VIA ELECTRONIC SUBMISSION

The Honorable Chiquita Brooks-LaSure
Centers for Medicare and Medicaid Services Administrator
200 Independence Avenue, S.W.
Washington, D.C. 20201

RE: 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

Dear Administrator Brooks-LaSure:

We are writing to comment on the initial guidance, entitled: “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” (Guidance), published on March 15, 2023, by the Centers for Medicare and Medicaid Services (CMS). The Guidance addresses the implementation of sections 11001 and 11002 of the Inflation Reduction Act (IRA), which establishes the Medicare Drug Price Negotiation Program (Negotiation Program) to negotiate maximum fair prices (MFPs) for certain high-expenditure, single-source drugs and biologics. The Guidance provides further detail about CMS’s intended implementation of the Negotiation Program and solicits stakeholder feedback on specific issues surrounding this program, including the negotiation factors, how CMS will determine its pricing offer to a drug manufacturer, the negotiations process, and others.

While Congress exempted the IRA’s implementation from a requirement for a formal notice-and-comment rulemaking process, CMS has described in the Guidance a process for timely public input on how the MFP for a drug will be determined. We appreciate CMS’s efforts to solicit comments on most aspects of the Guidance pertaining to the implementation of the Negotiation Program, which has a tight statutory timeline for initial application in 2026.

The Robert J. Margolis, MD Center for Health Policy at Duke University (the Duke-Margolis Center or the Center) generates and analyzes evidence across the spectrum of health policy with the goal of improving health care, health, and health equity while avoiding unnecessary costs. A core mission of the Center is to focus on increasing the value of biomedical innovation to patients. As part of these efforts, we study the design, implementation, and feasibility of value-based payment (VBP) arrangements for medical technologies, which shift away from payments based on volume and promote payments based on the impact of the treatment. These approaches include payments linked to better evidence and outcomes, and “subscription” or population-based payments, for biomedical technologies, complementary to shifts in payments to health care providers that are similarly linked to improving outcomes and decreasing total medical expenditures. The suggestions below are informed by the Center’s experience and research in developing approaches to payment reform that support better evidence and outcomes for patients and better value across the system; in analyzing the impact of the current legal and regulatory environment on their adoption; and in working with multiple stakeholders to address the operational
challenges to their use. They are also informed by the collaborative work of the Center’s Value for Medical Products Consortium (the Consortium), and by the work of the Center’s Real-World Evidence (RWE) Collaborative, but may not represent the opinions of every member of these collaborations. Our Consortium and/or RWE Collaborative members are in many cases providing their own comments on behalf of their organizations.

Our comments reflect Duke-Margolis’s independent analyses of the Guidance and recent work undertaken by the Consortium and the Collaborative. Our recommendations describe opportunities for CMS to refine the Guidance in light of considerations related to RWE and the use of quality evidence, program integrity and transparency, and arrangements that align drug payments with their observed value. An overarching theme in our comments is the importance of implementing the Negotiation Program in a sustainable way for years to come despite the substantial requirements with limited time statutorily imposed on CMS. To this end, we suggest that CMS lay out a clear initial framework for how it intends to carry out MFP determinations while also describing a pathway for refinements over time as experience with the program grows beyond Price Applicability Year 2026. Specifically, our recommendations are for CMS to:

1. Implement a clear framework for assessing comparative effectiveness and translating such analyses to prices
2. As part of this framework, describe how real-world evidence development, including evidence related to additional indications, will impact CMS’s MFP determinations
3. Develop mechanisms to facilitate alternative payment arrangements for drugs that accomplish the intended goals of the IRA
4. Clarify how the manufacturer-specific factors will be used to guide the MFP, and collaborate to support accurate and efficient data collection
5. Clarify additional considerations for implementing the Negotiation Program

Our detailed comments are as follows:

Implement a clear framework for assessing comparative effectiveness and translating such analyses to prices

As described in the Guidance, CMS intends to consider evidence about therapeutic alternatives for a drug selected for price negotiation through an evaluation of the body of clinical evidence by considering factors in two areas: outcomes and safety. This evidence review will be informed by evidence submitted by members of the public, including drug manufacturers, Medicare beneficiaries, academic experts, clinicians, and other interested parties. CMS also intends to conduct its own literature review as part of this evidence review, prioritizing research that is methodologically rigorous. CMS intends to consider research on, and RWE relating to, Medicare populations as particularly significant to its assessment. CMS will place significant weight on assessing whether the drug fills an unmet medical need, which CMS defines as treating a disease or condition in cases where very limited or no other treatment options exist. CMS will then use this assessment of comparative effectiveness to adjust the initial price it set for the drug, which will generally be the net price of the closest therapeutic alternative in Medicare. CMS
should clarify its methodology for setting the initial price in case there are multiple therapeutic alternatives (for example, via some type of weighted average).

The Guidance provides a thoughtful overview of how it will consider evidence about therapeutic alternatives and the evidence assessment’s impact on the determination of the negotiated price. The final guidance should build on stakeholder comments, including ours, to provide a more detailed framework that encompasses the major comparative effectiveness considerations, including how evidence and stakeholder engagements would contribute to the overall evidence assessments concerning the drug and its alternative treatment(s). CMS proposes a very broad and flexible “qualitative” approach which involves "adjusting the starting point upward or downward relative to the clinical benefit offered by the selected drug compared to its therapeutic alternatives." The agency also suggests that it wants to retain broad discretion regarding the evidence it will consider for setting the MFP, stating that it intends to consider a range of evidence types pertaining to the selected drug’s therapeutic alternatives from a range of stakeholders, including evidence submitted by the public and patient-reported data, giving itself substantial flexibility to consider evidence from a variety of sources.

Such flexibility and broad discretion are understandable, especially for a new program facing a complexity of factors under a tight implementation deadline. However, flexibility also means uncertainty about how different types of evidence and contributions will matter (or not) in the assessment and the final MFP determination. Uncertainty will result in less effective investment and less investment in developing evidence that could improve the understanding of a drug’s comparative effectiveness and thus its impact and use in Medicare beneficiaries. To encourage investment in drugs and supporting evidence that matter for Medicare beneficiaries, CMS should develop a plan for implementing an increasingly clear and rich framework for how different kinds of comparative effectiveness assessments will be integrated. Along with transparency about how it applies this qualitative framework to assessments over time, the assessment framework will become clearer and more robust with additional experience, potentially encouraging more drug development and supporting evidence development in ways that demonstrably improve outcomes and safety for Medicare beneficiaries.

To start this process, CMS should do more now to describe an initial guiding qualitative framework that will clarify the dimensions of comparative effectiveness that it will consider, how it will weigh different kinds of potentially relevant evidence (including RWE), and what evidence would lead to upward or downward price adjustments (including whether additional product improvements or indications could lead to upward adjustments, as we discuss further below).

As the IRA gave CMS considerable flexibility in how to incorporate comments and experience in the implementation of the price negotiation, CMS could describe the most important aspects of its comparative effectiveness assessments that should be detailed now and what aspects will require additional time and experience with the Negotiation Program implementation to help achieve better clarity. This more explicit Negotiation Program framework should describe how CMS intends to treat various evidence types in this process and lay out a framework for how the agency will engage with, and consider evidence from, different types of publicly reported studies and other submissions from stakeholders to support predictable, reliable assessments of comparative effectiveness.
For example, according to the Guidance, the use of RWE in its comparative effectiveness assessments may include evidence generated from patient-reported outcomes (PRO) data. In fact, value assessments that can systematically describe real-world value through PROs derived from electronic medical records or other RWE sources can address uncertainty around the real-world value of any drug under comparison, but meaningful PRO studies can be costly to implement reliably. CMS could begin by describing PRO evidence likely to be most relevant to assessments in therapeutic areas that will be included in early negotiations, solicit further comments (and rely on existing tools and examples to incorporate PRO data) to help clarify how it will consider such evidence, and then provide transparent summaries of how such evidence contributed to the early assessments. Over time, this process would provide an increasingly clear and rich framework on how PRO-related evidence impacts CMS’s qualitative assessments, which will drive more effective investment in relevant studies that include PROs.

CMS could create an initial “dashboard,” and refine it over time, to track and characterize key potential dimensions of the drug’s impact on outcomes and safety that influence its assessments. Such a dashboard should focus on dimensions that matter to beneficiaries and improving health equity, goals that align with CMS strategic priorities and measures across its Medicare payment programs. This would help improve clarity about the basis for MFP determinations, and help guide input from beneficiary, consumer groups, and other stakeholders, to help CMS achieve its stated goals for the program. Below we provide additional suggestions for the use of such dashboard by CMS in the context of the other factors that it will consider in setting the MFP, as well as tracking the potential broader impacts that the Negotiation Program could have on drug access and innovation.

In developing its initial qualitative framework for comparative effectiveness and associated key metrics, CMS can draw on experience in the United States and elsewhere to describe how its comparative effectiveness assessments will inform a drug’s price relative to its comparator. Several countries, such as France and Germany, use qualitative frameworks to integrate evidence on the comparative benefits and risks of alternative treatments in their drug price negotiations. These countries use scoring systems that rate the level of the “added benefit” the drug in question provides over a comparator product, and each level is typically tied to a range of payment adjustments. Some private payers use similar approaches.

This qualitative framework can also provide increasingly clear guidance on how CMS will consider the strength of evidence for the added health benefit, as described above, by prioritizing methodologically rigorous research. For example, the Institute of Clinical and Economic Review (ICER) assigns a level of certainty to its evidence finding, combining the magnitude of the comparative benefit with the level of certainty in the existing body of evidence for a drug. (In contrast to CMS’s stated goal, Germany’s framework appears to place most weight on more traditional randomized clinical trials, not other types of RWE; we support CMS’s emphasis on RWE especially since its framework will be applied years after a product reaches the market.) Here, CMS could describe the kinds of evidence (and strength) likely to achieve the statutory ceiling price for a drug that presents a substantial clinical benefit compared to its

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alternative treatment(s) in a relevant therapeutic area, while creating various payment “tiers” below the statutory ceiling for drugs demonstrating various levels of evidence short of a major improvement.

Similarly, CMS could describe the kinds of limited differences in meaningful outcomes and safety that would not support additional payment compared to a less expensive treatment. The comparative effectiveness methods CMS will use should provide increasingly clear illustrations of how to integrate differential impacts in the different dimensions of outcomes that may matter to patients, and how much any given difference in outcomes that matter would increase or decrease a selected drug’s “price category” from the price of its therapeutic alternative.

In addition to a pathway to an increasingly detailed qualitative framework, and a growing set of summary reports on implemented cases of price negotiation, CMS could provide more clarity to involved manufacturers through regular opportunities for manufacturers to consult early with CMS – beginning soon after a potentially relevant product comes to market and perhaps even before, in the pivotal trial design and implementation stage. CMS should also consider opportunities for input from a broad range of stakeholders to help flesh out its framework in particular relevant therapeutic areas. Especially in the early stages of Medicare price negotiation, these steps will help reduce uncertainty and generate the evidence and drug investments aligned with CMS broad goals. Food and Drug Administration (FDA) programs that provide regular and predictable meetings and public engagement opportunities have been very helpful for supporting investments by product developers in efficient and effective evidence development for products to demonstrate whether they meet FDA safety and effectiveness standards. Such programs could be similarly helpful here.

We note that, because these comparative effectiveness systems do not assess the evidence on benefits relative to costs, they will not clearly and easily reduce to a single-dimensional measure like cost-effectiveness. CMS comparative effectiveness methods must therefore consider how to integrate differential impacts in the multiple dimensions of outcomes that may matter to patients, and how much any given improvement in outcomes that matter should impact price. To augment its qualitative analyses, CMS could describe how particular quantitative assessment methodologies (other than quality-adjusted life years, or QALYs) could inform its qualitative framework. Potentially useful quantitative comparative effectiveness metrics such as equal value life years (evLY) have been developed to address concerns of potential discrimination from the use of QALYs.

Finally, price differences may well be anchored to quite different pricing or value levels across different therapeutic classes, even if CMS describes a clear and consistent basis for assessing an MFP relative to a reference product across different therapeutic areas. CMS should monitor whether such differences emerge, and develop ways to address them over time. This makes it even more important for CMS to continue to work toward transparent and predictable methodologies for tying its findings on comparative clinical benefits to its price determinations. A clear framework with a path toward greater clarity will lead to a smoother implementation of the Negotiation Program by reducing stakeholder misperceptions, increasing program stability from administration to administration, and encouraging better evidence development while preventing avoidable impacts on innovation and access.
The implementation burden for CMS in the coming months and years is substantial, and the agency has sought to quickly build its internal capabilities to carry out the Negotiation Program. Alongside CMS’s internal implementation capabilities that it has been recently ramping up, CMS could contract the comparative effectiveness assessment process out to an independent organization or entity that would specialize in such activities, with the development of transparent methodologies and technical expertise, as needed. CMS could also support or encourage evaluations from multiple organizations with the goal of more robust assessment.

As part of this framework, describe how real-world evidence development, including evidence related to additional indications, will impact CMS’s MFP determinations

Until now, formal health technology assessments (HTAs) of drugs have focused on new products, to help guide initial payer and manufacturer negotiations about coverage and payment. These assessments must rely mostly on premarket evidence, particularly from randomized controlled trials (RCTs). They often include only limited evidence on comparative effectiveness and impacts in real-world populations and conditions of use, and in particular, on diverse subgroups of patients and “off-label” uses, as such questions are not well suited to be answered through traditional RCTs in academic settings. Evidence from well-controlled studies is essential for FDA approval. But such premarket studies generally leave the important real-world questions for Medicare and other beneficiaries unresolved. Consequently, drugs are usually approved with quite limited evidence on comparative effectiveness, with limited evidence on potential impacts in different types of patients, and naturally, with limited prescriber experience. Drugs may be marketed in narrower indications that expand over time, with peak revenues coming some years after the drug’s initial adoption. Many drugs have had important indications added long enough after initial marketing, typically five to six years after approval, but sometimes later. Many drugs are also used “off-label,” without such regulatory-grade evidence.

Because the CMS price negotiations will apply to drugs and biologics that have been on the market for at least 7 and 11 years, respectively, CMS has a critically important opportunity to encourage and support the development of much better RWE, both well-designed observational studies and real-world randomized trials (such as clinical trials embedded in routine practice with simpler data collection). To do so, CMS will need to provide more clarity that these types of evidence will have a significant impact on decisions, and provide some illustrative examples of the kinds of studies that would be impactful, just as we have described for the overall CMS comparative effectiveness framework.

More specifically, CMS should provide illustrations of the kinds of RWE that will impact comparative effectiveness and how it will weigh the quality and methods of RWE. There are extensive experiences and frameworks to draw on for this work, both in terms of how RWE can impact key dimensions of comparative effectiveness and how to consider data quality, as well as confounding variables and resulting biases. For example, several international HTA bodies have developed recommendations concerning the use of RWE in comparative effectiveness assessments that may be useful for CMS to

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consider. The United Kingdom’s National Institute for Health and Care Excellence (NICE) published a study design and analysis framework[^1] for using various types of non-randomized real-world studies in comparative effectiveness evaluations. This framework includes study eligibility criteria that mimic a hypothetical pragmatic trial, comparator requirements, defined follow-up period guidance, and ways for addressing bias and confounding with a detailed analysis plan to describe how the causal effect of interest is to be estimated. The FDA has also published a series of guidances on the use of information from routine clinical practice to derive “fit-for-purpose” RWE to inform its evaluations of product effectiveness.[^2][^3]

We understand that the development of a detailed framework is a substantial undertaking. However, CMS could support an iterative process to implement and refine its own framework that would detail how RWE should be used by drug manufacturers as a potentially major part of relevant evidence for the key dimensions of outcomes and safety in its overall comparative effectiveness assessment. This would describe the major kinds of RWE that would be considered—for example, providing guidance on observational target trial approaches and practical randomized studies. It should also discuss ways for ensuring data quality and that data is fit-for-purpose, and ways to address confounding and biases in real-world studies (e.g., use of negative controls). CMS should also describe how the initial (relatively broad) guidance could be refined through further comments and experience—including CMS’s transparent summary of the impact of RWE on each comparative effectiveness assessment.

In particular, CMS should also provide additional clarity on how it intends to treat postmarket studies that add value to a drug through, for example, new formulations and delivery systems that increase patients’ ease of use and thus improve outcomes, and whether such product improvements could lead to upward price adjustments. In fact, the Guidance potentially creates a chilling effect on the development of new product modifications through its expansive definition of “Qualifying Single Source Part D Drugs” (QSSDs), which effectively aggregates all drug versions based on the drug’s active ingredient/moieity, including different New Drug Applications (NDAs) and Biologic License Applications (BLAs), for the purpose of price negotiations, based on the date of the introduction of the first-approved product. We understand that the definition of QSSD is not open for public comment. However, to minimize any adverse effects on the development of important RWE that can add significant value to a selected drug, CMS could clarify what types of evidence it will encourage in this context and whether and how such additional evidence related to product improvements could yield a higher MFP for the negotiated product “group.”

By providing a clearer pathway for implementing and completing RWE studies, and relying on their results, CMS could help shift manufacturer investments toward needed RWE and also reduce delays in drug access for patients who might benefit from this additional evidence generation. For example,

[^2]: Food and Drug Administration, “Real World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drugs and Biological Products,” September, 2021, [https://www.fda.gov/media/152503/download](https://www.fda.gov/media/152503/download)
collaborations with The National Patient-Centered Clinical Research Network (PCORnet), which can be used for manufacturer-supported studies, can accelerate RWE studies on important safety or comparative effectiveness questions. Specific collaborations are likely to be possible across different therapeutic areas, building on a range of RWE platforms and resources.

Because RWE generation is often a lengthy and challenging process, it would be helpful for CMS to consider ways in which it can help accelerate the completion of these studies that tend to be more reflective of important Medicare subgroups than traditional RCTs. For example, CMS could facilitate the timely use of CMS data. It could also provide payment incentives for certain data reporting or quality improvement payment adjustments for developing evidence on comparative effectiveness and safety for treatments that are potentially important for the well-being of Medicare beneficiaries. This will likely be a “work in progress” in the early years of the Price Negotiation Program, which is all the more reason to provide a more detailed path forward for how it could be developed.

The IRA is being implemented at an important time in terms of closing these evidence gaps through postmarket, “real-world” evidence. The potential to learn more about drugs after they are on the market is growing, with increasing use of richer digitized and interoperable data, and progress in such areas as precision medicine, postmarket trial platforms, and statistical methods using increasingly rich data. Indeed, CMS has emphasized the goal of enhancing such evidence development to support care for Medicare beneficiaries. However, it is possible that the IRA may have a potentially adverse effect on the use of RWE to inform how to use drugs effectively once they are on the market through label expansions because it may reduce the drug’s price for newer indications that have not yet been on the market for 7 or 11 years (the timeframe for selecting drugs for negotiations for small molecule drugs and biologics, respectively).

CMS should therefore clarify whether and (at least qualitatively) how much the MFP could rise, or if it would be possible to implement a differentiated MFP for the additional indication (something which seems unlikely based on the Guidance) in the event of postmarket label expansions or, since label expansions can take some time, completion and publication of meaningful postmarket studies related to additional populations. Further work by the FDA and other health care stakeholders to clarify faster paths and additional opportunities for timely RWE studies—an area of considerable FDA activity and bipartisan Congressional interest—would encourage and enable product developers and other researchers to contemplate and plan for the systematic execution of such studies to obtain results faster and more efficiently. In addition to providing advance clarity on the Negotiation Program’s expected impact on drug indication expansions, we recommend that CMS support these activities, particularly in instances where postmarket surveillance and/or RWE studies (e.g., point-of-care or pragmatic trials) can support the generation of RWE that is highly relevant and valuable to the Medicare and Medicaid programs and their beneficiaries.

Develop mechanisms to facilitate alternative payment arrangements for drugs that accomplish the intended goals of the IRA

Alternative payment arrangements for drugs, such as subscription or outcome-based payment arrangements, have been proposed and implemented as a mechanism for increasing the health impact
and the value of pharmaceutical products. These models shift from a fee-for-service (FFS) payment structure with high unit prices to payments designed for increased uptake and impact on utilization and outcomes. The implementation of VBP arrangements for drugs might be meaningfully viewed on a spectrum, beginning with payments that remain FFS-based but that are adjusted based on expected value, as determined by existing evidence (e.g., indication-based pricing). Payments with larger shifts from FFS include outcome-based contracts that link payments to a product’s actual performance or demonstrated value in a patient or a population, and extend to per-member per-month or whole population “subscription” payments that are not related to the volume of sales at all but rather to access and outcomes in a population.

The IRA could impact adoption of such innovative payment models, which in principle are highly aligned with the IRA goal of lower per-unit drug prices, but also with the equally important goal (from a beneficiary perspective) of increased access and uptake by beneficiaries who would be expected to have better outcomes with the use of the drug – including those who face nonfinancial barriers to access. For example, even though we have more low-cost, effective drugs for heart disease, diabetes, and behavioral health conditions than ever before (with more coming), rates of underdiagnosis and undertreatment remain high, particularly for lower-income and minority populations. CMS should take steps as part of the IRA’s implementation to avoid barriers to the development of alternative payment models for drugs, and potentially to encourage them, since their intent is fully aligned with CMS’s goals for the IRA as well as for payment reform more broadly in Medicare.

For example, Medicaid Best Price has often been cited as one of the key obstacles for manufacturers to enter into VBP arrangements with payers because providing a substantial rebate to a single commercial payer could require them to extend the same rebate to the entire Medicaid program. Recently-implemented CMS policy changes created Medicaid Best Price flexibilities, such as by allowing manufacturers to report “Multiple Best Prices”6 to address these concerns and spur more VBP in the commercial market. Similar concerns may be raised in the context of the impact of VBP arrangements on Medicare MFPs. We believe we can expect less disruption for VBP arrangements from the IRA requirements so long as such arrangements remain a relatively small part of the market. Unlike Medicaid Best Price, where a bad result for a single patient in a single contract could potentially reset Best Price for the entire Medicaid market, the prices leveraged in the IRA to determine the ceiling price (such as non-Federal average manufacturer price, or non-FAMP, and Average Sales Price, or ASP) are weighted averages that will be less influenced by low payments in alternative payment models. Furthermore, if a negotiated drug’s ceiling price is based on its gross price (i.e., the non-FAMP, which does not include payer rebates), manufacturers and payers may have some flexibility to implement alternative payments via adjusting list prices and rebates without disrupting non-FAMP and thus MFP ceiling calculations.

However, in some cases, alternative payment models for drugs may have advantages over “FFS” drug price reductions alone—and thus could become a larger part of the market. For example, “subscription

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models” that pay for drugs on a population and not per-unit basis could be better aligned with CMS-driven shifts in payments to health care organizations on a risk-adjusted, per-person basis. If payments are further linked to population outcomes (e.g., lower disease complication rates and lower total costs of care – including both drug and non-drug costs), these incentives have the potential to encourage manufacturers to collaborate with providers to further expand access to drugs in ways that are beneficial to patients as well as payers. For example, the administration is encouraging such drug payment reforms to increase access and uptake of curative treatments for hepatitis C infection.

CMS should clarify how alternative payment models for drugs that achieve better outcomes and lower total spending compared to FFS drug payments can be encouraged under the IRA. These arrangements, meant to have a substantially lower price per unit and substantially higher use compared to baseline FFS drug pricing models, could involve a low effective unit price linked to certain steps by drug manufacturers in collaboration with providers, such as outreach to patients who could most benefit from screening and drug treatment. Manufacturers could also receive additional “shared savings” payments when costly complications and non-drug spending for these patients are reduced. If widespread enough, these approaches could reduce the ceiling MFP, even though they lower total health care costs and advance Medicare’s strategic goal of providing more coordinated, accountable care for all beneficiaries.

To address these potential challenges, CMS should consider a regulatory safe harbor or other clarifications for well-designed alternative payment models when the combined drug pricing and access reforms would lead to significantly lower unit drug prices coupled with much higher utilization. CMS should only apply this approach when the manufacturer (and any participating Medicare Advantage or Part D plan) provide clear evidence that per-unit drug net price will be significantly lower than under FFS, with the same or a lower expected unit price than would occur through the MFP, and that, in conjunction with manufacturer, provider, and payer steps (e.g., less or no utilization review) to increase uptake and improve patient outcomes, outcomes will be better as a result of higher utilization with lower total costs of care.

There is a strong policy rationale for exploring these arrangements because they provide incentives for drug manufacturers to work with payers and providers to increase drug access in ways that improve patient outcomes. These payment approaches should also become more attractive under the IRA, since, for the reasons described above, it would provide a pathway for the manufacturer to ramp up sales and reach additional populations faster – but with clear accountability that the increased utilization improves beneficiary outcomes and total Medicare spending.

For the reasons described above, we propose that CMS consider a regulatory safe harbor or similar explicit steps to highlight and encourage such alternative payment arrangements for drugs. In the absence of an exemption for such arrangements that lower total spending, manufacturers could be deterred from implementing alternative payment arrangements with payers and providers who are accountable for total costs of care, despite the alignment of these reforms with overall CMS goals.
Clarify how the manufacturer-specific factors will be used to guide the MFP, and collaborate to support accurate and efficient data collection

After considering the selected drug’s price of alternative treatment(s) and its clinical benefit compared to the alternatives, CMS will move to consider a range of manufacturer-specific factors listed in the IRA. These factors include the drug’s research and development (R&D) costs, production and distribution costs, revenue and sales volume, patent and regulatory exclusivity protections, and prior federal funding of R&D. Unlike CMS’s comparative effectiveness determinations, these factors are not reflective of the selected drug’s value, but instead consider its revenues versus its associated costs. This approach has been used less widely in drug price negotiations, and so it would be helpful to implement a stepwise approach to help assure the benefits in terms of reasonable and significant adjustments in the MFP outweigh the potentially costly and complex data collection and analysis.

The IRA provides little detail on how these factors would impact CMS’s pricing offer to a manufacturer. Consequently, to limit concerns about cost and uncertainty about potentially valuable investments in drugs, CMS appears to have broad discretion in deciding how to weigh these various data elements when making its pricing offer to the manufacturer. In the Guidance, CMS provides some insight into how these factors could directionally impact the price following the conclusion of the comparative effectiveness assessment. To prevent legal and perception risks, CMS should outline a clear, predictable, and transparent process that would describe how all these factors would be integrated to inform the price negotiation offers and counteroffers. This process should prioritize clarifying data provision and incorporation in MFP calculation based on the likely importance of the factor and the ease of obtaining reliable data to determine impact.

For example, a longer period of market exclusivity for a selected costly drug has a major impact on its revenues; as a result, how CMS considers remaining patent life is likely have a significant impact on the MFP determination. Consequently, CMS should consider prioritizing efforts to distinguish “clinically meaningful” secondary patents from those that were awarded for inventions that add little significant benefit to patients. Related, the agency should prioritize clarifying the standards it will be using to determine when a selected drug’s remaining patent life is “too long” to warrant a downward price adjustment.

Conversely, R&D costs and public support for R&D are more challenging to consider and factor into decisions, and at least in many cases, may have less impact on the MFP. First, the cost of capital will be difficult to determine (and could be quite high in the early stages of product development). Furthermore, a manufacturer may not even know the level of private investment in the selected drug if it acquired it from another company, which is the case for most drug products. Further, if a product was acquired, the expected value of any previous public investment was presumably incorporated in the acquisition price, meaning that it was the initial developer and not the acquirer who benefitted financially from said government support.

Finally, the agency plans to rely on several proprietary data elements submitted by the manufacturer in making its pricing adjustments, while maintaining transparency at the same time. It would be helpful for the agency to clarify how much of the negotiation process will be subject to public transparency and
how it intends to explain the MFP without sharing any proprietary information in the event that proprietary factors played an important role in its pricing decision. Providing and a clear and detailed summary of the reasons for a final MFP determination, while protecting proprietary information, will be critical for the Negotiation Program’s predictability and public support over time.

Clarify additional considerations for implementing the Negotiation Program

Especially in the early years of the Negotiation Program, some enforcement discretion from CMS on implementing the MFP may be appropriate to avoid adverse effects from MFP application. Potential examples where CMS may wish to use its enforcement discretion and exempt a selected drug from MFP application may include the following, non-exhaustive list of examples:

1. A selected drug’s comparative effectiveness assessment clearly yields a price that is significantly higher than the MFP ceiling. The drug’s manufacturer is also planning additional RWE development and product modifications that will lead to greater patient benefit. Applying the MFP in this case would limit incentives for further evidence and product improvements if the selected drug’s price cannot exceed the ceiling. Additionally, in this case, the manufacturer-reported factors do not lead to a price decrease (for example, the manufacturer has incurred high R&D costs with no prior government support, the drug has a short remaining patent life and high costs of production and distribution).

2. An orphan drug exempt from price negotiations as per the IRA’s requirements seeking to pursue label extension studies for additional indications. Such studies, which could benefit patients, might not occur given that expanding to additional indications would eliminate the drug’s exemption from negotiations.

3. Other areas where innovation is needed but is not occurring to a sufficient degree due to already-existing limited incentives. CMS should monitor for evidence of diminished investment in certain critical therapeutic areas that present their own distinct challenges and barriers after the IRA’s implementation, potentially through the dashboard described above.

Aside from care in implementing more aggressive negotiations in cases like these, especially in the early years of the Program, clarifying potential problem areas over time could also provide the basis for developing bipartisan support for any needed future revisions in the IRA, which are typically needed for the long-term success and sustainability of major complex legislation. Despite best efforts, any major new policy initiative may have undesirable consequences. The CMS implementation approach should also include a dashboard at the therapeutic class level to monitor for such consequences and have room to develop plans to address them if necessary. For example, some commenters have raised concerns that the relatively limited time that a manufacturer will now have before price reductions take place may have implications on the launch sequence of drugs, particularly small-molecule drugs, with manufacturers shifting marketing plans toward other highly developed countries first. Relevant RWE and clinical experience can be generated there and subsequently used in the U.S. immediately upon launch to gain broader adoption more quickly than would have occurred otherwise if the manufacturer had to generate that evidence after FDA approval. Such decisions, delaying access for U.S. patients,
would allow the manufacturer to capture greater financial benefit of the drug during the full 9 or 13 years before the Medicare price cuts take place. (At the same time, the IRA’s Part D redesign to provide more generous drug coverage with no beneficiary payments beyond $2000 may also have a significant impact on drug uptake and innovation by reducing financial barriers for beneficiaries that limit drug use, with no new tools for plans to negotiate lower prices.)

CMS should track metrics like U.S. versus ex-U.S. initial introductions of new drugs, particularly those that add value according to its own comparative assessment framework. Similarly, the CMS dashboard and regulatory process could track markers of potential issues in other areas where concerns about adverse impacts have been raised, such as diminished investment in therapeutic areas focused on Medicare beneficiaries and small-molecule versus biologic drugs, as well as the timing and extent (“effectiveness”) of generic and biosimilar competition. CMS could create a mechanism for stakeholder input into this evolving dashboard and the data that it collects on an ongoing basis, focusing on the beneficiary’s perspective.

Finally, CMS should use public comments like these and further internal analysis to clarify its general proposed standard for “robust and meaningful” competition from a generic or a biosimilar drug. Whether this standard has been met determines whether a selected drug should cease being a selected drug – a major regulatory decision point. A standard for how much generic or biosimilar entry has occurred does not appear in the IRA. At the very least, it would be helpful for CMS to establish clear guidelines and illustrations of how this standard could be satisfied, while noting that there are also issues that could prevent effective competition from a follow-on entrant in a way that is beyond their control (for example, certain rebates that may limit competitive entry). Setting the bar too high for this standard might deter generic and biosimilar competition, something which appears concerning as it is from the applications of the IRA’s negotiation provisions.

Conclusion

The Duke-Margolis Center appreciates this opportunity to provide feedback to CMS on the Guidance and CMS’s consideration of our comments. Our recommendations on the use of high-quality evidence and the design of drug payments to improve outcomes in conjunction with the IRA’s Negotiation Program can enable CMS to advance its mission of supporting the high-value, evidence-based, and affordable use of pharmaceuticals. Furthermore, we believe that a clear and predictable initial process for conducting the negotiations and mechanisms for public input and transparency in refining it over time will be important for a predictable and sustainable Negotiation Program and outcome. We and our colleagues would be pleased to provide more information on these issues if that would be helpful. If you have any questions, please contact Nitzan Arad (nitzan.arad@duke.edu) for more information. These comments are those of the authors at Duke-Margolis and are not reflective of the view of Duke University leadership, staff, or other affiliated individuals or organizations.

Sincerely,

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DISCLOSURE
Mark B. McClellan, MD, PhD, is an independent director on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and PrognomIQ; co-chairs the Guiding Committee for the Health Care Payment Learning and Action Network; and receives fees for serving as an advisor for Arsenal Capital Partners, Blackstone Life Sciences, and MITRE.