Comment on Medicare Drug Price Negotiation Program: Draft Guidance, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2027 and Manufacturer Effectuation of the Maximum Fair Price (MFP) in 2026 and 2027

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Introduction

Thank you for the opportunity to comment on the updated draft guidance for the upcoming 2027 negotiations under the Medicare Drug Price Negotiation Program (Negotiation Program), facilitated by the Centers for Medicare and Medicaid Services (CMS). We are members of the Yale Collaboration for Regulatory Rigor, Integrity, and Transparency (CRRIT), an interdisciplinary initiative aligning research on medical product evaluation, approval, and coverage with the goal of advancing policies that improve patient outcomes.

On behalf of CRRIT, we laud CMS for the detailed proposed guidance document, which provides significant clarity into CMS's negotiation process with manufacturers, addresses concerns from manufacturers and the general public regarding the Negotiation Program, and once again reiterates CMS's commitment to reducing drug expenditure for the benefit of patients and the sustainability of the Medicare program. We agree with many aspects of the updated guidance, particularly sections that address ambiguity surrounding certain Negotiation Program clauses that could have been exploitable by manufacturers (such as the Exception for Small Biotech Drugs or the Application of the MFP Across Dosage Forms and Strengths), sections that provide further clarity into CMS's negotiation process with manufacturers, and sections that reiterate CMS's commitment to ensuring that manufacturers are encouraged to participate in the Negotiation Program fairly.

As clinicians and health policy researchers, we are optimistic that the Negotiation Program will lower Medicare drug expenditures for both the government and patients. However, as detailed in our prior research[1] and writing[2], there may be opportunities to further strengthen the program to better enable affordable access to expensive medicines. In our comments below, we offer suggestions to strengthen specific sections of the guidance document and also offer support for sections we believe to be critical to the Negotiation Program's effectiveness at a time when U.S. patients are increasingly facing challenges with prescription drug affordability.

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

CMS clarifies the definition of a qualifying single source drug as it pertains to selecting drugs for consideration in the Negotiation Program to be: a drug which is approved and marketed under either the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act for small molecule and biologic drugs, respectively; a drug has been FDA-approved for ≥7 or ≥11 years for small molecule and biologic drugs, respectively; a drug which is neither approved under an Abbreviated New Drug Application nor the reference product for any biological product that is licensed and marketed under section 351(k) of the PHS Act for small molecule and biologic drugs, respectively. These clarifying points are well taken, especially with regards to the additional clarification that the active marketing of an authorized generic drug does not disqualify a branded drug from consideration from the Negotiation Program so long as the authorized generic drug is the only marketed alternative to a branded product. However, we urge CMS to consider what course of action to take if an authorized generic drug commands an outsized share of sales for a particular medication even when traditional generics are also simultaneously marketed, as is seen in the case of the drug aliskiren, a drug used to treat high blood pressure. Aliskiren, an authorized generic for the branded drug Tekturna launched by the manufacturer of Tekturna, was launched and marketed before any generic drugs produced by other manufacturers were allowed to come to market so that Tekturna's manufacturer could secure a first mover advantage in the drug's generics market.[3] As a result, even after other manufacturers launched independent generics to Tekturna, the aliskiren authorized generic remained the best-selling version of Tekturna despite having a higher price than other independent generics.[3] This situation is not unique. Research conducted using Medicaid prescription drug data from 2014-2020 found that 35% of authorized generics launched during this period were marketed for ≥1 year before independent generics had launched and that authorized generic drugs commanded accounted for disproportionately large market share in the first 3 years in which a branded drug faces competition from independent generics.[4]

Given the current treatment of authorized generics under the Negotiation Program, certain branded drugs and their authorized generic counterparts from the same manufacturer may be exempt from the negotiation program if independent generics are marketed, even when the independent generics do not pose any real commercial competition to the branded or authorized generic equivalent. We recognize that the guidance may have been constructed this way by design, but nonetheless encourage CMS to consider the inclusion of additional measures which may include branded and authorized generic drugs for consideration for the Negotiation Program if traditional generics do not provide material competition to a manufacturer's branded and authorized generic drug.

Section 30.2.1 – Exception for Small Biotech Drugs

CMS clarifies the terms and conditions of the Exception for Small Biotech Drugs (SBE), including the stipulation that that "a qualifying single source drug is not eligible for an SBE if the manufacturer of such drug is acquired after 2021 by another manufacturer that does not meet the definition of a specified manufacturer." We strongly support the inclusion and clarification of the SBE as it would disincentivize large drug manufacturers from acquiring manufacturers of biotech drugs that meet the definition of a specified manufacturer solely for the purpose of

acquiring drug products which would be exempt from eligibility for the Negotiation Program. We agree with CMS's approach in evaluating on case-by-case basis the applicability of the SBE and definition of a qualifying manufacturer for each instance of a drug manufacturer acquiring another manufacturer with biologic drugs in its portfolio in order to determine whether an acquisition is occurring for the sole purpose of acquiring biologic drug products to ensure exemption from the Negotiation Program. We also support this approach because we believe it would not disincentivize mergers and acquisitions activity conducted by drug manufacturers for other reasons such as to achieve economies of scale or diversify their drug product portfolio, as these may represent legitimate reasons for mergers and acquisitions which may drive value for patients.

Section 30.4 – Publication of the Selected Drug List

CMS specifies that the Selected Drug List for 2027 will "include the 15 (or all, if such number is less than 15) drugs covered under Part D." We appreciate that CMS recognizes that less than 15 drugs may be eligible for 2027 negotiations under the Negotiation Program's drug eligibility criteria and also appreciate the clarification that if such is the case, CMS will include less than 15 drugs on the Selected Drug List. We recently published a study that simulated the number of drugs, and attributable drug expenditure from those drugs, that would be eligible for the Negotiation Program from 2016-2019.[1] Our findings corroborate what CMS has recognized: current drug eligibility criteria made approximately two-thirds of drugs with ≥$200 million in annual expenditure ineligible for the Negotiation Program, which may prevent CMS from filling all spots on the Selected Drug List in some years. We encourage Congress and CMS to consider expanding eligibility requirements for price negotiation to ensure there are a sufficient number of high-expenditure drugs eligible for negotiation or make certain ineligible drugs contributing to significant annual Medicare spending eligible for negotiation on a case-by-case basis.

Moreover, we encourage Congress and CMS to consider modifying eligibility requirements pertaining to launch date recency or consider aligning the post-launch timeframes for small molecule and biologic drugs to consist of the same number of years post-launch of 7 years or less rather than the distinct periods of >7 and >11 years for small molecule and biologic drugs, respectively. Prior work investigating pre-market development times for small molecule and biologic drugs using FDA approval and US Patent and Trademark Office data found no significant difference in pre-market development times between the two classes of drugs.[5] Additionally, this work's analysis of the Merck Index found that biologic drugs were associated with development times 2.5-2.9 years shorter than those of small molecule drugs, on average.[5] These observations corroborate our push for small molecule and biologic drugs to have identical launch date recency eligibility requirements applied to them under the Negotiation Program to enhance the Negotiation Program's ability to generate savings for Medicare by making more drugs eligible for negotiation under the Negotiation Program.

Section 40.1 – Entrance into an Agreement with CMS and Alternatives

CMS has reiterated in this draft guidance that if a manufacturer refuses to participate in the Negotiation Program, the manufacturer may "may expedite its exit from the CGDP and the Manufacturer Discount Program". While this information has been previously conveyed, we affirm CMS's decision to adhere to the decision to impose material consequences, including

inaccessibility to the Medicare market, should manufacturers opt out of the Negotiation Program. Doing so is critical to promote manufacturer participation in the Negotiation Program and achieve savings on drug expenditure.

Section 40.2.1 – Confidentiality of Proprietary Information

CMS states that it "must determine which information submitted to CMS by a manufacturer of a selected drug is proprietary information". We appreciate CMS's efforts to ensure that manufacturers retain competitiveness from proprietary information pertaining to their drug development, manufacturing, and commercial processes. However, we suggest that CMS consult experts outside the CMS and manufacturers without conflicts of interest to definitively determine whether information is truly confidential to ensure the validity of manufacturer claims around confidentiality. Such information can be critical for outside expert parties to assist CMS in their negotiations and in setting a fair price. The availability of such data can allow others to conduct studies to better understand the consequences of ensuring a fair price for negotiations while also allowing outside experts to weigh in on the validity of the figures put forward by the manufacturers to CMS.

Additionally, we support CMS's decision to deem information pertaining to Federal financial support received by manufacturers for selected drug research and development as non-proprietary. We also encourage CMS to treat any manufacturer-related information disclosed to public equity investors of manufacturers on investor calls or SEC-sanctioned documentation as non-proprietary information, if such information is not considered non-proprietary already.

Section 40.2.2 – Data and Information Use Provisions and Limitations

CMS states that it "will make public a narrative explanation of the negotiation process and share redacted information" as appropriate. As with all other measures in the guidance document that further enhance transparency surrounding the negotiation process, we support this effort. Additionally, we encourage CMS to solicit retrospective feedback on negotiation processes undertaken as part of the Negotiation Program from outside experts in order to further improve CMS's performance in negotiations with manufacturer in subsequent years.

Section 40.4 - Providing Access to the MFP in 2026 and 2027

CMS states that they will provide commercial and other payors with access to Maximum Fair Prices (MFPs) established through the Negotiation Program, allowing private payors to "to have discretion to consider Medicare payment rates, including the MFP, in establishing their own payment policies". We commend CMS for being transparent with established MFPs. Prior work has found that employer-sponsored insurance plans pay more than Medicare on common physician-administered drugs.[6] Additionally, out-of-pocket drug expenditures for patients covered by commercial payors have been found to exceed those for patients covered by Medicare[7], exacerbated further by the $2000 out-of-pocket cap established by the Inflation Reduction Act for Medicare beneficiaries. Thus, CMS releasing MFPs negotiated through the Negotiation Program to private payors may allow them to negotiate more competitive prices with manufacturers on prescription drugs, as well as physician-administered products when the Negotiation Program is expanded to drugs covered by Medicare Part B to allow for greater

pricing parity relative to that negotiated by Medicare. Should private payors leverage MFPs to negotiate more competitive prices on drugs included on the Selected Drugs List, which is comprised of some of the costliest drugs by annual expenditure, they may be able to ultimately provide greater value for the patients they insure through lower out-of-pocket expenditures or lower insurance premiums attributable to cost savings on drug expenditure.

Section 50.1 – Manufacturer-Specific Data

CMS requires that manufacturers submit information on certain factors for further consideration including, but not limited to, research & development (R&D) costs, cost of production, prior federal financial support for novel therapeutic discovery with respect to the selected drug, FDA-recognized exclusivities, among other factors, to inform considerations of a "fair profit" for the selected drug. We support CMS's aspirations to establish such a "fair profit" MFP. However, we are concerned that some potential ambiguities in the guidance may limit its usefulness and present challenges in its application.

- R&D: The guidance notes that the preliminary price may be adjusted upward in cases where R&D costs have not been recouped, and downwards where they have. Appendix A divides R&D into five categories, including acquisition costs, base pre-clinical research costs, post-investigational new drug application costs, abandoned and failed drug costs, and all other R&D direct costs. At present, it is not clear in the guidance whether manufacturers are required to report R&D costs disaggregated by these categories, or whether categories are constitutive of a simple total of R&D costs that can be reported. We strongly urge CMS to require that R&D costs be reported within the disaggregated categories proposed. Without disaggregation by category, manufacturers may be able to "double count" the same "abandoned and failed drug costs" across multiple products, if they share the same active moiety or mechanism of action. Similarly, when drugs are acquired – particularly in late-stage clinical development – the manufacturer is not taking on risk, and so related failed research should not be considered in the same way in assessing total R&D spend. The guidance should also clarify that R&D spending should be reported as out-of-pocket spending, and not be capitalized or risk-adjusted. CMS may consider providing stylized case examples, as were included in National Institute of Standards and Technology's "Draft Interagency Guidance Framework for Considering the Exercise of March-In Rights", to further clarify acceptable reported costs.

- Unit production costs: We commend CMS for including unit production costs, which are routinely considered by health systems globally, but have thus far been used in comparatively limited contexts in the United States (for example, through some DoD cost-plus contracts). There is no standard methodology for reporting production costs, and the guidance provided in Appendix A is generally clear, detailed, and comprehensive. However, we are concerned that "allocated shared operating and other indirect costs (such as capitalized production facility costs, benefits, generalized and administrative costs, and overhead expenses)" is vague. Capitalized production facility costs could be interpreted to include investments in a given facility. To avoid double-counting across products, the guidance should be updated so that capitalized production facility costs are proportional to their volume or revenue across the full facility.

- Prior federal financial support: In addition to definitions that financial support include "tax credits, direct financial support, grants or contracts, [and] in-kind contributions", we suggest that federal financial support also include some measure of the value of incentives such as priority review vouchers (PRVs). PRVs in many cases constitute the largest federal investment, valued between by Ridley and Régnier (2016) to be worth between $67.5 million (July 2014) and $350 million (August 2015).[8] Uncertainty in the value of the voucher is related to the number of total vouchers on the market, and to the profitability of the drug to which it is applied. Ridley and Régnier's method for estimating the value of a given PRV combines the number of months of acceleration in approval with fifth-year sales for the product to which the PRV is applied.[8] This model has been applied to a range of other drugs, and could be included within this guidance to facilitate the inclusion of federal investments through PRVs. We are also concerned that the window of included federal investments should be longer than the proposed 52 months in cases where manufacturers cannot calculate the length of the basic pre-clinical research period. In practice, we anticipate most manufacturers will default to 52 months where beneficial, as there is no universally defined measure of what the pre-clinical phase should include. According to the guidance, 52 months was chosen as the average reported in reviewed studies on R&D costs and timelines. An average is not appropriate in this context: public investment in research is in most cases undertaken in the earliest and riskiest phases of research. We would therefore anticipate that federal investments be skewed earlier, and any *average* measure of the duration of pre-clinical research therefore disproportionately exclude federal versus manufacturer investments. As one example, in the case of blockbuster GLP-1 drugs, estimated to cost CMS $166 billion per year if used by all eligible adults on Medicare and Medicaid, federal investments stretch back to the 1970s and 1980s for semaglutide, for which an Investigational New Drug (IND) application was filed only in 2019.[9,10]

The inclusion of these factors is an important step forward in achieving both fairer prices for CMS, but also generates valuable transparency and insight into costs across the value chain. At present, even the Congressional Budget Office (CBO) does not have access to R&D and clinical trial costs, and instead relies on industry-reported figures from anonymous surveys collected in industry-funded research studies.[11] This has curtailed the objectivity and accuracy of models assessing the impact of legislation such as the IRA on future innovation. We encourage CMS to continue to work with stakeholders and expert to develop and refine methodologies used for reporting costs of R&D, production, and the value of federal funding and incentives. To ensure the accuracy and completeness of data provided, CMS could contract a third party auditor to review a random sample of submissions.

Section 50.2 Evidence About Therapeutic Alternatives

CMS states that they will "consider evidence about alternative treatments to the selected drug" during Negotiation Program negotiations which is to be submitted by manufacturers, members of the public, clinicians, academic experts, and other interested parties. We support CMS's efforts in this regard, as the identification of clinically interchangeable drugs or therapies would allow for more productive and informed negotiations with manufacturers. However, we

encourage CMS to work alongside other agencies on this effort, such as international agencies which assess drugs' clinical interchangeability or Veterans Affairs, which assesses drugs' clinical interchangeability to some extent to determine drugs' tier placement and applicable utilization management strategies on drug formularies. These agencies that likely have extensive data and expertise regarding drugs' real-world and post-approval efficacy and safety profiles including comparative effectiveness data, may help CMS to develop even more well-informed stances on therapeutic alternatives for selected drugs prior to negotiations with manufacturers.
Moreover, CMS could not only partner with these agencies, but also payors, to proactively generative evidence around the negotiation-eligible drug and other alternative treatments should such data not be available. Payors may prove to be effective partners in such evidence generation given their vested interest in determining which therapeutics are most effective and the ability to use payers' extensive claims data as a source of real-world evidence for drug efficacy and safety.[12] Being able to confidently assess selected drugs' clinical interchangeability with alternative therapeutics through the generation of such evidence would allow CMS to make appropriate decisions regarding selected drugs' formulary tier placement and utilization management on Medicare formularies after MFPs are negotiated. Our previous research regarding 2016 Medicare prescription drug plan formularies found that a substantial portion of Medicare formularies did not fully capitalize on opportunities to incentivize prescribing of generic drugs over their more expensive branded drug counterparts due to suboptimal branded drug tier placement and utilization management.[13] After negotiating MFPs, there is room for CMS to further decrease Medicare drug expenditure by choosing appropriate formulary tier placement and implementing appropriate utilization management strategies for drugs selected for the Negotiation Program on Medicare formularies.

Additionally, we encourage CMS to consider making drug efficacy and safety analyses between selected drugs and identified therapeutic alternatives publicly available. Making these analyses public would not only allow outside experts to provide insight on CMS's conclusions but also potentially allow clinicians to enhance clinical care provided to patients by informing them of selected drugs' efficacy and safety relative to alternative therapeutics.

Section 60.4 – Negotiation Process

CMS states that they will host patient-focused events to seek verbal input from "patients, beneficiaries, caregivers, and consumer and patient organizations" to inform negotiations. We support CMS's aspiration to integrate varied perspectives into the negotiation process. However, our previous research demonstrated that among the 50 highest-revenue PAOs in the US, three-fourths had board members, senior paid staff, or executives with prior or current ties to the pharmaceutical and medical device industries.[14] Additionally, a report by Patients for Affordable Drugs found that several patient advocacy groups actually oppose drug pricing reforms, such as those included in the Inflation Reduction Act and the Negotiation Program, despite their claims to fight for improved patient access to healthcare.[15] These groups receive millions of dollars in funding from the pharmaceutical industry, have leadership with significant ties to the pharmaceutical industry, and support policy paradigms which would undoubtedly worsen patient access to care, such as policies which would provide unfettered pricing power to drug manufacturers.[15] Given that representatives at patient-focused events may have conflicts of interest pertaining to selected drugs, we encourage CMS to ensure parity of voices and perspectives among those represented at these events. Additionally, we encourage CMS to

include the voices of clinicians at these events, including generalist physicians, as they often assist patients in navigating access challenges to their medications and finding strategies to manage prescription drug costs.

Section 60.5 – Application of the MFP Across Dosage Forms and Strengths

CMS states that they will "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." We support CMS's treatment of different dosage forms and strengths with regards to MFP given the prevalence of strategies employed by branded drug manufacturers to extend drugs' market exclusivity protection or delay generic launches, and thus protect revenue associated with drugs, such as "evergreening" or "product hopping". We found that between 1995 and 2010, approval of new formulations was 4 times more likely among blockbuster drugs and 5.5 times more likely among drugs granted accelerated approval, indicating that manufacturers likely launch new drug formulations or dosage forms for commercial reasons.[16] We believe that by applying the MFP across all dosage forms or formulations of a selected drug, CMS is taking steps to disincentivize manufacturers from launching products which repackage an existing drug into a new dosage form or formulation for commercial gain, and instead incentivizes manufacturers to do so only if it truly improves patients' experience or care.

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