Act*, by Jane G. Gravelle. • CRS Report R46377, *The Tax Treatment and Economics of Net Operating Losses*, by Mark P. Keightley.

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	business loss is the amount that a taxpayer's aggregate deductions attributable to trades and businesses exceed the sum of (1) aggregate gross income or gain attributable to such activities and (2) $250,000 ($500,000 if married filing jointly), adjusted for inflation. For partnerships and S corporations, this provision was applied at the partner or shareholder level. This provision would extend the temporary limitation through 2028.	
Removal of Harmful Small Business Taxes; Extension of Limitation of Deduction for State and Local, etc., Taxes Section 13904	In addition to the modification noted in Section 10101 above, this provision would have extended the $10,000 state and local tax (SALT) limitation from 2025 through 2026. However, the SALT change would effectively be reversed by changes made in Section 13903 of the bill.	For background, see • CRS Report R46246, *The SALT Cap: Overview and Analysis*, by Grant A. Driessen and Joseph S. Hughes.

Source: CRS analysis of the legislative text of the Senate amendment to H.R. 5376, "Inflation Reduction Act of 2022," as posted on the House Rule Committee Website at https://rules.house.gov/bill/117/hr-5376-sa.

Notes: Energy provisions that extend expiring provisions are generally effective in 2022, with new provisions generally effective in 2023. Exceptions are noted. Sections 13903 and 13904 were added during Senate consideration of the bill. The changes that would be made by the provisions are permanent, unless otherwise noted. Within the description, "Section" citations refer to the section within the Internal Revenue Code (IRC), 26 U.S.C., unless otherwise noted. Section 13802 would provide appropriations of $500 million to remain available until September 30, 2031, for the IRS to carry out this subtitle.

Table 5. Estimated Budgetary Effect of the Revenue Provisions of the "Inflation Reduction Act of 2022"

Provision	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-2031
SUBTITLE A—DEFICIT REDUCTION											
Part 1—Corporate Tax Reform	—	34,679	34,258	22,039	17,702	18,699	20,798	22,756	24,658	26,659	222,248
Part 2—Excise Tax on Repurchase of Corporate Stock	—	5,697	7,875	8,070	8,581	8,882	8,838	8,603	8,500	8,641	73,686
Part 3—Funding the Internal Revenue Service and Improving Taxpayer Compliance	Estimates to be provided by the Congressional Budget Office (CBO)										
Total of Subtitle A	**—**	***40,376***	***42,133***	***30,109***	***26,283***	***27,581***	***29,636***	***31,359***	***33,158***	***35,300***	***295,934***
SUBTITLE B—PRESCRIPTION DRUG PRICING REFORM | SUBTITLE C—AFFORDABLE CARE ACT SUBSIDIES											
Totals of Subtitle B and C	*Estimates to be provided by the Congressional Budget Office (CBO)*										
SUBTITLE D—ENERGY SECURITY											
Part 1—Clean Electricity and Reducing Carbon Emissions											
Extension and modification of credit for electricity produced from certain renewable resources	—	-1,562	-2,183	-3,317	-4,822	-6,428	-7,677	-8,232	-8,329	-8,511	-51,062
Extension and modification of energy credit	—	-2,140	-1,559	-2,458	-5,367	-2,359	-48	-38	-9	15	-13,962
Increase in energy credit for solar facilities placed in service in connection with low-income communities	Estimated included in "Extension and modification of credit for electricity produced from certain renewable resources" and "Extension and modification of energy credit" above										
Extension and modification of credit for carbon oxide sequestration	—	-42	-303	-469	-495	-463	-429	-388	-343	-296	-3,229
Zero-emission nuclear power production credit	—	—	-2,188	-3,524	-3,710	-3,838	-3,960	-4,050	-4,279	-4,452	-30,001
Total of Part 1	**—**	***-3,744***	***-6,233***	***-9,768***	***-14,394***	***-13,088***	***-12,115***	***-12,709***	***-12,961***	***-13,243***	***-98,254***

Provision	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-2031
Part 2—Clean Fuels											
Extension of incentives for biodiesel, renewable diesel, and alternative fuels	—	-2,776	-1,780	-1,015	—	—	—	—	—	—	-5,571
Extension of second-generation biofuel incentives	—	-24	-20	-10	—	—	—	—	—	—	-54
Sustainable aviation fuel credit	—	-10	-25	-14	—	—	—	—	—	—	-49
Credit for production of clean hydrogen	—	-131	-362	-610	-918	-1,251	-1,627	-2,082	-2,667	-3,518	-13,166
Total of Part 2	**—**	***-2,941***	***-2,187***	***-1,649***	***-918***	***-1,251***	***-1,627***	***-2,082***	***-2,667***	***-3,518***	***-18,840***
Part 3—Clean Energy and Efficiency Incentives for Individuals											
Extension, increase, and modifications of nonbusiness energy property credit	—	-1,887	-1,348	-1,324	-1,345	-1,327	-1,277	-1,301	-1,314	-1,327	-12,451
Extension of residential clean energy credit	—	-459	-1,021	-2,692	-2,770	-2,850	-2,935	-3,019	-3,092	-3,185	-22,022
Energy efficient commercial buildings deduction	—	-62	-50	-46	-42	-38	-35	-32	-30	-28	-362
Extension, increase, and modifications of new energy efficient home credit	—	-273	-193	-203	-216	-230	-241	-240	-229	-217	-2,043
Total of Part 3	**—**	***-2,681***	***-2,612***	***-4,265***	***-4,373***	***-4,445***	***-4,488***	***-4,592***	***-4,665***	***-4,757***	***-36,879***
Part 4—Clean Vehicles											
Clean vehicle credit	—	-85	-451	-557	-681	-854	-1,024	-1,155	-1,303	-1,429	-7,541
Credit for previously-owned qualified plug-in electric drive motor vehicles	—	-99	-96	-120	-132	-146	-162	-179	-197	-215	-1,347
Credit for qualified commercial clean vehicles	—	-189	-177	-228	-298	-388	-469	-539	-607	-687	-3,583
Alternative fuel refueling property credit	—	-138	-128	-145	-164	-184	-207	-231	-257	-284	-1,738

Provision	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-2031
Total of Part 4	**—**	***-511***	***-852***	***-1,050***	***-1,275***	***-1,572***	***-1,862***	***-2,105***	***-2,365***	***-2,615***	***-14,209***
Part 5—Investment in Clean Energy Manufacturing and Energy Security											
Extension of the advanced energy project credit	—	-1,463	-1,377	-915	-926	-614	-442	-280	-196	-42	-6,255
Advanced manufacturing production credit	—	-1,755	-2,503	-2,691	-3,165	-3,563	-3,938	-4,534	-4,562	-3,921	-30,632
Total of Part 5	**—**	***-3,218***	***-3,880***	***-3,606***	***-4,091***	***-4,177***	***-4,380***	***-4,814***	***-4,758***	***-3,963***	***-36,887***
Part 6—Reinstatement of Superfund											
Total of Part 6	**—**	***902***	***1,230***	***1,271***	***1,304***	***1,336***	***1,368***	***1,402***	***1,436***	***1,470***	***11,719***
Part 7—Incentives for Clean Electricity and Clean Transportation											
Clean electricity production credit	—	—	—	—	-12	-45	-571	-1,864	-3,497	-5,215	-11,204
Clean electricity investment credit	—	—	—	-39	-57	-6,575	-10,315	-10,742	-11,264	-11,865	-50,858
Cost recovery for qualified facilities, qualified property, and energy storage technology	—	—	—	—	—	-26	-83	-134	-171	-211	-624
Clean fuel production credit	—	—	—	-641	-791	-1,177	-337	—	—	—	-2,946
Total of Part 7	**—**	**—**	**—**	***-680***	***-860***	***-7,823***	***-11,306***	***-12,740***	***-14,932***	***-17,291***	***-65,632***
Part 8—Credit Monetization and Appropriations											
Total of Part 8					***Estimates Contained in Relevant Items Above***						
Part 9—Other Provisions											
Permanent extension of tax rate to fund Black Lung Disability Trust Fund	—	103	135	131	130	130	131	132	133	134	1,159
Increase in research credit against payroll tax for small businesses	—	-16	-13	-15	-16	-18	-21	-22	-23	-24	-168

Provision	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-2031
Limitation on excess business losses of noncorporate taxpayers extended for two years	—	—	—	—	—	17,666	26,198	9,453	-274	-284	52,759
Total of Part 9	**—**	***87***	***122***	***116***	***114***	***17,778***	***26,308***	***9,563***	***-164***	***-174***	***53,750***
Total of Subtitle D	**—**	***-12,107***	***-14,412***	***-19,631***	***-24,493***	***-13,243***	***-8,101***	***-28,076***	***-41,076***	***-44,091***	***-205,231***
NET TOTAL	**—**	**28,269**	**27,721**	**10,478**	**1,790**	**14,338**	**21,535**	**3,283**	**-7,918**	**-8,791**	**90,703**

Source: Joint Committee on Taxation, *Estimated Budgetary Effect of the Revenue Provisions of Title I -Committee on Finance, of an Amendment in the Nature of a Substitute to H.R. 5376, "An Act to Provide for Reconciliation Pursuant to Title II of S. Con. Res. 14," as Passed by the Senate on August 7, 2022, and Scheduled for Consideration by the House of Representatives on August 12, 2022,"* JCX-18-22, August 9, 2022, https://www.jct.gov/publications/2022/jcx-18-22/.

Notes: A "—" indicates no estimated budget effect.

Appendix. Inflation Reduction Act as Initially Proposed in the Senate

Table A-1. Subtitle A—Deficit Reduction

Section Title	Description	CRS Resources
Part 1—Corporate Tax Reform		
Corporate Alternative Minimum Tax Section 10101	This provision would impose a new alternative minimum tax of 15% on corporations based on financial income. It would apply to corporations with $1 billion or more in average annual earnings in the previous three years. In the case of U.S. corporations that have foreign parents, it would apply only to income earned in the United States of $100 million or more of average annual earnings in the previous three years (and apply when the international financial reporting group has income of $1 billion or more). It would apply to a new corporation in existence for less than three years based on the earnings in the years of existence. The provision would exclude Subchapter S corporations, regulated investment companies (RICs), and real estate investment trusts (REITs). The tax would apply to private equity companies. Firms that file consolidated returns would include income allocable to the firm from related firms including controlled foreign corporations (and any disregarded entities); for other related firms, dividends would be included. The provision would allow special deductions for cooperatives and Alaska Native Corporations. It would make adjustments to conform financial accounting to tax accounting for certain defined benefit pension plans. It would apply with respect to items under the unrelated business income tax for tax-exempt entities. The additional tax would equal the amount of the minimum tax in excess of the regular income tax plus the additional tax from the Base Erosion and Anti-Abuse tax. Income would be increased by federal and foreign income taxes to place income on a pretax basis. Losses would be allowed in the same manner as with the regular tax, with loss carryovers limited to 80% of taxable income. Domestic credits under the general business tax (such as the R&D credit) would be allowed to offset up to 75% of the combined regular and minimum tax. Foreign tax credits would be allowed based on the allowance for foreign taxes paid in a corporation's financial statement. A credit for additional minimum tax could be carried over to future years to offset regular tax when that tax is higher. This tax would apply to taxable years beginning after December 31, 2022.	For background, see • CRS In Focus IF12179, *The Corporate Minimum Tax Proposal*, by Jane G. Gravelle. • CRS Report R46887, *Minimum Taxes on Business Income: Background and Policy Options*, by Molly F. Sherlock and Jane G. Gravelle. • CRS Insight IN11646, *A Look at Book-Tax Differences for Large Corporations Using Aggregate Internal Revenue Service (IRS) Data*, by Molly F. Sherlock and Jane G. Gravelle.
Part 2—Closing the Carried Interest Loophole		
Modification of Rules for Partnership	Under current law, partnership interest transferred to the taxpayer in connection with the provision of services to a	For background, see

Section Title	Description	CRS Resources
Interests Held in Connection with the Performance of Services Section 10201	trade or business (carried interest) held for at least three years is taxed as a long-term capital gain. This provision would modify the tax rules surrounding "carried interest" by extending the holding period to qualify for long-term capital gains to five years for taxpayers with adjusted gross income of $400,000 or more, broadening the definition of carried interest to include partnership assets under the taxpayer's direct or indirect control, and adding additional rules for measuring the holding period (including for tiered partnerships).	• CRS Report R46447, *Taxation of Carried Interest*, by Donald J. Marples.

Source: CRS analysis of the legislative text of the "Inflation Reduction Act of 2022," as posted on the Senate Democrats website on July 27, 2022, at https://www.democrats.senate.gov/imo/media/doc/inflation_reduction_act_of_2022.pdf.

Notes: Both provisions in this table are effective for taxable years beginning after December 31, 2022. The changes that would be made by these provisions are permanent. Part 3 of Subtitle A would provide additional appropriations of $79.6 billion over the next 10 years to enhance IRS service and enforcement activities. For background on IRS appropriations, see CRS In Focus IF12098, *Internal Revenue Service Appropriations, FY2023*, by Gary Guenther.

Table A-2. Subtitle B—Prescription Drug Reform

Section Title	Description	CRS Resources
Part 1—Lowering Prices Through Drug Price Negotiations		
Selected Drug Manufacturer Excise Tax Imposed During Noncompliance Period Section 11003	This provision would impose a new excise tax on drug manufacturers, producers, and importers who fail to enter into drug pricing agreements under Section 1193 of the Social Security Act, as added by the bill on selected drugs (i.e., are noncompliant with Section 1193). This excise tax would be found under the new Internal Revenue Code (IRC) Section 5000D. The excise tax rate would range from 185.71% to 1,900% of the selected drug's price depending on the duration of noncompliance. The provision does not specify these rates explicitly, but instead defines an applicable percentage which equals the share of the post-tax sale price attributable to the excise tax. Specifically, the applicable percentage as defined in the statute equals tax/(tax+price) which simplifies to tax rate/(tax rate+1) with the applicable percentages being 65% for the sales of selected drugs during the first 90 days of noncompliance, 75% for sales during the 91st to 180th days of noncompliance, 85% for sales during the 181st to 270th days of noncompliance, and 95% for sales after the 270th day of noncompliance. Hence, the corresponding tax rates would be calculated as (applicable percentage)/(1-applicable percentage) and equal 185.71%, 300%, 566.67% and 1,900% respectively, depending on the duration of noncompliance. For example, if a selected drug was subject to the top tax rate of 1,900% and cost $10 pre-tax, it would cost $200 post-tax with $190 of the $200 cost (or 95%, the applicable percentage) being attributable to the excise tax. Selected drugs would be those defined in Section 1192(a) of the Social Security Act, as enacted under this bill, which are manufactured or produced in the United States or	For background, see • CRS Report R47056, *Build Back Better Act (BBBA) Health Coverage Provisions: House-Passed and Senate-Released Language*, coordinated by Vanessa C. Forsberg and Ryan J. Rosso.

Section Title	Description	CRS Resources
	entered the United States for consumption, use, or warehousing. The excise tax would not apply to drugs sold for export, and the provision addresses the refund or credit process if tax is paid. Noncompliance periods as defined in the bill would generally begin after the deadline to enter into an agreement to negotiate or renegotiate, or to agree upon a maximum price, had passed. Such periods would end when such agreement has been reached. The earliest potential noncompliance period would begin on October 2, 2023. For sales that were timed to avoid the excise tax, the Secretary of the Treasury could treat the sale as occurring during a day in a noncompliance period. Manufacturers would be prohibited from deducting excise tax payments from their federal income taxes. Internal IRS appeals would not be permitted with respect to this new excise tax. Additionally, no suit or proceeding for a refund of the tax would be permitted until the taxpayer had made full payment of the tax (including applicable interest and penalties).	

Source: CRS analysis of the legislative text of the "Inflation Reduction Act of 2022," as posted on the Senate Democrats website on July 27, 2022, at https://www.democrats.senate.gov/imo/media/doc/inflation_reduction_act_of_2022.pdf.

Notes: This provision would apply after the date of enactment to the sale of drugs during a noncompliance period. The first noncompliance period could begin on October 2, 2023. Within the description, "Section" citations refer to the section within the Internal Revenue Code (IRC), 26 U.S.C., unless otherwise noted.

Table A-3. Estimated Budgetary Effect of the Revenue Provisions of the "Inflation Reduction Act of 2022"

Provision	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-2031
SUBTITLE A—DEFICIT REDUCTION											
Part 1—Corporate Tax Reform	—	52,618	44,000	29,738	26,464	27,191	29,697	32,160	34,463	36,808	313,138
Part 2—Closing the Carried Interest Loophole	—	1,594	1,511	1,430	1,389	1,379	1,389	1,413	1,445	1,487	13,037
Part 3—Funding the Internal Revenue Service and Improving Taxpayer Compliance	Estimates to be provided by the Congressional Budget Office (CBO)										
Total of Subtitle A	**—**	***54,212***	***45,511***	***31,168***	***27,853***	***28,570***	***31,086***	***33,573***	***35,908***	***38,295***	***326,175***
SUBTITLE B—PRESCRIPTION DRUG PRICING REFORM | SUBTITLE C—AFFORDABLE CARE ACT SUBSIDIES											
Totals of Subtitle B and C	*Estimates to be provided by the Congressional Budget Office (CBO)*										
SUBTITLE D—ENERGY SECURITY											
Part 1—Clean Electricity and Reducing Carbon Emissions											
Extension and modification of credit for electricity produced from certain renewable resources	—	-1,562	-2,183	-3,317	-4,822	-6,428	-7,677	-8,232	-8,329	-8,511	-51,062
Extension and modification of energy credit	—	-2,140	-1,559	-2,458	-5,367	-2,359	-48	-38	-9	15	-13,962
Increase in energy credit for solar facilities placed in service in connection with low-income communities	Estimated included in "Extension and modification of credit for electricity produced from certain renewable resources" and "Extension and modification of energy credit" above										
Extension and modification of credit for carbon oxide sequestration	—	-42	-303	-469	-495	-463	-429	-388	-343	-296	-3,229
Zero-emission nuclear power production credit	—	—	-2,188	-3,524	-3,710	-3,838	-3,960	-4,050	-4,279	-4,452	-30,001
Total of Part 1	**—**	***-3,744***	***-6,233***	***-9,768***	***-14,394***	***-13,088***	***-12,115***	***-12,709***	***-12,961***	***-13,243***	***-98,254***

Provision	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-2031
Part 2—Clean Fuels											
Extension of incentives for biodiesel, renewable diesel, and alternative fuels	-104	-2,672	-1,780	-1,015	—	—	—	—	—	—	-5,571
Extension of second-generation biofuel incentives	-7	-17	-20	-10	—	—	—	—	—	—	-54
Sustainable aviation fuel credit	—	-10	-25	-14	—	—	—	—	—	—	-49
Credit for production of clean hydrogen	—	-131	-362	-610	-918	-1,251	-1,627	-2,082	-2,667	-3,518	-13,166
Total of Part 2	***-111***	***-2,830***	***-2,187***	***-1,649***	***-918***	***-1,251***	***-1,627***	***-2,082***	***-2,667***	***-3,518***	***-18,840***
Part 3—Clean Energy and Efficiency Incentives for Individuals											
Extension, increase, and modifications of nonbusiness energy property credit	-253	-1,634	-1,348	-1,324	-1,345	-1,327	-1,277	-1,301	-1,314	-1,327	-12,451
Extension of residential clean energy credit	-52	-407	-1,021	-2,692	-2,770	-2,850	-2,935	-3,019	-3,092	-3,185	-22,022
Energy efficient commercial buildings deduction	—	-62	-50	-46	-42	-38	-35	-32	-30	-28	-362
Extension, increase, and modifications of new energy efficient home credit	—	-273	-193	-203	-216	-230	-241	-240	-229	-217	-2,043
Total of Part 3	***-305***	***-2,376***	***-2,612***	***-4,265***	***-4,373***	***-4,445***	***-4,488***	***-4,592***	***-4,665***	***-4,757***	***-36,879***
Part 4—Clean Vehicles											
Clean vehicle credit	—	-85	-451	-557	-681	-854	-1,024	-1,155	-1,303	-1,429	-7,541
Credit for previously-owned qualified plug-in electric drive motor vehicles	—	-99	-96	-120	-132	-146	-162	-179	-197	-215	-1,347
Credit for qualified commercial clean vehicles	—	-189	-177	-228	-298	-388	-469	-539	-607	-687	-3,583
Alternative fuel refueling property credit	—	-138	-128	-145	-164	-184	-207	-231	-257	-284	-1,738

Provision	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-2031
Total of Part 4	**—**	***-511***	***-852***	***-1,050***	***-1,275***	***-1,572***	***-1,862***	***-2,105***	***-2,365***	***-2,615***	***-14,209***
Part 5—Investment in Clean Energy Manufacturing and Energy Security											
Extension of the advanced energy project credit	—	-1,463	-1,377	-915	-926	-614	-442	-280	-196	-42	-6,255
Advanced manufacturing production credit	—	-1,754	-2,502	-2,690	-3,164	-3,562	-3,937	-4,533	-4,561	-3,920	-30,622
Total of Part 5	**—**	***-3,217***	***-3,879***	***-3,605***	***-4,090***	***-4,176***	***-4,379***	***-4,813***	***-4,757***	***-3,962***	***-36,877***
Part 6—Reinstatement of Superfund											
Total of Part 6	**—**	***902***	***1,230***	***1,271***	***1,304***	***1,336***	***1,368***	***1,402***	***1,436***	***1,470***	***11,719***
Part 7—Incentives for Clean Electricity and Clean Transportation											
Clean electricity production credit	—	—	—	—	-12	-45	-571	-1,864	-3,497	-5,215	-11,204
Clean electricity investment credit	—	—	—	-39	-57	-6,575	-10,315	-10,742	-11,264	-11,865	-50,858
Cost recovery for qualified facilities, qualified property, and energy storage technology	—	—	—	—	—	-26	-83	-134	-171	-211	-624
Clean fuel production credit	—	—	—	-641	-791	-1,177	-337	—	—	—	-2,946
Total of Part 7	**—**	**—**	**—**	***-680***	***-860***	***-7,823***	***-11,306***	***-12,740***	***-14,932***	***-17,291***	***-65,632***
Part 8—Credit Monetization and Appropriations											
Total of Part 8					***Estimates Contained in Relevant Items Above***						
Part 9—Other Provisions											
Permanent extension of tax rate to fund Black Lung Disability Trust Fund	—	103	135	131	130	130	131	132	133	134	1,159
Increase in research credit against payroll tax for small businesses	—	-16	-13	-15	-16	-18	-21	-22	-23	-24	-168

Provision	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-2031
Total of Part 9	*—*	*87*	*122*	*116*	*114*	*112*	*110*	*110*	*110*	*110*	*991*
Total of Subtitle D	*-416*	*-11,690*	*-14,411*	*-19,630*	*-24,492*	*-30,908*	*-34,298*	*-37,528*	*-40,801*	*-43,806*	*-257,980*
NET TOTAL	**-416**	**42,522**	**31,100**	**11,538**	**3,361**	**-2,338**	**-3,212**	**-3,955**	**-4,893**	**-5,511**	**68,195**

Source: Joint Committee on Taxation, *Estimated Budgetary Effect of the Revenue Provisions of Title I -Committee on Finance, of an Amendment in the Nature of a Substitute to H.R. 5376, the "Inflation Reduction Act of 2022,"* #22-2-027, July 28, 2022, https://www.finance.senate.gov/imo/media/doc/7.29.22%20Estimate%20of%20Manchin%20Schumer%20agreement.pdf.

Notes: A "—" indicates no estimated budget effect.

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Acknowledgments

Bernadette Fernandez, Specialist in Health Care Financing, contributed content related to the provision in **Table 3**.

Disclaimer

EXHIBIT H

Part III - Administrative, Procedural, and Miscellaneous

Section 5000D Excise Tax on Sales of Designated Drugs; Reporting and Payment of the Tax

Notice 2023-52

SECTION 1. PURPOSE

This notice announces that the Department of the Treasury (Treasury Department) and the Internal Revenue Service (IRS) intend to propose regulations (forthcoming proposed regulations) addressing § 5000D of the Internal Revenue Code (Code), including how taxpayers would report and pay the excise tax imposed by § 5000D (§ 5000D tax).[1]

SECTION 2. BACKGROUND

.01 Sections 1191 through 1198 of the Social Security Act (SSA), added by §§ 11001 and 11002 of Public Law 117-169, 136 Stat. 1818 (August 16, 2022), commonly referred to as the Inflation Reduction Act of 2022 (IRA), require the Secretary of Health and Human Services to establish a Medicare prescription drug price negotiation program (Program) to negotiate maximum fair prices (MFPs) for certain high expenditure, single-source drugs covered under Medicare. Under the Program, the

[1] Unless otherwise specified, all "section" or "§" references are to sections of the Code or the Excise Tax Procedural Regulations (26 CFR part 40).

Secretary of Health and Human Services must, among other things: (1) publish a list of selected drugs in accordance with § 1192 of the SSA; (2) enter into agreements with willing manufacturers of selected drugs in accordance with § 1193 of the SSA; and (3) negotiate MFPs for such selected drugs in accordance with § 1194 of the SSA. Under § 1193(a)(3) of the SSA, manufacturers of selected drugs that choose to enter into agreements with the Secretary of Health and Human Services and that agree to an MFP commit to provide access to selected drugs at the negotiated prices to MFP-eligible individuals (as defined in § 1191(c)(2) of the SSA), as well as to pharmacies and other dispensers, hospitals, physicians, other providers of services, and suppliers with respect to such individuals.

.02 Section 5000D, added to the Code by § 11003 of the IRA, imposes the § 5000D tax on the sale by the manufacturer, producer, or importer (manufacturer or taxpayer) of any designated drug[2] during a day that falls within a period described in § 5000D(b) (statutory period). The amount of § 5000D tax imposed on such a manufacturer equals the amount that causes the ratio of (1) the § 5000D tax, divided by (2) the sum of the § 5000D tax and the price for which the designated drug was sold, when such ratio is expressed as a percentage, to equal the "applicable percentage." Section 5000D(a).

.03 Section 5000D(d) defines the term "applicable percentage" as follows: (1) in the case of sales of a designated drug during the first 90 days in a statutory period with respect to such drug, 65 percent; (2) in the case of sales of such drug during the 91st day through the 180th day in a statutory period with respect to such drug, 75 percent;

[2] The term "designated drug" means any negotiation-eligible drug (as defined in § 1192(d) of the SSA) included on the list published under § 1192(a) of the SSA that is manufactured or produced in the United States or entered into the United States for consumption, use, or warehousing. See § 5000D(e)(1).

(3) in the case of sales of such drug during the 181st day through the 270th day in a statutory period with respect to such drug, 85 percent; and (4) in the case of sales of such drug during any subsequent day in a statutory period, 95 percent.

SECTION 3. GUIDANCE TO BE ISSUED

.01 Scope of taxable sales. The Treasury Department and the IRS intend that, under the forthcoming proposed regulations, the § 5000D tax would be imposed on taxpayer sales of designated drugs dispensed, furnished, or administered to individuals under the terms of Medicare. The Treasury Department and the IRS intend that the forthcoming proposed regulations will also propose a method for taxpayers to calculate their § 5000D liability.

.02 Separately charged tax not part of price; presumption where no separate charge for tax is made. The Treasury Department and the IRS intend that the forthcoming proposed regulations will propose a rule providing that when the § 5000D tax is separately charged on the invoice or records pertaining to the sale of a designated drug by the manufacturer, the tax is not part of the price of the designated drug. Thus, if a manufacturer computes the § 5000D tax and charges it as a separate item on the invoice or records pertaining to the sale in addition to the stated sale price, the amount of § 5000D tax so charged does not become part of the price and no § 5000D tax is due on the amount of § 5000D tax so charged. When no separate charge is made as to the § 5000D tax on the invoice or records pertaining to the sale of a designated drug, it will be presumed that the amount charged for the designated drug includes the proper amount of § 5000D tax and the price of the designated drug; therefore, the amount charged will be allocated between the amount of the § 5000D tax and the price. For

example, if a manufacturer charges a purchaser $100 for a designated drug during the first 90 days in a statutory period and does not make a separate charge for the § 5000D tax, $65 is allocated to the § 5000D tax and $35 is allocated to the price of the designated drug. This example only illustrates the presumption in section 3.02 of this notice; it does not illustrate other concepts described in this notice.

.03 Procedural rules. The Treasury Department and the IRS intend that the forthcoming proposed regulations will propose applying the Excise Tax Procedural Regulations in 26 CFR part 40 (Excise Tax Procedural Regulations) generally to chapter 50A of the Code (and thus to § 5000D), with some limited exceptions. In particular, the Treasury Department and the IRS intend to propose that the Excise Tax Procedural Regulations will apply to chapter 50A of the Code as follows:

(1) Returns: § 40.6011(a)-1(a)(1). The Treasury Department and the IRS intend to propose that taxpayers would be required to report any § 5000D tax liability on IRS Form 720, *Quarterly Federal Excise Tax Return*, according to the instructions applicable to the form. The IRS also intends to issue a new form that taxpayers would be required to attach to Form 720 to compute any § 5000D tax liability and report the § 5000D tax.

(2) Time for filing returns: § 40.6071(a)-1(a). The Treasury Department and the IRS intend to propose that the deadline for filing quarterly returns on Form 720 to report any § 5000D tax liability would be the last day of the first calendar month following the quarter of a calendar year (calendar quarter) for which the return is made. Therefore, taxpayers would be required to file a Form 720 reporting any § 5000D tax liability arising in a calendar quarter as follows:

Calendar Quarter Covered by Form 720	Due Date for Form 720 Would Be[3]
1st calendar quarter (Jan., Feb., Mar.)	April 30 of same calendar year
2nd calendar quarter (Apr., May, June)	July 31 of same calendar year
3rd calendar quarter (July, Aug., Sept.)	October 31 of same calendar year
4th calendar quarter (Oct., Nov., Dec.)	January 31 of following calendar year

(3) No semimonthly deposits. The Treasury Department and the IRS intend that the forthcoming proposed regulations would not apply § 40.6302(c)-1(a)(1) or any of the other semimonthly deposit rules in the Excise Tax Procedural Regulations to chapter 50A of the Code. Therefore, taxpayers liable for the § 5000D tax would not be required to make semimonthly deposits of § 5000D tax.

(4) Payment of tax: § 40.6151(a)-1. The Treasury Department and the IRS intend to propose that the deadline for payment of the § 5000D tax would be the same as the filing deadline for Form 720. Taxpayers liable for the § 5000D tax would, therefore, be required to pay the § 5000D tax when they file the Form 720 for the calendar quarter during which the § 5000D liability arose. See § 40.6071(a)-1(a).

SECTION 4. RELIANCE

Until the Treasury Department and the IRS issue further guidance, taxpayers may rely on section 3 of this notice.

SECTION 5. DRAFTING INFORMATION

This notice was authored by the Office of the Associate Chief Counsel (Passthroughs & Special Industries). For further information regarding this notice, contact Passthroughs & Special Industries at (202) 317-6855 (not a toll-free call).

[3] If any due date for filing Form 720 falls on a Saturday, Sunday, or legal holiday, the Form 720 would be due on the next business day. See § 301.7503-1 of the Procedure and Administration Regulations (26 CFR part 301).

EXHIBIT I

JOINT COMMITTEE ON TAXATION
November 19, 2021
JCX-46-21

ESTIMATED BUDGET EFFECTS OF THE REVENUE PROVISIONS OF TITLE XIII - COMMITTEE ON WAYS AND MEANS, OF H.R. 5376, THE "BUILD BACK BETTER ACT," AS PASSED BY THE HOUSE OF REPRESENTATIVES

Fiscal Years 2022 - 2031

[Millions of Dollars]

Provision	Effective	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-26	2022-31
SUBTITLE E - INFRASTRUCTURE FINANCING AND COMMUNITY DEVELOPMENT													
Part 1 - Low Income Housing Credit													
1. Increases in State allocations	cyba 12/31/21	-3	-20	-73	-252	-345	-359	-326	-264	-228	-213	-693	-2,083
2. Tax-exempt bond financing requirement (sunset 12/31/26)	[1]	-57	-200	-424	-736	-1,010	-1,062	-1,226	-1,291	-1,305	-1,307	-2,426	-8,617
3. Buildings designed to serve extremely low-income households	[2]	-7	-31	-75	-130	-183	-227	-275	-319	-362	-416	-426	-2,025
4. Repeal of qualified contract option	DOE	2	7	16	27	38	49	60	72	84	101	91	457
5. Modification and clarification of rights relating to building purchase	[3]	2	8	18	32	45	59	74	88	103	124	105	553
Total of Part 1 - Low Income Housing Credit		**-63**	**-236**	**-538**	**-1,058**	**-1,454**	**-1,540**	**-1,693**	**-1,715**	**-1,708**	**-1,712**	**-3,349**	**-11,716**
Part 2 - Neighborhood Homes Investment Act	**tyba 12/31/21**	**-192**	**-481**	**-1061**	**-1170**	**-1177**	**-1086**	**-494**	**-198**	**---**	**---**	**-4,082**	**-5,859**
Part 3 - Investments in Tribal Infrastructure													
1. Treatment of Indian Tribes as States with respect to bond issuance	oii cyba DOE	[4]	-1	-3	-4	-6	-8	-10	-12	-15	-17	-14	-77
2. New markets tax credit for Tribal Statistical Areas	cya 12/31/21	---	[4]	-2	-6	-13	-21	-29	-34	-37	-36	-22	-178
3. Inclusion of Indian areas as difficult development areas for purposes of certain buildings	bpisa 12/31/21	[4]	-2	-4	-8	-11	-13	-16	-18	-21	-24	-25	-117
Total of Part 3 - Investments in Tribal Infrastructure		**[4]**	**-3**	**-9**	**-18**	**-30**	**-42**	**-55**	**-64**	**-73**	**-77**	**-61**	**-372**
Part 4 - Other Provisions													
1. Possessions economic activity credit	[5]	-406	-853	-938	-1,017	-1,091	-1,169	-1,229	-1,270	-1,312	-1,356	-4,305	-10,641
2. Tax treatment of certain assistance to farmers, etc	[6]	*Estimate to be Provided by the Congressional Budget Office*											
3. Exclusion of amounts received from State-based catastrophe loss mitigation programs	tyba 12/31/20	-8	-10	-10	-11	-12	-13	-14	-15	-16	-17	-52	-126
Total of Part 4 - Other Provisions		**-414**	**-863**	**-948**	**-1,028**	**-1,103**	**-1,182**	**-1,243**	**-1,285**	**-1,328**	**-1,373**	**-4,357**	**-10,767**
TOTAL OF SUBTITLE E - INFRASTRUCTURE FINANCING AND COMMUNITY DEVELOPMENT		**-668**	**-1,583**	**-2,556**	**-3,274**	**-3,764**	**-3,850**	**-3,485**	**-3,262**	**-3,109**	**-3,162**	**-11,848**	**-28,715**

Provision	Effective	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-26	2022-31
SUBTITLE F - GREEN ENERGY													
THE "GROWING RENEWABLE ENERGY AND EFFICIENCY NOW (GREEN') ACT OF 2021"													
Part 1 - Renewable Electricity and Reducing Carbon Emissions													
1. Extension and modification of credit for electricity produced from certain renewable resources (sunset 12/31/26) [7]	fpisa 12/31/21 & ftcowba 12/31/21	-331	-1,087	-1,983	-3,014	-4,380	-5,846	-7,489	-9,306	-10,470	-10,981	-10,795	-54,887
2. Extension and modification of energy credit (sunset 12/31/26) [7]	generally ppisa 12/31/21	-769	-1,380	-1,565	-2,655	-5,946	-7,557	-7,587	-7,795	-8,194	-8,633	-12,315	-52,081
3. Increase in energy credit for solar facilities placed in service in connection with low-income communities (sunset 12/31/26)	1/1/22	*Estimate Included in Item F.1.2. Above*											
4. Elective payment for energy property and electricity produced from certain renewable resources, etc	tyba 12/31/21	*Estimate Included in Items F.1.1. through F.1.3. Above*											
5. Investment credit for electric transmission property (sunset 12/31/31) [7]	ppisa 12/31/21 & ptcowba 12/31/21	---	---	---	-788	-1,213	-1,213	-1,213	-2,001	-2,426	-2,425	-2,001	-11,279
6. Extension and modification of credit for carbon oxide sequestration (sunset 12/31/31)	foetcowba 12/31/21	-26	-103	-276	-426	-450	-222	-141	-161	-162	-160	-1,281	-2,128
7. Green energy publicly traded partnerships	tyba 12/31/21	-148	-126	-137	-144	-99	-50	-56	-64	-72	-80	-654	-975
8. Zero-emission nuclear power production credit (sunset 12/31/27) [7]	epasa 12/31/21 itybasd	-4,383	-2,909	-3,253	-3,524	-3,710	-3,838	-1,357	---	---	---	-17,779	-22,975
Total of Part 1 - Renewable Electricity and Reducing Carbon Emissions		**-5,657**	**-5,605**	**-7,214**	**-10,551**	**-15,798**	**-18,726**	**-17,843**	**-19,327**	**-21,324**	**-22,279**	**-44,825**	**-144,324**
Part 2 - Renewable Fuels													
1. Extension of incentives for biodiesel, renewable diesel and alternative fuels (sunset 12/31/26)	fsoua 12/31/21	-149	-2,688	-3,721	-3,802	-3,816	-1,028	---	---	---	---	-14,177	-15,205
2. Extension of second generation biofuel incentives (sunset 12/31/26)	qsgbpa 12/31/21	-10	-19	-20	-22	-24	-11	---	---	---	---	-95	-106
3. Sustainable aviation fuel credit (sunset 12/31/26)	fsoua 12/31/22	---	-7	-16	-24	-29	-13	---	---	---	---	-76	-90
4. Credit for production of clean hydrogen [7]	[8]	-70	-195	-347	-550	-785	-1,027	-1,283	-1,565	-1,681	-1,690	-1,947	-9,193
Total of Part 2 - Renewable Fuels		**-229**	**-2,909**	**-4,104**	**-4,398**	**-4,654**	**-2,079**	**-1,283**	**-1,565**	**-1,681**	**-1,690**	**-16,295**	**-24,594**
Part 3 - Green Energy and Efficiency Incentives for Individuals													
1. Extension, increase, and modifications of nonbusiness energy property credit (sunset 12/31/31)	generally ppisa 12/31/21 & apoia 12/31/21	-259	-1,681	-1,427	-1,402	-1,424	-1,405	-1,352	-1,377	-1,391	-1,405	-6,193	-13,123
2. Extension and modification of residential energy efficient property credit (sunset 12/31/31)	ema DOE	-46	-514	-1,216	-3,012	-3,098	-3,188	-3,283	-3,378	-3,459	-3,563	-7,886	-24,756
3. Energy efficient commercial buildings deduction (sunset 12/31/31)	tyba 12/31/21 & ppisa 12/31/21 ityeasd	-18	-72	-70	-68	-67	-66	-65	-66	-67	-69	-295	-626
4. Extension, increase, and modifications of new energy efficient home credit (sunset 12/31/31)	duaa 12/31/21	-132	-233	-258	-271	-289	-307	-321	-320	-305	-289	-1,182	-2,724
5. Modifications to income exclusion for conservation subsidies	ara 12/31/18	-6	-2	-2	-3	-4	-5	-6	-6	-7	-7	-17	-48

Provision	Effective	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-26	2022-31
6. Credit for qualified wildfire mitigation expenditures...........	epoia DOE ityeasd	-12	-28	-31	-36	-42	-44	-46	-48	-49	-50	-149	-387
Total of Part 3 - Green Energy and Efficiency Incentives for Individuals…...................		**-473**	**-2,530**	**-3,004**	**-4,792**	**-4,924**	**-5,015**	**-5,073**	**-5,195**	**-5,278**	**-5,383**	**-15,722**	**-41,664**
Part 4 - Greening the Fleet and Alternative Vehicles													
1. Refundable new qualified plug-in electric drive motor vehicle credit for individuals (sunset 12/31/31) [7].............	vaa 12/31/21 & vaa 12/31/22	-96	-494	-576	-709	-832	-1,001	-1,171	-1,304	-1,447	-1,559	-2,709	-9,192
2. Credit for previously-owned qualified plug-in electric drive motor vehicles (sunset 12/31/31)...	vaa 12/31/21	-33	-104	-119	-150	-166	-183	-202	-224	-247	-269	-572	-1,696
3. Qualified commercial electric vehicles (sunset 12/31/31).....	vaa 12/31/21	-79	-171	-235	-303	-396	-516	-624	-717	-808	-914	-1,184	-4,762
4. Qualified fuel cell motor vehicles (sunset 12/31/31)...........	ppisa 12/31/21	-4	-7	-8	-9	-11	-4	---	---	---	---	-40	-44
5. Alternative fuel refueling property credit (sunset 12/31/31)...	ppisa 12/31/21	-93	-404	-461	-523	-591	-666	-749	-837	-932	-1,027	-2,072	-6,283
6. Reinstatement and expansion of employer-provided fringe benefits for bicycle commuting [9].....................................	tyba 12/31/21	-20	-21	-23	-24	-16	-16	-18	-18	-19	-19	-103	-194
7. Credit for certain new electric bicycles (sunset 12/31/25)....	ppisa 12/21/21 ityeasd	-254	-683	-889	-1,157	-1,126	-8	-7	-6	-6	-4	-4,108	-4,139
Total of Part 4 - Greening the Fleet and Alternative Vehicles…......................................		**-579**	**-1,884**	**-2,311**	**-2,875**	**-3,138**	**-2,394**	**-2,771**	**-3,106**	**-3,459**	**-3,792**	**-10,788**	**-26,310**
Part 5 - Investment in the Green Workforce													
1. Extension of the advanced energy project credit [7][10]......	1/1/22	-1,476	-2,053	-1,184	-787	-796	-528	-380	-240	-169	-36	-6,296	-7,649
2. Labor costs of installing mechanical insulation property (sunset 12/31/25)..	apoia 12/31/21 ityeasd	-371	-745	-939	-1,099	-813	-532	-480	-428	-326	-207	-3,967	-5,940
3. Advanced manufacturing investment credit (sunset 12/31/25) [7]...	[11]	-1,501	-2,706	-2,931	-2,842	-913	115	130	145	151	157	-10,895	-10,197
4. Advanced manufacturing production credit (sunset 12/31/29) [7]...	cpasa 12/31/21	-214	-336	-348	-372	-401	-353	-256	-151	-40	---	-1,672	-2,472
Total of Part 5 - Investment in the Green Workforce…..		**-3,562**	**-5,840**	**-5,402**	**-5,100**	**-2,923**	**-1,298**	**-986**	**-674**	**-384**	**-86**	**-22,830**	**-26,258**
Part 6 - Qualified Environmental Justice Credit (sunset 12/31/31) [7][10]…..	**1/1/22**	**---**	**-400**	**-700**	**-800**	**-900**	**-1,000**	**-1,000**	**-1,000**	**-1,000**	**-1,000**	**-2,800**	**-7,800**
Part 7 - Reinstatement of Superfund…..	**7/1/22**	**290**	**1,229**	**1,280**	**1,323**	**1,357**	**1,390**	**1,424**	**1,459**	**1,494**	**1,530**	**5,479**	**12,776**
Part 8 - Incentives for Clean Electricity and Clean Transportation													
1. Clean electricity production credit [7].................................	[12]	---	---	---	---	---	---	-19	-546	-1,878	-3,558	---	-6,002
2. Clean electricity investment credit [7].................................	[12]	---	---	---	---	---	-723	-1,082	-8,774	-13,127	-13,519	---	-37,225
3. Increase in clean electricity investment credit for facilities placed in service in connection with low-income communities...	1/1/27	*Estimate Included in Item F.8.2. Above*											
4. Cost recovery for qualified facilities, qualified property, and grid improvement property..	fappisa 12/31/26	---	---	---	---	---	-26	-83	-134	-171	-211	---	-624
5. Clean fuel production credit [7]..	tfpa 12/31/26	---	---	---	---	---	-1,499	-2,104	-2,204	-2,320	-1,590	---	-9,716
Total of Part 8 - Incentives for Clean Electricity and Clean Transportation…...............		**---**	**---**	**---**	**---**	**---**	**-2,248**	**-3,288**	**-11,659**	**-17,496**	**-18,878**	**---**	**-53,567**
TOTAL OF SUBTITLE F - GREEN ENERGY…..		**-10,210**	**-17,940**	**-21,456**	**-27,193**	**-30,980**	**-31,369**	**-30,819**	**-41,067**	**-49,128**	**-51,578**	**-107,782**	**-311,741**

Provision	Effective	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-26	2022-31
SUBTITLE G - SOCIAL SAFETY NET													
Part 1 - Child Tax Credit: Extend and modify ARP modifications to CTC, income lookback for phase out, expanded safe harbor, fully advanced credit with MAGI limit, no child SSN requirement (sunset 12/31/22); no child SSN requirement, full refundability of CTC (not the $500 credit) (taxable years beginning after 12/31/22) [7]….	**tyba 12/31/21**	**-101,390**	**-28,936**	**-12,236**	**-11,714**	**-12,669**	**-3,604**	**-3,527**	**-3,503**	**-3,515**	**-3,551**	**-166,945**	**-184,646**
Part 2 - Earned Income Tax Credit													
1. Certain improvements to the earned income tax credit extended through 2022 [7].....	tyba 12/31/21	-578	-12,693	---	---	---	---	---	---	---	---	-13,271	-13,271
2. Funds for administration of earned income tax credits in the territories [7].....	pmf cyba 12/31/21	---	-5	-5	-5	-5	-5	-5	-5	-5	-5	-20	-45
Total of Part 2 - Earned Income Tax Credit….		**-578**	**-12,698**	**-5**	**-5**	**-5**	**-5**	**-5**	**-5**	**-5**	**-5**	**-13,291**	**-13,316**
Part 3 - Expanding Access to Health Coverage and Lowering Costs													
1. Improve affordability and reduce premium costs of health insurance for consumers (sunset 12/31/25).....	tyba 12/31/21	*Estimate to be Provided by the Congressional Budget Office*											
2. Modification of employer sponsored coverage affordability test in health insurance premium tax credit (sunset 12/31/25).....	tyba 12/31/21	*Estimate to be Provided by the Congressional Budget Office*											
3. Treatment of lump-sum Social Security benefits in determining household income.....	tyba 12/31/21	*Estimate to be Provided by the Congressional Budget Office*											
4. Temporary expansion of health insurance premium tax credits for certain low-income populations (sunset 12/31/25) [13].....	tyba 12/31/21	*Estimate to be Provided by the Congressional Budget Office*											
5. Special rule for individuals receiving unemployment compensation (sunset 12/31/22).....	tyba 12/31/21	*Estimate to be Provided by the Congressional Budget Office*											
6. Permanent credit for health insurance costs [7].....	cmba 12/31/21	-8	-18	-19	-20	-31	-44	-47	-49	-52	-56	-96	-344
7. Exclusion of certain dependent income for purposes of premium tax credit (sunset 12/31/26).....	tyba 12/31/22	*Estimate to be Provided by the Congressional Budget Office*											
8. Requirements with respect to cost-sharing for certain insulin products.....	pybo/a 1/1/23	*Estimate to be Provided by the Congressional Budget Office*											
9. Oversight of pharmacy benefit manager services.....	pybo/a 1/1/23	*Estimate to be Provided by the Congressional Budget Office*											
Total of Part 3 - Expanding Access to Health Coverage and Lowering Costs….		**-8**	**-18**	**-19**	**-20**	**-31**	**-44**	**-47**	**-49**	**-52**	**-56**	**-96**	**-344**
Part 4 - Pathway to Practice Training Programs - Establishing rural and underserved pathway to practice training programs for post-baccalaureate students, medical students, and medical residents [7]….	**tyba DOE**	**---**	**---**	**-74**	**-165**	**-262**	**-387**	**-589**	**-844**	**-1,136**	**-1,420**	**-500**	**-4,877**

Provision	Effective	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-26	2022-31
Part 5 - Higher Education													
1. Credit for public university research infrastructure	qccma 12/31/21	-33	-37	-36	-36	-26	-9	---	---	---	---	-168	-177
2. Treatment of Federal Pell Grants for income tax purposes (sunset 12/31/25) [7]	tyba 12/31/21	-6	-229	-225	-215	-205	---	---	---	---	---	-880	-880
3. Repeal of denial of American Opportunity Tax Credit on basis of felony drug conviction [7]	tyba 12/31/21	-3	-21	-21	-20	-20	-20	-20	-19	-18	-18	-85	-180
Total of Part 5- Higher Education		**-42**	**-287**	**-282**	**-271**	**-251**	**-29**	**-20**	**-19**	**-18**	**-18**	**-1,133**	**-1,237**
Part 6 - Limit Itemized Deductions for State and Local Taxes to $80,000	**tyba 12/31/20**	**-52,133**	**-51,827**	**-54,028**	**-56,277**	**-15,733**	**44,182**	**40,129**	**41,607**	**43,198**	**75,677**	**-229,998**	**14,795**
TOTAL OF SUBTITLE G - SOCIAL SAFETY NET		**-154,151**	**-93,766**	**-66,644**	**-68,452**	**-28,951**	**40,113**	**35,941**	**37,187**	**38,472**	**70,627**	**-411,963**	**-189,625**
SUBTITLE H - RESPONSIBLY FUNDING OUR PRIORITIES													
Part 1 - Corporate and International Tax Reforms													
A. Corporate Provisions													
1. Corporate alternative minimum tax	tyba 12/31/22	4,481	55,753	49,165	32,588	24,695	22,747	25,789	30,535	34,969	38,189	166,682	318,911
2. Excise tax on repurchase of corporate stock	rosa 12/31/21	8,212	11,782	12,011	12,343	13,149	13,632	13,569	13,208	13,051	13,267	57,497	124,226
B. Limitations on Deduction for Interest Expense	tyba 12/31/22	---	1,520	3,123	3,285	3,254	3,173	3,279	3,398	3,435	3,430	11,182	27,896
C. Outbound International Provisions													
1. Modifications to deduction for foreign-derived intangible income and global intangible low-taxed income	[14]	---	12,597	26,422	28,687	20,624	11,481	11,432	11,109	11,000	10,926	88,330	144,278
2. Repeal of election for 1-month deferral in determination of taxable year of specified foreign corporations	tyosfcba 11/30/22	---	3,353	3,353	[15]	---	---	---	---	---	---	6,706	6,706
3. Modifications of foreign tax credit rules applicable to certain taxpayers receiving specific economic benefits	apoaa 12/31/21	217	438	469	619	802	769	903	941	772	791	2,545	6,721
4. Modifications to foreign tax credit limitations	[16]	-18	698	1,621	2,010	2,006	1,597	1,207	966	850	1,064	6,317	12,000
5. Foreign oil and gas extraction income and foreign oil related income to include oil shale and tar sands	tyba 12/31/21	*Estimate Included in Item H.1.C.6. Below*											
6. Modifications to inclusion of global intangible low-taxed income	[17]	150	1,273	4,102	6,175	5,997	5,896	6,837	8,022	8,838	9,691	17,697	56,980
7. Modifications to determination of deemed paid credit for taxes properly attributable to tested income	[18]	---	-1,514	-3,155	-3,250	-3,057	-3,022	-3,194	-3,350	-3,397	-3,255	-10,976	-27,194
8. Deduction for foreign source portion of dividends limited to controlled foreign corporations, etc	[19]	21	42	44	45	46	48	49	51	52	54	198	451
9. Limitation on foreign base company sales and services income	[20]	9	814	1,754	1,913	1,534	1,144	1,162	1,190	1,232	1,287	6,025	12,041
D. Inbound International Provisions													
1. Modifications to base erosion and anti-abuse tax	tyba 12/31/21	-1,633	-2,531	1,529	7,233	9,260	9,412	10,191	10,578	11,144	11,904	13,858	67,088
E. Other Business Tax Provisions													
1. Credit for clinical testing of orphan drugs limited to first use or indication	tyba 12/31/21	88	186	208	234	260	286	314	346	380	418	975	2,720
2. Modifications to treatment of certain losses	lai tyba 12/31/21 & lo/a DOE	25	165	172	179	186	193	201	209	217	226	726	1,773
3. Adjusted basis limitation for divisive reorganization	roo/a DOE	689	1,294	1,769	1,917	1,944	1,975	2,006	2,037	2,069	2,103	7,613	17,803

Provision	Effective	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-26	2022-31
4. Rents from prison facilities not treated as qualified income for purposes of REIT income tests	tyba 12/31/21	5	9	10	10	6	3	3	3	3	3	40	55
5. Modifications to exemption for portfolio interest	oia DOE	576	876	405	118	25	20	16	13	10	8	2,000	2,067
6. Certain partnership interest derivatives	pma 12/31/22	4	9	9	9	9	10	10	10	10	10	41	90
7. Adjustments to earnings and profits of controlled foreign corporations	[21]	150	325	375	425	475	525	575	625	675	725	1,750	4,875
8. Certain dividends from controlled foreign corporations to United States shareholders treated as extraordinary dividends	[22]	*Estimate Included in Item H.1.C.4. Above*											
9. Limitation on certain special rules for section 1202 gains	generally saeoa 9/13/21	69	470	517	572	639	698	705	710	677	661	2,267	5,718
10. Constructive sales	generally csa DOE	*Estimate Included in Item H.1.E.12. Below*											
11. Rules relating to common control	tyba 12/31/21	628	1,267	1,276	1,313	1,434	1,601	1,788	2,011	2,248	2,457	5,919	16,023
12. Modification of wash sale rules	sdata 12/31/21	3,226	4,946	2,725	1,626	1,074	804	653	587	562	559	13,597	16,762
13. Research and experimental expenditures (sunset 12/31/25)	DOE	-29,091	-39,856	-32,161	-24,133	19,284	38,009	29,958	19,853	9,269	4,851	-105,956	-4,016
Total of Part 1 - Corporate and International Tax Reforms		**-12,192**	**53,916**	**75,743**	**73,918**	**103,646**	**111,001**	**107,453**	**103,052**	**98,066**	**99,369**	**295,033**	**813,974**
Part 2 - Tax Increases for High-Income Individuals													
1. Application of net investment income tax to trade or business income of certain high income individuals	tyba 12/31/21	12,742	19,543	21,734	24,050	25,861	27,966	28,997	29,675	30,439	31,156	103,930	252,163
2. Limitations on excess business losses of noncorporate taxpayers made permanent, with carryforward modification	tyba 12/31/20	3,127	2,046	2,123	2,204	2,288	21,665	31,221	30,130	31,909	33,563	11,788	160,276
3. Surcharge on high income individuals, estates, and trusts (initial surtax on AGI of 5% in excess of $10,000,000 and additional surtax of 3% on AGI in excess of $25,000,000)	tyba 12/31/21	40,035	-18,667	22,215	23,436	24,332	24,223	25,465	27,540	28,779	30,413	91,350	227,771
Total of Part 2 - Tax Increases for High-Income Individuals		**55,904**	**2,922**	**46,072**	**49,690**	**52,481**	**73,854**	**85,683**	**87,345**	**91,127**	**95,132**	**207,068**	**640,210**
Part 3 - Modifications of Rules Relating to Retirement Plans													
A. Limitations on High-Income Taxpayers with Large Retirement Account Balances													
1. Contribution limit for individual retirement plans of high-income taxpayers with large account balances	tyba 12/31/28 & pyba 12/31/28	*Estimate Included in Item H.3.A.2. Below*											
2. Increase in minimum required distributions for high-income taxpayers with large retirement account balances	tyba 12/31/28 & pyba 12/31/28	---	---	---	---	---	---	---	3,269	2,713	1,362	---	7,344
B. Other Provisions Relating to Individual Retirement Plans													
1. Tax treatment of rollovers to Roth IRAs and accounts	[23]	73	151	177	195	211	227	239	251	322	878	808	2,724
2. Statute of limitations with respect to IRA noncompliance	[24]	[15]	1	1	1	1	1	1	1	1	1	3	7
3. IRA owners treated as disqualified persons for purposes of prohibited transaction rules	toa 12/31/21	---	1	1	1	1	1	2	2	2	2	5	13
Total of Part 3 - Modifications of Rules Relating to Retirement Plans		**73**	**153**	**179**	**196**	**213**	**229**	**241**	**3,522**	**3,038**	**2,242**	**815**	**10,087**

Provision	Effective	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-26	2022-31
Part 4 - Funding the Internal Revenue Service and Improving Taxpayer Compliance													
1. Enhancement of Internal Revenue Service resources	DOE	*Estimate to be Provided by the Congressional Budget Office*											
2. Application of backup withholding with respect to third party network transactions	cyba 12/31/21	-2	-1	[4]	[4]	[4]	[4]	[4]	[4]	[4]	[4]	-3	-4
3. Modification of procedural requirements relating to assessment of penalties	[25]	201	221	113	116	119	122	125	128	132	135	771	1,414
Total of Part 4 - Funding the Internal Revenue Service and Improving Taxpayer Compliance		**199**	**220**	**113**	**116**	**119**	**122**	**125**	**128**	**132**	**135**	**768**	**1,410**
Part 5 - Other Provisions													
1. Modifications to limitation on deduction of excessive employee remuneration	tyba 12/31/21	315	639	656	674	683	692	868	881	893	905	2,966	7,205
2. Extension of tax to fund Black Lung Disability Trust Fund [26]	sa 12/31/21	101	137	135	131	32	---	---	---	---	---	536	536
3. Prohibited transactions relating to holding DISC or FSC in individual retirement account	saoiaoho/a 12/31/21	39	95	126	157	187	217	249	277	292	301	605	1,940
4. Clarification of treatment of DISC gain and distributions of certain foreign shareholders	goda 12/31/21	41	86	92	95	96	97	99	101	103	106	410	915
5. Treatment of certain qualified sound recording productions [27]	pci tyea DOE	-310	-59	6	43	112	86	43	21	11	12	-208	-35
6. Payment to certain individuals who dye fuel	[28]	[4]	[4]	[4]	[4]	[4]	[4]	[4]	[4]	[4]	[4]	-2	-4
7. Treatment of financial guaranty insurance companies as qualifying insurance corporations under passive foreign investment company rules	tyba 12/31/17 & rma DOE	[4]	-2	-4	-5	-8	-9	-12	-14	-14	-14	-18	-81
8. Extension of period of limitation for certain legally married couples	DOE	-33	-22	---	---	---	---	---	---	---	---	-55	-55
9. Allow an above-the-line deduction of up to $250 in union dues paid (sunset 12/31/25)	tyba 12/31/21	-66	-442	-442	-443	-377	---	---	---	---	---	-1,770	-1,770
10. Temporary increase in employer-provided child care credit (sunset 12/31/25)	tyba 12/31/21	-30	-41	-42	-43	-11	---	---	---	---	---	-166	-166
11. Payroll credit for compensation of local news journalists (sunset 12/31/26)	cqba DOE	-207	-366	-310	-308	-320	-162	---	---	---	---	-1,511	-1,674
12. Allow an above-the-line deduction of up to $250 for employee uniforms (sunset 12/31/24)	tyba 12/31/21	-111	-742	-756	-650	---	---	---	---	---	---	-2,259	-2,259
13. Expenses in contingency fee cases	apiori tyba DOE	-172	-659	-532	-390	-231	-101	-105	-101	-95	-66	-1,985	-2,453
14. Increase in research credit against payroll tax for small businesses	tyba 12/31/21	-51	-81	-85	-89	-94	-98	-102	-107	-111	-113	-401	-932
15. Imposition of tax on nicotine	[29]	180	1129	1173	1126	1028	940	865	792	720	654	4,635	8,606
16. Termination of employer credit for paid family and medical leave [30]	tyba 12/31/23	---	---	101	219	168	77	44	26	7	---	489	642
Total of Part 5 - Other Provisions		**-304**	**-328**	**118**	**517**	**1,265**	**1,740**	**1,949**	**1,876**	**1,806**	**1,785**	**1,266**	**10,415**
TOTAL OF SUBTITLE H - RESPONSIBLY FUNDING OUR PRIORITIES		**43,680**	**56,883**	**122,225**	**124,437**	**157,725**	**186,945**	**195,452**	**195,923**	**194,169**	**198,663**	**504,950**	**1,476,096**

Provision	Effective	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-26	2022-31
SUBTITLE I - DRUG PRICING: Selected Drug Manufacturer Excise Tax Imposed During Noncompliance Periods….....	**sa DOE**	*No Revenue Effect*											
NET TOTAL …….		**-121,349**	**-56,406**	**31,569**	**25,519**	**94,030**	**191,839**	**197,088**	**188,781**	**180,404**	**214,550**	**-26,643**	**946,015**

Joint Committee on Taxation

NOTE: Details may not add to totals due to rounding. The date of enactment is assumed to be December 1, 2021.

Legend for "Effective" column:

apiori = amounts paid, incurred, or received in
apoia = amounts paid or incurred after
apoaa = amounts paid or accrued after
ara = amounts received after
bpisa = buildings placed in service after
cpasa = components produced and sold after
cqba = calendar quarters beginning after
csa = constructive sales after
cya = calendar years after
cyba = calendar years beginning after
da = days after
DOE = date of enactment
duaa = dwelling units acquired after
ema = expenditures made after
epasa = electricity produced and sold after
epoia = expenditures paid or incurred after
fappisa = facilities and property placed in service after
foetcowba = facilities or equipment the construction of which begins after
fpisa = facilities placed in service after
fsoua = fuel sold or used after
ftcowba = facilities the construction of which begins after
goda = gains or distributions after
itybasd = in taxable years beginning after such date
ityeasd = in taxable years ending after such date
lai = losses arising in
lii = losses incurred in
lo/a = liquidations on or after
oia = obligations issued after
oii = obligations issued in
pa = periods after
pci = productions commencing in
pmf = payments made for
pma = payments made after
ppisa = property placed in service after
ptcowba = property the construction of which begins after
pybo/a = plan years beginning on or after
roo/a = reorganizations occurring on or after
rosa = repurchases of stock after
rma = reports made after
qccma = qualified cash contributions made after
qsgbpa = qualified second generation biofuel production after
sa = sales after
saeoa = sales and exchanges only after
saoiaoho/a = stock and other interests acquired or held on or after
sdata = sales, dispositions, and terminations after
tfpa = transportation fuel produced after
toa = transactions occurring after
too/a = transfers occurring on or after
tyba = taxable years beginning after
tyea = taxable years ending after
tyosfcba = taxable years of specified foreign corporations beginning after
vaa = vehicles acquired after

[1] Effective for buildings some portion of which, or of the land on which the building is located, is financed by an obligation which is described in section 42(h)(4)(A) and which is part of an issue the issue date of which is after December 31, 2021.

[2] Effective for allocations of housing credit dollar amount after December 31, 2021, and for buildings that are described in section 42(h)(4)(B) taking into account only obligations that are part of an issue the issue date of which is after December 31, 2021.

[3] The amendments made by subsections (a) and (c) shall apply to agreements entered into or amended after the date of the enactment. The amendments made by subsection (b) shall apply to agreements among the owners of the project (including partners, members, and their affiliated organizations) and persons described in section 42(i)(7)(A) of the Internal Revenue Code of 1986 entered in of the Internal Revenue Code of 1986 entered into before, on, or after the date of the enactment.

[4] Loss of less than $500,000.

[5] Applies to taxable years beginning after the date of the enactment of this Act, and in the case of a qualified corporation that is foreign corporation, to taxable years beginning after the date of enactment and to taxable years of United States shareholders in which or with which taxable years of foreign corporations end. The credit is not available for taxable years beginning after December 31, 2031.

[6] Effective as if included in sec. 1005 of the American Rescue Plan Act of 2021 (Public Law 117-2).

[7] Estimate contains the following outlay effects:

	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-26	2022-31
Credit for electricity produced from certain renewable resources (sunset /12/31/26)……	87	281	498	825	1,375	2,008	2,712	3,489	4,229	5,064	3,066	20,568
Extension and modification of energy credit (sunset 12/31/26)….....	369	663	751	1,274	2,854	3,627	3,642	3,741	3,933	4,144	5,911	24,999
Investment credit for electric transmission property (sunset 12/31/31)….....	---	---	---	328	504	504	504	832	353	---	832	3,024

[Footnotes for JCX-46-21 continue on the following pages]

Footnotes for JCX-46-21 continued:

[7] Estimate contains the following outlay effects (continued):	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-26	2022-31
Zero-emission nuclear power production credit (sunset 12/31/27)	2,104	1,396	1,562	1,692	1,781	1,842	651	---	---	---	8,534	11,028
Credit for production of clean hydrogen	34	87	143	220	311	409	518	640	684	677	795	3,723
Refundable new qualified plug-in electric drive motor vehicle credit for individuals (sunset 12/31/31)	55	62	70	82	98	117	130	145	159	159	367	1,077
Extension of the advanced energy project credit	708	986	569	378	382	253	183	115	81	17	3,022	3,672
Advanced manufacturing investment credit (sunset 12/31/25)	627	1,130	1,223	1,186	1,116	349	---	---	---	---	5,282	5,632
Advanced manufacturing production tax credit (sunset 12/31/29)	93	147	152	162	175	154	112	66	17	---	730	1,079
Qualified environmental justice credit (sunset 12/31/31)	---	380	665	760	855	950	950	950	950	950	2,660	7,410
Clean electricity production credit	---	---	---	---	---	---	9	262	901	1,708	---	2,881
Clean electricity investment credit	---	---	---	---	---	347	519	4,212	6,301	6,489	---	17,868
Clean fuel production credit	---	---	---	---	---	720	1,010	1,058	1,113	763	---	4,664
Child tax credit	78,647	21,355	12,236	11,714	12,669	3,604	3,527	3,503	3,515	3,551	136,621	154,322
Certain improvements to the earned income tax credit extended through 2022	---	10,381	---	---	---	---	---	---	---	---	10,381	10,381
Funds for administration of earned income tax credits in the territories	---	5	5	5	5	5	5	5	5	5	20	45
Permanent credit for health insurance costs	5	7	8	8	15	18	19	20	21	22	43	143
Federal Pell Grants excluded from gross income	---	167	159	153	150	---	---	---	---	---	629	629
Repeal of denial of American Opportunity Tax Credit on basis of felony drug conviction	---	6	6	6	6	6	6	5	5	5	23	50
Establishing rural and underserved pathway to practice training programs for post-baccalaureate students, medical students, and medical residents [31]	---	---	37	82	131	205	370	614	899	1,176	250	3,514

[8] Effective for hydrogen produced after December 31, 2021, at facilities for which construction commenced on or before December 31, 2028; for facilities the construction of which begins after December 31, 2021, for electricity produced after December 31, 2021, for property placed in service after December 31, 2021, and, for any property the construction of which begins prior to January 1, 2022, only to the extent of the basis thereof attributable to the construction, reconstruction, or erection after December 31, 2026.

[9] Estimate includes the following budget effects:	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-26	2022-31
Total Revenue Effect	-20	-21	-23	-24	-16	-16	-18	-18	-19	-19	-103	-194
On-budget effects	-12	-13	-14	-15	-9	-10	-10	-11	-11	-12	-63	-117
Off-budget effects	-8	-8	-9	-9	-6	-7	-7	-7	-8	-8	-40	-77

[10] Annual base allocation amounts end 2031, unused amounts may be reallocated through 2036.

[11] Effective for property placed in service after December 31, 2021, and, for any property the construction of which begins prior to January 1, 2022, only to the extent of the basis thereof attributable to the construction, reconstruction, or erection after December 31, 2021.

[12] Effective for property placed in service after December 31, 2026, and, for any property the construction of which begins prior to January 1, 2027, only to the extent of the basis thereof attributable to the construction, reconstruction, or erection after December 31, 2026.

[13] For purposes of this subsection, the term 'termination date' means the later of January 1, 2025, or the date on which the Secretary of Health and Human Services makes a written certification to the Secretary that the Secretary of Health and Human Services has fully implemented the program described in section 1948.

[14] Generally applies to tyba 12/31/22, except that certain other modifications apply to taxable years beginning after the date of enactment.

[15] Gain of less than $500,000.

[16] Generally effective for taxable years beginning after December 31, 2022, with the following exceptions: changes with respect to foreign tax credit carryback or carryover are effective for taxes paid or accrued in taxable years beginning after December 31, 2022; changes to the treatment of certain asset dispositions are generally effective for transactions after the date of enactment; changes to elections of claims or deductions are effective for taxes paid or accrued for taxable years beginning after December 31, 2021; changes related to redeterminations of foreign taxes are effective for changes that occur 60 days or more after DOE; and changes to the special limitations period are effective for taxes paid, accrued or deemed paid in in taxable years beginning after December 31, 2021.

[Footnotes for JCX-46-21 continue on the following page]

Footnotes for JCX-46-21 continued:

[17] Generally applies to taxable years of foreign corporations beginning after December 31, 2022, and to taxable years of United States shareholders in which or with which such taxable years of foreign corporations end, except that changes to regulatory authority and coordination with other provisions apply to taxable years of foreign corporations beginning after date of enactment, and to taxable years of United States shareholders in which or with which such taxable years of foreign corporations end.

[18] Generally applies to taxable years of foreign corporations beginning after December 31, 2021 2022, and to taxable years of United States shareholders in which or with which such taxable years of foreign corporations end, except that changes to the application of the foreign tax credit limitation to amounts included under section 78 and the disallowance of foreign tax credit and deduction with respect to distributions of previously taxed global intangible low-taxed income apply to taxable years of foreign corporations beginning after date of enactment, and to taxable years of United States shareholders in which or with which such taxable years of foreign corporations end.

[19] Generally applies to distributions made after date of enactment, exception that modifications related to the determination of status as controlled foreign corporation apply to taxable years of foreign corporations beginning after the date of the enactment, and taxable years of United States persons in which or with which such taxable years of foreign corporations end.

[20] Applies to taxable years of foreign corporations beginning after December 31, 2021, and to taxable years of United States shareholders in which or with which such taxable years of foreign corporations end.

[21] Applies to taxable years of foreign corporations ending after the date of enactment, and to taxable years of United States shareholders in which or with which such taxable years of foreign corporations end.

[22] Applies to dividends paid (or amounts treated as dividends) after the date of enactment.

[23] The amendments made by subsection (a) shall apply to distributions, transfers, and contributions made after December 31, 2021. The amendments made by subsection (b) shall apply to distributions, transfers, and contributions made in taxable years beginning after December 31, 2031.

[24] Applicable for taxes with respect to which the 3-year period under section 6501(a) of the Internal Revenue Code of 1986 (without regard to the amendment made by this section) ends after December 31, 2021.

[25] Repeal of Internal Revenue Code section 6751(b) is effective as if included in section 3306 of the Internal Revenue Service Restructuring and Reform Act of 1998. Quarterly certifications of compliance with procedural requirements apply to notices of penalty issued after date of enactment.

[26] The temporary increase in the amount of tax on coal terminates for sales after December 31, 2025.

[27] Sunsets 12/31/25 (section 181) and 12/31/26 (section 168(k)).

[28] Effective for eligible indelibly dyed diesel fuel or kerosene removed on or after the date which is 180 days after the date of enactment.

[29] The amendments made by this section shall apply to articles removed in calendar quarters beginning after the date which is 180 days after the date of enactment.

[30] Estimate includes the following budget effects:

	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2022-26	2022-31
Total Revenue Effect	---	---	101	219	168	77	44	26	7	---	489	642
On-budget effects	---	---	107	227	171	77	44	26	7	---	505	659
Off-budget effects	---	---	-6	-8	-2	---	---	---	---	---	-17	-17

[31] Outlays arising from Medicare funding of residency positions are provided by the Congressional Budget Office.

EXHIBIT J

Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau OMB No. 0915-0327; Expiration Date: 08/31/2019

General Instructions for Completing the Pharmaceutical Pricing Agreement (PPA)

In accordance with the guidance found in the May 7, 1993, *Federal Register*, (link here) Section 340B provides that a manufacturer who sells covered outpatient drugs to eligible entities must sign a pharmaceutical pricing agreement (the "Agreement") with the Secretary of Health and Human Services (the "Secretary") in which the manufacturer agrees to charge a price for covered outpatient drugs that will not exceed the average manufacturer price ("AMP") decreased by a rebate percentage.

Manufacturer is defined in the guidance listed above, as follows:
The term "Manufacturer" has the meaning as set forth in section 1927(k)(5) of the Social Security Act and includes all entities engaged in –

(1) the production, preparation, propagation, compounding, conversion, or processing of prescription drug products, either directly or indirectly by extraction from substances of natural origin, or independently by means of chemical synthesis, or by a combination of extraction and chemical synthesis, or

(2) the packaging, repackaging, labeling, relabeling, or distribution of prescription drug products. A manufacturer must hold legal title to or possession of the NDC number for the covered outpatient drug. Such term does not include a wholesale distributor of drugs or a retail pharmacy licensed under State law.

"Manufacturer" also includes an entity, described in (1) or (2) above, that sells outpatient drugs to covered entities, whether or not the manufacturer participates in the Medicaid rebate program. Furthermore, the Pharmaceutical Pricing Agreement provides that the term also includes any contractor who fulfills the responsibilities pursuant to the PHS drug pricing agreement.

Please print the attached Pharmaceutical Pricing Agreement (PPA) in its entirety and have it signed by a corporate officer, such as the Chief Executive Officer. The form utilizes Adobe Acrobat Reader in an interactive format allowing you to input all applicable information on the computer. However, the form cannot be saved with your information for future use. You must print the form to submit it to the Office of Pharmacy Affairs Branch (OPA).

If your organization would like to receive a signed original, please ensure that you submit TWO signed originals to the OPA. Otherwise, the OPA will send you a copy of the document once it is counter-signed by the Associate Administrator, Healthcare Systems Bureau, Health Resources and Services Administration.

If you have any questions, please contact the 340B Prime Vendor at 1-888-340-2787 or via email at ApexusAnswers@340BPVP.com.

Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau OMB No. 0915-0327;
Expiration Date: 08/31/2019

PHARMACEUTICAL PRICING AGREEMENT
(hereinafter referred to as the "Agreement")
Between
THE SECRETARY OF HEALTH AND HUMAN SERVICES
(hereinafter referred to as the "Secretary") and
THE MANUFACTURER
Identified in Section IX of this Agreement
(hereinafter referred to as the "Manufacturer")

The Secretary, on behalf of the Department of Health and Human Services, and the Manufacturer for purposes of section 602 of the Veterans Health Care Act of 1992, Public Law No. 102-585, which enacted section 340B of the Public Health Service Act (hereinafter referred to as "the Act"), 42 U.S.C. 256b, hereby agree to the following:

I. Definitions

The terms defined in this section will, for the purposes of this agreement, have the meanings specified in the Act and section 1927(k) of the Social Security Act, as interpreted and applied herein:

(a) **"Average Manufacturer Price (hereinafter referred to as the "AMP")"** means the average unit price paid to the Manufacturer for the drug in all States by wholesalers for drugs distributed to the retail pharmacy class of trade, after deducting customary prompt pay discounts (excluding direct sales to hospitals, health maintenance organizations and to wholesalers where the drug is relabeled under the distributor's national drug code number). Federal Supply Schedule prices are not included in the calculation of AMP. AMP includes cash discounts allowed and all other price reductions (other than rebates under section 1927 of the Social Security Act), which reduce the actual price paid. It is calculated as a weighted average of each drug of prices for all the Manufacturer's package sizes for each calendar quarter. Specifically, it is calculated as net sales divided by the numbers of units sold, excluding free goods (i.e., drugs or any other items given away, but not contingent on any purchase requirements). For bundled sales, the allocation of the discount is made proportionately to the dollar value of the units of each drug sold under the bundled arrangements. The AMP for a calendar quarter must be adjusted by the Manufacturer, if cumulative discounts or other arrangements subsequently adjust the prices actually realized.

(b) **"Best Price"** has the meaning given it in section 1927(c)(1)(C) of the Social Security Act, and section I(d) of the Medicaid Rebate Agreement.

(c) **"Bundled Sale"** refers to the packaging of drugs of different types where the total price for the package is less than the purchase price of the drugs, if purchased separately.

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(d) **"Covered Drug"** means an outpatient drug as set forth in section 1927(k) of the Social Security Act. For purposes of coverage under the Agreement, all covered outpatient drugs are identified by the NDC number.

(e) **"Covered Entity"** means:

(1) certain Public Health Service grantees, "look-alike" Federally Qualified Health Centers and disproportionate share hospitals as described in section 340B(a)(4) of the Act; and

(2) in the case of a covered entity that is a distinct part of a hospital, the hospital itself shall not be considered a covered entity unless it meets the requirements of section 340B(a)(4)(L) of the Act, as determined by the Secretary.

(f) **"Manufacturer"** has the meaning as set forth in section 1927(k)(5) of the Social Security Act except that, for purposes of the Agreement, it shall also mean the entity holding legal title to or possession of the NDC number for the covered outpatient drug. The term includes:

(1) any Manufacturer who sells covered outpatient drugs to covered entities, whether or not the Manufacturer participates in the Medicaid rebate program; and

(2) any contractors which fulfill the responsibilities pursuant to the Agreement, unless excluded by the Secretary.

(g) **"Centers for Medicare and Medicaid Services (CMS) (formerly the Health Care Financing Administration)"** means the agency of the Department of Health and Human Services having the delegated authority to administer the Medicaid and Medicare Programs.

(h) **"Medicaid Rebate Program and Medicaid Rebate Agreement"** mean, respectively, the program, and a signed agreement between the Secretary and the Manufacturer, to implement the provisions of section 1927 of the Social Security Act.

(i) **"National Drug Code (NDC)"** means the identifying drug number maintained by the Food and Drug Administration (FDA). For purposes of the Agreement, the NDC number will be used including labeler code (which is assigned by the FDA and identifies the establishment), product code (which identifies the specified product or formulation), and package size code when reporting requested information.

(j) **"Over the Counter Drug"** means a drug that may be sold without a

prescription and which is prescribed by a physician (or other persons authorized to prescribe such drugs under State law).

(k) **"Quarter"** means a calendar quarter unless otherwise specified.

(l) **"Rebate Percentage"** means an amount (expressed in a percentage) equal to the average total rebate required under section 1927(c) of the Social Security Act with respect to each dosage, form, and strength of a single source or innovator multiple source drug during the preceding calendar quarter; divided by the AMP for such a unit of the drug during such quarter.

(m) **"the Secretary"** means the Secretary of Health and Human Services, or any successor thereto, or any officer or employee of the Department of Health and Human Services or successor agency to whom the authority to implement this agreement has been delegated.

(n) **"Unit of the Drug"** means a drug unit in the lowest identifiable amount (e.g., tablet or capsule for solid dosage forms, milliliter for liquid forms, gram for ointments or creams). The Manufacturer will specify the unit associated with each covered outpatient drug, as part of the submission of data, in accordance with the Secretary's instructions provided pursuant to Section II of the Agreement.

(o) **"Wholesaler"** means any entity, having a wholesale distributor's license, to which a Manufacturer sells the covered outpatient drug, but which does not relabel or repackage the covered outpatient drug.

II. MANUFACTURER'S RESPONSIBILITIES

Pursuant to requirements under section 340B of the Act, the Manufacturer agrees to the following:

(a) for single source and innovator multiple source drugs, to charge covered entities a price for each unit of the drug that does not exceed an amount equal to the AMP for the covered outpatient drug reported (or which would have been reported had the Manufacturer participated in the Medicaid rebate program) to the Secretary in accordance with the Manufacturer's responsibilities under section 1927(b)(3) of the Social Security Act, reduced by the rebate percentage;

(b) for multiple source, noninnovator multiple source, and over the counter drugs, the AMP is reduced by 11%, as described in 1927(c)(3)(B)(ii) of the Social Security Act;

(c) for those Manufacturers that do not have a reporting requirement under section 1927(b)(3) of the Social Security Act for covered outpatient drugs, to submit to the Secretary upon request, a list of such covered outpatient drugs, and the AMP,

baseline AMP, and the Best Price of such covered outpatient drugs;

(d) to retain all records that may be necessary to provide the information described in paragraph (c) of this section for not less than 3 years from the date of their creation;

(e) to afford the Secretary or his designee reasonable access to records of the Manufacturer relevant to the Manufacturer's compliance with the terms of the Agreement;

(f) to permit CMS to share AMP and unit rebate amount submitted under the Medicaid Rebate Agreement on covered outpatient drugs with the Secretary or his designee for purposes of carrying out the Agreement; and

(g) to participate in the HRSA Prime Vendor Program as provided by section 340B(a)(8) of the Act unless otherwise agreed to by the Secretary.

III. SECRETARY'S RESPONSIBILITIES

Pursuant to the requirements under section 340B of the Act, the Secretary agrees to the following:

(a) to make available a list of covered entities on the HRSA Office of Pharmacy Affairs web site (http://www.bphc.hrsa.gov/opa/), or otherwise, for access by participating Manufacturers, covered entities, State Medicaid agencies, and the general public. This information will be updated, to the extent practicable, on a quarterly basis;

(b) with respect to a covered entity that bills Medicaid using a cost basis for drug purchases, to require the entity to submit its pharmacy Medicaid provider number. The Secretary shall provide respective State Medicaid agencies with the list of such entities and their Medicaid provider numbers. Based on these provider numbers, the State agencies will create an exclusion file which will exclude data from these entities when generating Medicaid rebate requests.

(c) to require each covered entity to retain purchasing and dispensing records of covered outpatient drugs under the Agreement and of any claims for reimbursement submitted for such drugs under Title XIX of the Social Security Act for not less than 3 years.

Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau OMB No. 0915-0327;
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IV. DISPUTE RESOLUTION

(a) If the Manufacturer believes that a covered entity has violated the prohibition against resale or transfer of covered outpatient drugs, section 340B(a)(5)(B), or the prohibition against duplicate discounts or rebates, section 340B(a)(5)(A), the Manufacturer can access the elective dispute resolution process in the following manner:

(1) The Manufacturer shall attempt in good faith to resolve the matter with the covered entity.

(2) If unable to resolve the dispute, the Manufacturer may provide written notice of the discrepancy to the Secretary.

(3) The Secretary, at his discretion, will initiate an informal dispute resolution process.

(4) If the Secretary finds, after conclusion of the dispute resolution process, that the entity is in violation of such prohibitions, the entity shall be liable to the Manufacturer of the covered outpatient drug that is the subject of the violation in an amount equal to the reduction in the price of the drug as described in section II(a) of the Agreement. Pursuant to section 340B(a) (4) and (5) a covered entity also could be removed from the list of eligible entities.

(b) The Manufacturer may challenge the presence of an entity on the list of eligible entities issued by the Secretary. Upon presentation of appropriate information documenting the entity's ineligibility, the Secretary shall take such steps as necessary to carry out his responsibilities under paragraph III(a) of the Agreement.

(c) If the Secretary believes that the Manufacturer has not complied with the provisions of the Agreement, or has refused to submit reports, or has submitted false information pursuant to the Agreement, the Secretary, at his discretion, may initiate the informal dispute resolution process. If so found, the Secretary may require the Manufacturer to reimburse the entity for discounts withheld and can also terminate the Agreement. A Manufacturer who does not have an agreement with the Secretary pursuant to the Act, will no longer be deemed to meet the requirements of section 1927(a)(5)(A) of the Social Security Act.

(d) A covered entity's failure to comply with the audit requirement pursuant to section 340B(a)(5)(C) of the Act shall be cause for the Manufacturer to notify the Secretary or his designee and for the Secretary to initiate the informal dispute resolution process. Such action will not relieve the Manufacturer from its obligation to conform to the pricing requirements as provided in section 340B(a) of

the Act and the Agreement.

(e) Nothing in this paragraph shall preclude the Manufacturer or the Secretary from exercising such other remedies as may be available by law.

V. CONFIDENTIALITY PROVISIONS

(a) Information disclosed by the Manufacturer in connection with the Agreement, except as otherwise required by law, will not be disclosed by the Secretary or his designee in a form which reveals the Manufacturer, except as necessary to carry out the provisions of section 340B of the Act, and to permit review by the Comptroller General.

(b) The Manufacturer will hold audit information obtained from the covered entities confidential. If the Manufacturer receives further information on such data, that information shall also be held confidential. Nothing in this paragraph shall preclude the Manufacturer from making such information available to the Secretary to enable the Secretary to carry out the provisions of section 340B of the Act.

VI. NONRENEWAL AND TERMINATION

(a) Unless otherwise terminated by either party pursuant to the terms of the Agreement, the Agreement shall be effective for an initial period of 1 year, beginning on the date specified in section IX of the Agreement. It shall be automatically renewed for additional successive terms of 1 year unless the Manufacturer gives written notice of intent not to renew the Agreement at least 30 days before the end of the applicable period.

(b) The Manufacturer may terminate the Agreement for any reason. Such termination shall become effective the later of the first day of the first calendar quarter beginning 60 days after the Manufacturer gives written notice requesting termination, and the ending date of the term of the Agreement, if notice has been given 90 days before the end of the term.

(c) The Secretary may terminate the Agreement for a violation of the Agreement or other good cause upon 60 days prior written notice to the Manufacturer of the existence of such violation or other good cause. The Secretary shall provide the Manufacturer, upon request, the opportunity to participate in an informal dispute resolution process concerning the termination, but such a process shall not delay the effective date of the termination. Disputes arising under a contract between a Manufacturer and a covered entity should be resolved according to the terms of that contract. Actions taken by the parties in such disputes are not grounds for termination of the Agreement with the Secretary, except to the extent that there is a violation of the provisions of the Agreement.

(d) If the Agreement is not renewed or is terminated, the Manufacturer is prohibited from entering into another Agreement as provided in section 340B of the Act until a period of one complete calendar quarter has elapsed from the effective date of the termination, unless the Secretary finds good cause for earlier reinstatement.

(e) Any nonrenewal or termination will not affect the ceiling price under paragraph II(a) for any covered outpatient drug purchased before the effective date of termination.

VII. GENERAL PROVISIONS

(a) Any notice required to be given pursuant to the terms and provisions of the Agreement will be sent in writing.

(1) Notice to the Secretary will be sent to:

Office of Pharmacy Affairs
Health Resources and Services Administration
5600 Fishers Lane Mail
Stop 8W03A
Rockville, Maryland 20857

(2) Notice concerning data transfer and information systems issues is to be sent to the same address as listed above (section VII(a)(1) of this Agreement).

(3) Notice to the Manufacturer will be sent to the address as provided with the Agreement and updated upon Manufacturer notification to the Secretary at the address in the Agreement.

(b) The Manufacturer will be permitted to audit the records of each covered entity

(1) that directly pertain to the entity's compliance with the prohibition on

(A) the resale or other transfer of covered outpatient drugs to persons not patients of the entity, section 340B(a)(5)(B), and

(B) duplicate discounts pertaining to the rebate under section 1927 of the Social Security Act, section 340B(a)(5)(A);

(2) in accordance with procedures established by the Secretary relating to the number, duration, and scope of audits; and

(3) at the Manufacturer's expense.

(c) No provision in the Agreement shall prohibit the Manufacturer from charging a price

for a drug that is lower than the ceiling price as described in section II(a) of the Agreement.

(d) In the event of a transfer in ownership of the Manufacturer, the Agreement is automatically assigned to the new owner.

(e) Nothing in the Agreement will be construed to require or authorize the commission of any act contrary to law. If any provision of the Agreement is found to be invalid by a court of law, the Agreement will be construed in all respects as if any invalid or unenforceable provisions were eliminated, and without any effect on any other provision.

(f) Nothing in the Agreement shall be construed as a waiver or relinquishment of any legal rights of the Manufacturer or the Secretary under the Constitution, the Act, or Federal laws, or State laws.

(g) The Agreement shall be construed in accordance with Federal common law, and ambiguities shall be interpreted in the manner which best effectuates the statutory scheme.

(h) Except for changes of addresses, the Agreement will not be altered except by an amendment in writing signed by both parties. No person is authorized to alter or vary the terms unless the alteration appears by way of a written amendment, signed by duly appointed representatives of the Secretary and the Manufacturer.

(i) In the event that a due date falls on a weekend or Federal holiday, items will be due on the first business day following that weekend or Federal holiday.

VIII. EFFECTIVE DATE

The Agreement will be effective upon signing but will in no way alter the effective date upon which drug discounts were to be given to covered entities under any previously signed Pharmaceutical Pricing Agreement between the Secretary and the Manufacturer.

Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau OMB No. 0915-0327;
Expiration Date: 08/31/2019

IX. SIGNATURES

FOR THE SECRETARY OF HEALTH AND HUMAN SERVICES

By:_____ Date: _____

Title: Associate Administrator
Healthcare Systems Bureau
Health Resources and Services Administration

ACCEPTED FOR THE MANUFACTURER

I certify that I have made no alterations, amendments, or other changes to this pricing agreement.

By: _____ Printed Name: _____
(Signature)

Title: _____ Date: _____

Phone Number: _____ Ext._____ FAX Number: _____

e-Mail Address:_____

Manufacturer Labeler Code(s): _____

Name of Manufacturer: _____

Manufacturer Address: _____

_____

Contact Person: _____

Title: _____

Phone Number: _____ Ext._____FAX Number: _____

e-Mail Address:_____

Public Burden Statement: An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this project is 0915-0327. Public reporting burden for this collection of information is estimated to average 0.5 hours per response, including the time for reviewing instructions, searching existing data sources, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to HRSA Reports Clearance Officer, 5600 Fishers Lane, Room 10C- 03I, Rockville, Maryland, 20857.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

NOVARTIS PHARMACEUTICALS CORPORATION,

Plaintiff,

v.

XAVIER BECERRA, in his official capacity as Secretary of Health and Human Services et al.,

Defendants.

Case No. 3:23-CV-14221-ZNQ-DEA

[PROPOSED] ORDER GRANTING PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT

Upon consideration of Plaintiff's Motion for Summary Judgment and submissions of the parties, and having heard oral argument, and that it appearing to the Court that summary judgment should be granted to Plaintiff, and for good cause shown, it is hereby ORDERED that Plaintiff's Motion for Summary Judgment is GRANTED.

The Court DECLARES that the "Drug Price Negotiation Program," 42 U.S.C. §§ 1320f *et seq.*, effects a taking of Plaintiff's private property without just compensation in violation of the Fifth Amendment, unlawfully compels Plaintiff's speech in violation of the First Amendment, and imposes an excessive fine in violation of the Eighth Amendment.

It is further ORDERED that Defendants are permanently enjoined from enforcing against Plaintiff any obligation to enter any "agreement" under 42 U.S.C. § 1320f-2 or § 1320f-3, or the terms of any "agreement" entered thereunder.

This is a final, appealable order.

HON. ZAHID N. QURAISHI
UNITED STATES DISTRICT JUDGE

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Attorneys for Plaintiff
Novartis Pharmaceuticals Corporation

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

NOVARTIS PHARMACEUTICALS CORPORATION,

Plaintiff,

v.

XAVIER BECERRA, in his official capacity as Secretary of Health and Human Services et al.,

Defendants.

Case No. 3:23-CV-14221-ZNQ-DEA

CERTIFICATE OF SERVICE

I, Gregory Mortenson, hereby certify that:

1. I am an associate of the law firm Latham & Watkins LLP, 1271 Avenue of the Americas, New York, New York 10020, counsel to Plaintiff Novartis Pharmaceuticals Corporation in the above captioned matter. I am admitted to the Bar of the State of New Jersey and of this Court.

2. On November 21, 2023, I caused the following documents to be filed via the Court's CM/ECF system which caused electronic notification upon all counsel of record:

- Plaintiff's Memorandum of Points and Authorities in Support of Motion for Summary Judgment;
- Declaration of Daniel Meron;
- Declaration of Mark Vineis; and
- Proposed Order Granting Motion for Summary Judgment.

Dated: November 22, 2023

s/ *Gregory Mortenson*
Gregory Mortenson