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April 14, 2023

The Honorable Meena Seshamani, M.D., Ph.D.  
CMS Deputy Administrator and Director of the Center for Medicare  
Centers for Medicare & Medicaid Services  
U.S. Department of Health and Human Services  
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Submitted Electronically via: [IRAREbateandNegotiation@cms.hhs.gov](mailto:IRAREbateandNegotiation@cms.hhs.gov)

**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 Deputy Administrator Seshamani:

The National Pharmaceutical Council (NPC) appreciates the opportunity to submit comments regarding the Centers for Medicare & Medicaid Services (CMS) Guidance, *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 or the Guidance).

NPC is a health policy research organization dedicated to the advancement of good evidence and science and to fostering an environment in the United States that supports medical innovation. We have rich experience conducting research and disseminating information about the critical issues of evidence, innovation and the value of medicines for patients. Our research helps inform important healthcare policy debates and supports the achievement of the best patient outcomes in the most efficient way possible.

NPC's research and that of others have found that public policies that reduce the incentives to invest in research and development result in less innovation, fewer treatment options, and lower life expectancy.<sup>1</sup> The Inflation Reduction Act (IRA or the Act) creates a new price-setting

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<sup>1</sup> Ciarametaro M and Buelt L. Assessing the effects of biopharmaceutical price regulation on innovation. 2022. <https://www.npcnow.org/resources/assessing-effects-biopharmaceutical-price-regulation-innovation>; Thomas A. Abbott & John A. Vernon, 2007. "The cost of US pharmaceutical price regulation: a financial simulation model of R&D decisions," *Managerial and Decision Economics*, John Wiley & Sons, Ltd., vol. 28(4-5), pages 293-306.; Leonard D. Schaeffer Center for

mechanism that will change the economic incentives for bringing new medicines to market, and evidence suggests manufacturers are already responding to those incentives.<sup>2</sup>

An important goal in implementation of the Act should be to set guidance that, to every extent possible, minimizes the deleterious impact of the IRA on the incentives for the development of innovative therapies as well as patient access. Unfortunately, we believe the Guidance does the opposite.

The price-setting mechanism described in the Guidance, incorrectly portrayed as “negotiation,” lacks clear standards for the evidence that will be used in the process and the transparency necessary for the public to reproduce or evaluate CMS’s process and decisions. It also minimizes the opportunity for patients, providers and other clinical experts to inform and participate continuously in the process. Furthermore, the effectuation of the Maximum Fair Price (MFP) and Part D formulary inclusion of selected drugs are built on a chassis ripe with perverse incentives and opportunities for fraud and abuse and provide minimal opportunity to prevent and detect unsavory activities.

The importance of implementing the price-setting provisions of the IRA in a manner that accurately values medicines and maintains patient access cannot be overstated. This new process forces manufacturers to accept CMS’s final price, face an unreasonable excise tax, or exit the market – all of which threaten the development of, and patient access to, new treatments or cures.

We understand that CMS has a statutory requirement to implement the IRA. We also note that many NPC members have long argued that the underlying structure of the negotiation program, as set forth by the statute and implemented here by CMS, is legally flawed. In review of the punishing penalties for non-compliance, and the general inflexibility of the process for product selection and maximum fair price (MFP) implementation, these legal flaws cannot be overcome through general guidance clarity at this stage.

Nevertheless, NPC appreciates the opportunity to provide input and provides herein several suggestions for CMS to consider that might be helpful in the transparency objective of the Agency as it implements this program. None of these resolve the more fundamental legal infirmities of the overall program, nor could they. NPC’s recommendations are summarized on the following pages:

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Health Policy & Economics. Annual Report 2020. <https://healthpolicy.usc.edu/wp-content/uploads/2021/03/Schaeffer-Center-2020-Annual-Report.pdf>

<sup>2</sup> Grogan J. (2022) The Inflation Reduction Act Is Already Killing Potential Cures. WSJ. <https://www.wsj.com/articles/the-inflation-reduction-act-killing-potential-cures-pharmaceutical-companies-treatment-patients-drugs-prescriptions-ira-manufacturers-11667508291> Longo, N. (2023). WTAS: Inflation Reduction Act already impacting R&D decisions. PhRMA. Available at: <https://catalyst.phrma.org/wtas-inflation-reduction-act-already-impacting-rd-decisions>; Powaleny, Andrew. (2023). IRA Impacts: Cancer treatment research and development. PhRMA. Available at: <https://catalyst.phrma.org/ira-impacts-cancer-treatment-research-and-development>; Longo, N. (2023). WTAS: Inflation Reduction Act already impacting R&D decisions. PhRMA. Available at: <https://catalyst.phrma.org/wtas-inflation-reduction-act-already-impacting-rd-decisions>; IRA survey: Biotech bracing for impact. Biocentury. March 16, 2023.

## **I. (Section 40) Requirements for Manufacturers of Selected Drugs**

- Allow the public to review the comments provided in response to the Guidance, as soon as possible after the end of the comment period while protecting the confidentiality and security of proprietary information.
- Remove the restrictions on manufacturers disclosing written or verbal information from CMS's offers or counteroffers, and the requirement that manufacturers destroy this information after the process is complete. This requirement deprives the public from learning about CMS's process and priorities and disadvantages manufacturers who may someday need to renegotiate with CMS.
- Provide manufacturers with Prescription Drug Event (PDE) data to verify the MFP is being provided only to MFP-eligible individuals.
- Commit to ensuring that providers report a "minimally necessary"<sup>3</sup> data set to the manufacturer or its vendor to be entitled to access the MFP.
- Abandon the burdensome and unworkable Primary/Secondary Manufacturer policy.

## **II. (Sections 50 and 60) Negotiation Factors and Process**

- Implement these sections with maximum transparency to provide manufacturers and other stakeholders the opportunity to inform, evaluate, and predict CMS's process and priorities in the overall negotiation process and the individual negotiations for selected drugs.
- Provide clarity on the choices of therapeutic alternative for each approved indication of selected drugs and ground those choices in current, evidence-based clinical practice. CMS should focus on clinical benefits and cost offsets when comparing treatments and determining value, and not reduce the preliminary price by information unrelated to the value of a treatment (e.g., cost-recovery, remaining exclusivity, etc.).
- Develop, communicate, and implement clear definitions of unmet need consistent with relevant patient populations' needs for each indication of selected drugs.
- Engage with patients and caregivers throughout the process to gain insights into the value, preferences for appropriate treatment, and the indirect costs that patients and their families bear, to inform the evaluation of the clinical benefit of a selected drug (evaluation process). It is essential to gain patient input to identify unmet needs, therapeutic alternatives, clinical and humanistic benefits.
- Create and implement a consistent framework that provides more information about how CMS will make decisions during the negotiation process, including the identification of therapeutic alternatives, a broader definition of unmet medical need, stakeholder involvement, and the evidence used to support CMS decisions. This information should be well-known before CMS begins its process, and the relative importance of these factors should be published in the final determination of the MFP.
- Apply well-established best practices for evidence evaluations from organizations including the Innovation and Value Initiative and ISPOR, the Professional Society for Health Economics and Outcomes Research. Provide clarity into the evidence standards

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<sup>3</sup> <https://www.hhs.gov/hipaa/for-professionals/faq/455/does-hipaa-permit-health-plans-to-disclose-information-to-pharmaceutical-manufacturers/index.html>

that CMS will use at all steps of the process, including when working with external organizations.

- CMS is making significant changes to Medicare policy and seeking to implement a complicated process in a short amount of time. In the interest of not harming patients' access to medicine – and the innovation ecosystem that creates new medicine - we encourage CMS to take the time needed to build a transparent and consistent process and methodology and to set prices at the ceiling price for initial price applicability year (IPAY) 2026.

### III. **(Section 110) Part D Formulary Inclusion of Selected Drugs**

- At a minimum, CMS should ensure people with Medicare do not experience decreased formulary access as a result of implementation.

We elaborate on these recommendations below.

#### **(Section 40) Requirements for Manufacturers of Selected Drugs**

##### *A. Improving Transparency in the Implementation Process*

The implementation of the Inflation Reduction Act (IRA) is the most significant prescription drug pricing intervention in the history of the Medicare program. It is being closely followed by those who invest in, research, and develop new cures. It is also being closely watched by health policy experts, pharmacoeconomic researchers, patient advocates, and others. CMS has a long history of publishing and responding to information provided by stakeholders when implementing new policies. Though the IRA text permitted implementation of the price-setting process via guidance, this Guidance opens CMS to criticism for creating an opaque process giving the agency maximum flexibility and latitude while failing to provide adequate clarity and details about how it will implement important provisions (e.g., identification of therapeutic alternatives, weighting of factors for initial offer, etc.).

We appreciate CMS communicating separately from the Guidance that it will make comments in response to the Guidance publicly available. CMS should allow the public to review the comments provided in response to the Guidance as soon as possible after the comment period ends, while protecting the confidentiality and security of proprietary information. Furthermore, CMS should respond to suggestions and comments provided in response to the Guidance to allow experts to evaluate the decisions made by CMS and the information on which these decisions were made. Depriving researchers and the public of the opportunity to learn from and provide continued input to this process is contrary to CMS's historical transparency and stakeholder engagement.

CMS should abandon the proposed data use provisions to enhance transparency, increase public confidence, and facilitate collaboration with manufacturers. Specifically, CMS should abandon the "data use provisions and limitations" that would prohibit manufacturers from disclosing information exchanged verbally or in writing about the agency's MFP decision-

making process. Scientific sessions attended by pharmacoeconomic researchers, managed care pharmacists, actuaries, and others are already rich with IRA content, and audiences are asking important questions about how the law will be implemented. Understanding what information CMS reviews, values, or excludes in the context of individual negotiations as well as with regard to the general process is essential to the advancement of learning in these disciplines.

More clarity about and transparency into this process also encourages industry scientists to create good pharmacoeconomic evidence during the drug development process. As useful pharmacoeconomic evidence takes time and money to create, it is important for all manufacturers to know what information CMS did or did not value during previous negotiations. Restricting the use of this information also prevents manufacturers from referring to these discussions when participating in the renegotiation process described in the statute but not included in this guidance.

Simply stated, squelching conversation between these disciplines not only hurts science; it also undermines the credibility of the agency's decision-making and further exposes it to public criticism.

#### *B. Decreasing the Potential for Payment Errors, Fraud, and Perverse Incentives*

We commend CMS for its desire to provide patients with access to the MFP at point of sale and for providing flexibility for manufacturers with MFP agreements to provide access to the MFP. As CMS heard in comments provided in response to the Office of the Inspector General's regulations to remove the safe harbor protection for prescription drug rebates, it is important to contemplate the workability of these new mechanisms.

NPC has a deep understanding of the pharmaceutical supply chain. As such, we have concerns and suggestions about the flow of funds and lack of data described in Section 40.4 (and the corresponding paragraphs in Section 90.2). Simply stated, the Guidance robustly describes manufacturer noncompliance, yet only offers one sentence about dispenser noncompliance. CMS should clarify that manufacturers require access to data or other mechanisms to verify eligibility or otherwise evaluate the process for providing access to MFP. Manufacturers should not be the only stakeholders (e.g., pharmacies, mail order services, and other dispensers) in the supply chain identified if an MFP is not made available to beneficiaries. CMS should monitor compliance across all parties if they proceed with establishing a toll-free phone line and email box that accepts claims of MFP non-compliance.

The pharmacy's actual acquisition cost is not known to or controlled by manufacturers, and the existing chargeback payments and rebate mechanisms are currently inadequate to effectuate the MFP, given the statutory responsibilities to provide access to the MFP and the 340B nonduplication provision. If, in the example CMS provides, the pharmacy's purchase price increased (or was reported to be higher) and the MFP remained constant, the amount of the reimbursement required from the manufacturer would increase. Likewise, if a prescription was

filled, billed, and returned to stock within the 14-day time frame proposed by CMS, the Part D plan would have the information necessary to reverse their payment to the pharmacy, but the manufacturer would not be aware of the need to reverse the MFP effectuation payment. This creates a significant economic incentive that could encourage inadvertent duplicate discounts or outright diversion or fraud that threatens the integrity of IRA implementation.

As such, we believe the 14-day timeframe proposed is unreasonable for manufacturers, and CMS should provide manufacturers with access to Prescription Drug Event (PDE) data to verify eligibility and base the MFP discount on a consistent, more widely available metric like Wholesale Acquisition Cost. CMS could also consider designating a third-party administrator to oversee this process for manufacturers choosing a retrospective approach.

Likewise, a lack of transparency in the 340B Drug Pricing Program, the potential for mixing mechanisms of chargebacks and rebates of 340B and MFP on the same National Drug Code (NDC), and the inconsistent timeframe and methods by which pharmacy claims are determined as 340B eligible, creates a significant potential for MFP and 340B duplicate discounts. Without additional verification from CMS, manufacturers will need to validate that 340B entities are only providing the MFP to eligible individuals.

To avoid duplication of 340B and MFP prices, CMS should require identification of 340B units at the point of sale at the time of dispensing (when the claim is created). The Agency should also commit to ensuring that providers report a “minimally necessary” data set to the manufacturer or its vendor to be entitled to access the MFP and for the purposes of validating their right to access in a timely manner, according to standard business practices and consistent with non-duplication requirements. CMS should expressly acknowledge that manufacturers will establish, receive, review, and, as necessary, audit MFP validation data to ensure MFP access is provided in accordance with the statute.

Given the complex interactions of the processes described above, CMS could establish a clearinghouse-type organization to identify 340B units dispensed or administered to Medicare enrollees. The 340B clearinghouse would act as a claims verifier, reviewing Part D PDE data as well as data submitted by 340B covered entities (or entities acting on their behalf) to confirm whether a claim is subject to a 340B agreement, similar to the role played by 340B third-party administrators (TPAs) and split-billing vendors today.

### C. *Primary/Secondary Manufacturer Definition*

NPC suggests that CMS abandon the Primary/Secondary Manufacturer policy. The primary and secondary manufacturer concept developed by CMS is unworkable, impractical, and not supported by the statute. Requiring one manufacturer to enter into an agreement with CMS that holds them responsible for the actions of another manufacturer (and potentially a competitor) unnecessarily complicates implementation and exposes manufacturers to potentially significant burden.

## **I. (Sections 50 and 60) Negotiation Factors and Process**

As stated earlier, many stakeholders are closely watching CMS's IRA implementation process. The price-setting process adopted for the first IPAY will be closely studied not just by manufacturers, but by the broader pharmacoeconomic, health policy, and patient advocacy communities. The credibility of CMS's process will be judged by the agency's use of good evidence and appropriate methods in a transparent and patient-centered process.

CMS has described a domestic reference price-setting mechanism that begins by identifying a therapeutic alternative and using its price as an initial starting point before adjusting for clinical benefits to achieve a preliminary price that is further adjusted by a variety of other factors unrelated to the value of a treatment.

We do not believe the Guidance describes a satisfactory process to determine the value of a medicine or set its price and note that it resembles processes used by countries outside of the United States that face significant delays in accessing innovation. We believe that only clinical benefit, health improvement and cost offsets associated with the treatment may be used to determine the value of a medicine. Adjusting reimbursement by the elements described in the manufacturer data elements (e.g., R&D costs, cost of production, patent life or exclusivity) will have disastrous effects on innovation and deny patients future treatments or future indications for existing treatments.

The statute requires CMS to use a "consistent methodology and process" for negotiation.<sup>4</sup> More clarity is needed than is provided in the Guidance to achieve that goal, especially related to the identification of therapeutic benefit and the weighting of factors used to determine the preliminary price and initial offer. Only when such clarity is provided can manufacturers and external stakeholders build their own models to anticipate, inform, and evaluate the process CMS operationalizes. Manufacturers in particular need more clarity to accurately prepare their submissions and meaningfully participate in the process.

As previously stated, CMS is making significant changes to Medicare policy and seeking to implement a complicated process in a short amount of time. In the interest of not harming patients' access to medicine – and the innovation ecosystem that creates new medicine – we encourage CMS to take the time needed to build a transparent and consistent process and methodology and to set prices at the ceiling price for IPAY 2026. Specific recommendations follow.

### **A. Development of a Transparent and Rigorous Evaluation and Price-Setting Process**

NPC encourages CMS to implement a transparent and inclusive evaluation process to promote credibility and support for their price-setting and counteroffer process. The agency is introducing comparative effectiveness to the Medicare program and making value determinations when establishing a "preliminary price" for selected drugs. A large and growing

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<sup>4</sup> SSA § 1194(b)(1).

body of research and guidance emphasizes the critical nature of transparency and methodological rigor during value assessment.<sup>5</sup> CMS should pursue analytic transparency by carefully considering data assumptions and highlighting the limitations and uncertainties of analyses to the public. By providing robust information about its evaluation criteria and the factors considered during the price-setting process, CMS can help build trust with all stakeholders and allow others to evaluate their process. Specifically, NPC encourages:

- **Engagement with key stakeholders throughout the assessment process** to ensure all perspectives are considered and have the opportunity to inform the assessment.<sup>6</sup> CMS should specifically seek and incorporate stakeholder feedback about their choice of therapeutic alternatives for each selected drug; the benefits of a selected drug to each stakeholder (including patients, clinicians, caregivers, manufacturers and other scientists); the meaning of unmet need to each stakeholder and the extent to which a selected drug meets that unmet need.<sup>7</sup>

CMS should seek patient input via a variety of mechanisms as the Information Collection Request process may not be the best way to reach this important stakeholder community. Given the important perspectives of patients and caregivers, we provide additional recommendations on meaningful patient input to the CMS process determining clinical benefit throughout this comment. Furthermore, manufacturers should be able to inform the selection of evidence about their products and verify information provided about their products from others.

- **The use of public comment periods during the negotiation process** with sufficient time to review materials and submit comments as well as transparency around how comments are considered and used or not used by the agency. The public has been given the ability to provide comments and read agency responses on policies with far

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<sup>5</sup> Berger ML, Sox H, Willke RJ, Brixner DL, Eichler HG, Goettsch W, Madigan D, Makady A, Schneeweiss S, Tarricone R, Wang SV, Watkins J, Mullins CD. Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Value Health*. 2017 Sep;20(8):1003-1008.; National Pharmaceutical Council. Guiding Practices for Patient-Centered Value Assessment. 2021. Washington, DC. Available at: <https://www.npcnow.org/sites/default/files/2021-04/npc-guiding-practices-for-patient-centered-value-assessment.pdf>; Drummond M, Schwartz JS, Jansson B, Luce BR, Neumann BR, Seibert U, Sullivan SD. Principle 10. Key Principles for the Improved Conduct of Health Technology Assessments for Resource Allocation Decisions. *International Journal of Technology Assessment in Health Care*. 2008. 24:3:250.; Oortwijn W, Huseareu D, Abelson J, Barasa E, Bayani DD, Canuto Santos V, Culyer A, Facey K, Grainger D, Kieslich K, Ollendorf D, Pichon-Riviere A, Sandman L, Strammiello V, Teerawattananon Y. Designing and Implementing Deliberative Processes for Health Technology Assessment: A Good Practices Report of a Joint HTAi/ISPOR Task Force. *Value Health*. 2022 Jun;25(6):869-886.; OMB, Circular A-4, Regulatory Analysis (April 6, 2023). Available at: <https://www.whitehouse.gov/wp-content/uploads/2023/04/DraftCircularA-4.pdf> (Circular A-4).

<sup>6</sup> Drummond M, Schwartz JS, Jansson B, Luce BR, Neumann BR, Seibert U, Sullivan SD. Key Principles for the Improved Conduct of Health Technology Assessments for Resource Allocation Decisions. *International Journal of Technology Assessment in Health Care*. 2008. 24:3:250.; Luce BR, Drummond MF, Dubois RW, Neumann PJ, Jönsson B, Siebert U, Schwartz JS. Principles for planning and conducting comparative effectiveness research. *J Comp Eff Res*. 2012 Sep;1(5):431-40; Oortwijn W, Huseareu D, Abelson J, et al. Designing and Implementing Deliberative Processes for Health Technology Assessment: A Good Practices Report of a Joint HTAi/ISPOR Task Force. *Int J Technol Assess Health Care*. 2022;38(1).

<sup>7</sup> Khavjou O, Bradley C, D'Angelo S, Buell N, Giombi K, Honeycutt A. Landscape Review and Summary of Patient and Stakeholder Perspectives on Value in Health and Health Care. August 2022. Available at: <https://www.pcori.org/sites/default/files/PCORI-Landscape-Review-Summary-Patient-Stakeholder-Perspectives-Value-Health-Health-Care-August-2022.pdf>



less patient impact, presumably not solely because of the Administrative Procedures Act but because it is the right thing to do. Public comments should be sought and published in an annual docket containing all key documents and decision points in an evaluation such as scoping documents, analytic protocols, and draft reports. Allowing sufficient time for interested stakeholders, including manufacturers of selected drugs, to review materials and prepare comments ensures that stakeholders can thoughtfully and comprehensively respond to the comment request. Providing transparency around how comments are addressed builds credibility and trust in the process.

- **Transparent and reproducible methods and results** to the extent possible, given the confidentiality required for proprietary information, methods, models (including all calculations). Assumptions should be transparent to interested stakeholders. This transparency, combined with the ability to reproduce results, will further build credibility and trust in the process.<sup>8</sup> Importantly, before negotiation begins, CMS should create and publish its decision-making framework – both generally and for selected drugs – which should include, at a minimum, information on:
  1. the therapeutic alternative(s) considered for each indication for selected drugs and the rationale for selection;
  2. the definition(s) of unmet need for each indication of selected drugs;
  3. the full range of benefits and impacts considered for each indication;
  4. the internal process and rationale for determining which benefits and impacts were included;
  5. a list of each stakeholder consulted;
  6. the source(s) of evidence considered, particularly clinicians and patients;
  7. how each benefit and impact considered influenced the final MFP, to include any algorithms, calculations, or modeling that related to MFP determination, as well as rationale for evidence that was not considered; and
  8. the limitations of the data collected and uncertainties in CMS’s decision-making. As is common in any rigorous, evidence-based process, this information should also be made clear when reported to the public.

These elements of CMS’s evaluation and MFP determination should be made public at distinct phases of evaluation. First, this draft framework should be made public as a scoping document prior to initiating stakeholder engagement and beginning data collection for CMS’s evaluation process. Secondly, preliminary results should be shared with manufacturers of selected drugs at least 60 days prior to initiating the negotiation process. Finally, results of this framework should be revealed to the public to explain the final MFP. Importantly, CMS should publish the required IPAY 2026 MFP explanations before IPAY 2027 negotiations begin.

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<sup>8</sup> Drummond M, Schwartz JS, Jansson B, Luce BR, Neumann BR, Seibert U, Sullivan SD. Key Principles for the Improved Conduct of Health Technology Assessments for Resource Allocation Decisions. *International Journal of Technology Assessment in Health Care*. 2008. 24:3:250.; Neumann PJ, et al. A Call for Open-Source Cost-Effectiveness Analysis. *Ann Intern Med*. 2017 Sep 19;167(6):432-433; Luce BR, Drummond MF, Dubois RW, Neumann PJ, Jönsson B, Siebert U, Schwartz JS. Principles for planning and conducting comparative effectiveness research. *J Comp Eff Res*. 2012 Sep;1(5):431-40.

- Robust engagement with manufacturers** consistent with the practices and policies of other payers and regulators.<sup>9</sup> Given their vast knowledge of their products and therapeutic areas, pharmaceutical manufacturers and their pharmacoeconomic researchers are critically important sources of information on the value of treatments for payer decision-making. Recognizing this, Congress and the U.S. Food and Drug Administration (FDA) have provided guidelines on how healthcare economic information (HCEI) can be provided to payers' pharmacy and therapeutics committees.<sup>10</sup> We encourage CMS to similarly provide opportunities for meaningful engagement with manufacturers. Existing industry best practices suggest the *minimum level of* engagement with manufacturers of selected drugs would be to meet with agency staff at three specific points during the MFP process: 1) after drug selection but prior to initiation of the price-setting process; 2) prior to CMS presenting the initial offer; and 3) the three meetings described by CMS as occurring after CMS presents the initial offer. All meetings should be offered as in-person, and we refer back to our comments on Section 40 about the importance of lessons learned during this process.

#### 1. Evaluation of data on product value for quality, particularly information on patient experience

The Guidance states that CMS will accept information on the benefits of selected drugs from the public and conduct its own literature reviews and database analyses. Open public submission of evidence is laudable and helpful, as stakeholders may have pertinent evidence that is not available in the published literature, or evidence which was not properly identified in the initial literature review. However, public submission comes with a cost of sorting through and identifying studies that are both high quality and relevant to the therapeutic alternatives and patient population.<sup>11</sup>

The results of an assessment depend on the evidence that underlies it, and the burden is on CMS to use and develop evidence in a systematic, transparent, and robust manner. To maximize credibility and trust in the assessment process, the procedures by which evidence is identified and included in the assessment should be objective, systematic, transparent, robust, reproducible, and made public as part of the scoping process. Not following widely accepted scientific best practices erodes trust in the process.

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<sup>9</sup> Smith JC, Snider DE, Pickering LK; Advisory Committee on Immunization Practices. Immunization policy development in the United States: the role of the Advisory Committee on Immunization Practices. *Ann Intern Med.* 2009 Jan 6;150(1):45-9.; Payer Engagement in HEOR. Ispor.org. Available at: <https://www.ispor.org/strategic-initiatives/payer-engagement-in-heor>

<sup>10</sup> Section 3630, "Facilitating Exchange of Product Information Prior to Approval" of H.R. 2617, Consolidated Appropriations Act, 2023; FDA. Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities Questions and Answers Guidance for Industry and Review Staff.; 2018. Available at: <https://www.fda.gov/media/133620/download>.

<sup>11</sup> Drummond M, Schwartz JS, Jansson B, Luce BR, Neumann BR, Seibert U, Sullivan SD. Principle 10. Key Principles for the Improved Conduct of Health Technology Assessments for Resource Allocation Decisions. *International Journal of Technology Assessment in Health Care.* 2008. 24:3:250.; Luce BR, Drummond MF, Dubois RW, Neumann PJ, Jönsson B, Siebert U, Schwartz JS. Principles for planning and conducting comparative effectiveness research. *J Comp Eff Res.* 2012 Sep;1(5):431-40.

Accordingly, we encourage CMS to develop robust, transparent standards for both submitted and internally generated data to ensure that evidence is methodologically rigorous and apply these same rigor and transparency standards to the agency's internal claims analysis and review when adjusting the MFP initial starting point based on clinical evidence. These standards can be informed by using accepted rubrics for evaluating study quality.<sup>12</sup> Evidence can be of varying quality and certainty, and the findings from individual studies can conflict with each other. To produce a meaningful and credible assessment, accepted methods should be used to evaluate quality and certainty of evidence and to determine how to handle conflicting evidence.<sup>13</sup> Grading rubrics should be fit for purpose and most appropriate for the type of evidence (e.g., clinical versus economic data). Procedures for evaluating evidence quality should be included in scoping documents, and the results should be made available through the value assessment.

We encourage CMS to follow and tailor as necessary consensus guidance on the conduct and evaluation of comparative effectiveness research (CER) that is both submitted and internally conducted.<sup>14</sup> Principles of good CER adopt elements of high-quality research methods, including: clear statements of objectives; transparency of process, data and methods; engagement of stakeholders and analytic perspectives reflecting multiple stakeholders; use of comparators relevant to current clinical practice; evaluation of outcomes relevant to the stated objectives; and explicit treatment of heterogeneity and uncertainty.

## 2. Inclusion of Treatment Costs and Cost Offsets

Costs should be representative of the net price most relevant to the user. Cost offsets are a driving component of drug value and actual transaction costs, and care should be taken to ensure that costs are as representative of the actual net cost to the payer and net revenue realized by the manufacturer as possible in order to achieve an accurate assessment. For biopharmaceuticals, following ISPOR good research practices for measuring drug costs can help

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<sup>12</sup> Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. *Value Health*. 2022 Jun;25(6):1060.; von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)statement: guidelines for reporting observational studies. *Lancet*. 2007 Oct 20;370(9596):1453-7.; The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness. *J Manag Care Spec Pharm*. 2016 Oct;22(10):1107-13.; Luce BR, Drummond MF, Dubois RW, Neumann PJ, Jönsson B, Siebert U, Schwartz JS. Principles for planning and conducting comparative effectiveness research. *J Comp Eff Res*. 2012 Sep;1(5):431-40.

<sup>13</sup> Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. *Value Health*. 2022 Jun;25(6):1060.; von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)statement: guidelines for reporting observational studies. *Lancet*. 2007 Oct 20;370(9596):1453-7.

<sup>14</sup> Berger ML, Sox H, Willke RJ, Brixner DL, Eichler HG, Goettsch W, Madigan D, Makady A, Schneeweiss S, Tarricone R, Wang SV, Watkins J, Mullins CD. Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Value Health*. 2017 Sep;20(8):1003-1008.; Dreyer NA, Bryant A, Velentgas P. The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness. *J Manag Care Spec Pharm*. 2016 Oct;22(10):1107-13.; Luce BR, Drummond MF, Dubois RW, Neumann PJ, Jönsson B, Siebert U, Schwartz JS. Principles for planning and conducting comparative effectiveness research. *J Comp Eff Res*. 2012 Sep;1(5):431-40.

achieve this objective.<sup>15</sup> In the case of MFP, CMS must ensure that cost data reflects discounts and rebates provided to Medicare and recognize that the net cost to the payer does not always represent the net revenue realized by the manufacturer.

We encourage CMS to also include comprehensive assessments of the economic benefits of selected drugs, in addition to the costs of the treatments themselves. In any assessment of the value of medical treatments, all healthcare costs and cost offsets should be included.<sup>16</sup> Treatments may have up-front costs that lead to long-term improvements in patient health. Those improvements may yield “cost offsets,” or savings due to reductions in resource needs, such as reduced hospitalizations. The full value of treatment can only be assessed by including both the treatment costs and cost offsets it may produce. Only considering the treatment costs but not the potential cost offsets would lead to an incomplete assessment of value.

When evaluating cost data, the time horizon should be long enough to incorporate the benefits of the treatment and the lower costs of medications when they become generic. Many of the cost-offset benefits of treatment, such as costs of avoided hospitalizations, show up in the longer-term. To measure the full value of a treatment, the time horizon for costs should be long enough to capture these cost offsets,<sup>17</sup> and to account for the lower costs of medications when generics and biosimilars are introduced.

### 3. Utilization of Best Practices Relevant to CMS’s Proposed Evidence Evaluation

We have cited in this response several publications on research best practices relevant to the agency’s evidence evaluation proposed in the Guidance. We encourage CMS to review and, wherever possible, utilize the guiding principles listed below to ensure the transparency, validity, and credibility of the annual price-setting process. In our foregoing recommendations, we have emphasized methodological issues that are relevant to the price-setting process proposed by CMS. We encourage CMS to consider these tools to the extent that the principles are appropriate for Medicare:

- *NPC’s Guiding Practices for Patient-Centered Value Assessment* includes 28 specific elements surrounding six key aspects of value assessment, including the assessment process, methodology, benefits, costs, evidence, and dissemination and utilization.<sup>18</sup>
- *Principles for planning and conducting comparative effectiveness research*, published by NPC researchers alongside a team of international collaborators, highlights thirteen principles for planning and conducting comparative effectiveness research.<sup>19</sup>

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<sup>15</sup> Hay JW, Smeeding J, Carroll NV, et al. Good research practices for measuring drug costs in cost effectiveness analyses: issues and recommendations: the ISPOR drug cost task force report – Part I. *Value Health* 2010;13:3-7.

<sup>16</sup> Drummond M, Schwartz JS, Jansson B, Luce BR, Neumann BR, Siebert U, Sullivan SD. Key Principles for the Improved Conduct of Health Technology Assessments for Resource Allocation Decisions. *International Journal of Technology Assessment in Health Care*. 2008. 24:3:250.

<sup>17</sup> Hay JW, Smeeding J, Carroll NV, et al. Good research practices for measuring drug costs in cost effectiveness analyses: issues and recommendations: the ISPOR drug cost task force report – Part I. *Value Health* 2010;13:3-7.

<sup>18</sup> National Pharmaceutical Council. *Guiding Practices for Patient-Centered Value Assessment*. 2021. Washington, DC. Available at: <https://www.npcnow.org/sites/default/files/2021-04/npc-guiding-practices-for-patient-centered-value-assessment.pdf>

<sup>19</sup> Luce BR, Drummond MF, Dubois RW, Neumann PJ, Jönsson B, Siebert U, Schwartz JS. Principles for planning and conducting comparative effectiveness research. *J Comp Eff Res*. 2012 Sep;1(5):431-40.

- *The Myth of Average: Why Individual Patient Difference Matter*, published by NPC, provides recommendations for ways improving the patient-centeredness of value assessment.<sup>20</sup>
- ISPOR and the International Society for Pharmacoepidemiology (ISPE) have published good practices for real-world data studies of comparative effectiveness with the goal of providing a trustworthy foundation for use of RWE in decision-making.<sup>21</sup>
- *Key principles for the improved conduct of health technology assessments for resource allocation decisions*, published by a leading team of value assessment experts, offers a set of 15 principles for health technology assessments.<sup>22</sup>
- The Innovation and Value Initiative provides recommendations applying the tools of value assessment, with an emphasis on consensus among stakeholder communities.<sup>23</sup>
- PhRMA's *Principles for Value Assessment Frameworks* offers 15 principles tailored to meeting patient needs and improving healthcare decision-making.<sup>24</sup>
- *Domains of Patient Centeredness in Value Assessment*, authored by the National Health Council (NHC), highlights the key areas for healthcare stakeholders to focus on when implementing patient perspectives in value assessments.<sup>25</sup>
- The NHC also created a Patient-Centered Value Model Rubric for healthcare stakeholders to assess the use of patient centeredness in value model development and to guide model developers on how to implement patient engagement throughout the value modeling process.<sup>26</sup>

#### B. Identification of Therapeutic Alternatives

The IRA instructs CMS to consider “the extent to which [a selected drug] represents a therapeutic advance as compared to existing therapeutic alternatives and the costs of such existing therapeutic alternatives”; however, it does not suggest that the cost of those alternatives should be used as a benchmark for an initial offer. The Guidance diverges from the statute because CMS intends to rely on Part D net price(s) or the Part B ASP of therapeutic alternatives “to determine a starting point for developing an initial offer.”<sup>27</sup>

<sup>20</sup> National Pharmaceutical Council. *The Myth of Average: Why Individual Patient Differences Matter*. 2022. Washington, DC. Available at: [https://www.npcnow.org/sites/default/files/2022-01/The\\_Myth\\_of\\_Average\\_01.2022.pdf](https://www.npcnow.org/sites/default/files/2022-01/The_Myth_of_Average_01.2022.pdf)

<sup>21</sup> Berger ML, Sox H, Willke RJ, Brixner DL, Eichler HG, Goettsch W, Madigan D, Makady A, Schneeweiss S, Tarricone R, Wang SV, Watkins J, Mullins CD. Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Value Health*. 2017 Sep;20(8):1003-1008.

<sup>22</sup> Drummond M, Schwartz JS, Jansson B, Luce BR, Neumann BR, Seibert U, Sullivan SD. Principle 10. Key Principles for the Improved Conduct of Health Technology Assessments for Resource Allocation Decisions. *International Journal of Technology Assessment in Health Care*. 2008. 24:3:250.

<sup>23</sup> Innovation and Value Initiative. Principles for Value assessment in the US. <https://thevalueinitiative.org/principles-for-value-assessment-in-the-us/>

<sup>24</sup> PhRMA. (2016). Principles for Value Assessment Frameworks. Available at: <https://phrma.org/resource-center/Topics/Cost-and-Value/Principles-for-Value-Assessment-Frameworks>

<sup>25</sup> National Health Council. Domains of Patient Centeredness in Value Assessment. 2020. Available at: [https://nationalhealthcouncil.org/wp-content/uploads/2020/03/NHC-One-Pagers\\_Domains.pdf](https://nationalhealthcouncil.org/wp-content/uploads/2020/03/NHC-One-Pagers_Domains.pdf)

<sup>26</sup> National Health Council. (2016). The Patient Voice in Value: The National Health Council Patient-Centered Value Model Rubric. Available at: <https://nationalhealthcouncil.org/wp-content/uploads/2020/11/20160328-NHC-Value-Model-Rubric-final.pdf>; National Health Council. (2021). Value Classroom. <https://nationalhealthcouncil.org/education/value-classroom/>

<sup>27</sup> SSA § 1194(e)(2)(A).

In any assessment of the relative clinical or economic benefits of a drug, the choice of the comparator is a fundamental driver in the outcomes and validity of the assessment with significant implications for patients, payers, and prescribers.<sup>28</sup> NPC recommends that the choice of comparators/therapeutic alternatives be driven by clinical appropriateness, informed by current treatment practices among a relevant patient population, and selected from potential comparators with the same treatment modality and class, rather than be dictated by cost, other concerns or implicit goals.<sup>29</sup> The selection of a less-costly therapeutic alternative lacking the safety, efficacy, and other clinical benefits of a selected drug – solely to lower the initial starting point of the price-setting process – fails to recognize the value of modern treatments and threatens to reverse the incentives that currently encourage innovation and access.

The use of a comparator that is not consistent with current clinical practice for given patients injects significant biases into the results and recommendations of a comparative assessment. Real world treatment decisions are based on numerous factors associated with the underlying disease and its severity, general health status or frailty, quality of life, and patient preferences.

The Agency for Healthcare Research and Quality's (AHRQ) Effective Health Care Program has produced guidance that may be helpful for CMS.<sup>30</sup> Specifically, the book reviews comparator selection in observational CER, noting that comparators “should reflect clinically meaningful choices in real-world practice and be chosen based on the study question being addressed.” AHRQ details how treatment selection bias (i.e., confounding by indication) may arise when disease severity, age, or other underlying health status differ between patients prescribed the drug being evaluated and the drug used as a comparator. The biases introduced by these factors can be minimized by choosing a comparator that has the same indication, similar contraindications, similar adverse effects, and the same treatment modality, class, and mechanism of action.

AHRQ also notes that selection of a comparator of the same treatment modality and class may result in less bias than comparison across modalities or classes.<sup>31</sup> We appreciate CMS's intent to begin identifying therapeutic alternatives within the same drug class based on chemical class, therapeutic class, or mechanism of action before considering therapeutic alternatives in other classes, and encourage CMS to prioritize reducing bias in treatment comparisons by identifying

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<sup>28</sup> Berger ML, Sox H, Willke RJ, et al. Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Value in Health*. 2017;20(8):1003-1008.

<sup>29</sup> Jaime Caro J, Eddy DM, Kan H, Kaltz C, Patel B, Eldessouki R, Briggs AH; ISPOR-AMCP-NPC Modeling CER Task Forces. Questionnaire to assess relevance and credibility of modeling studies for informing health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health*. 2014 Mar;17(2):174-82.; Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA, Sculpher MJ, Trikalinos TA, Russell LB, Siegel JE, Ganiats TG. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA*. 2016 Sep 13;316(10):1093-103.

<sup>30</sup> AHRQ. Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide. Content last reviewed March 2021. Effective Health Care Program, Agency for Healthcare Research and Quality, Rockville, MD. <https://effectivehealthcare.ahrq.gov/products/observational-cer-protocol>

<sup>31</sup> AHRQ. Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide. Content last reviewed March 2021. Effective Health Care Program, Agency for Healthcare Research and Quality, Rockville, MD. <https://effectivehealthcare.ahrq.gov/products/observational-cer-protocol>

therapeutic alternatives from potential comparators with the same treatment modality, class, and mechanism of action.

Furthermore, NPC encourages CMS to consult not only current disease-specific clinical guidelines created by physicians and peer-reviewed studies to identify potential therapeutic alternatives but also solicit input from clinicians with expertise in the disease or indication being considered, manufacturers, and patients. Guidelines are a very useful source of information, yet CMS should ensure the guidelines are up-to-date and incorporate the latest evidence.<sup>32</sup> CMS should also consider the use of market share data, comparative effectiveness studies and real-world evidence to support the selection of therapeutic alternative.

NPC cautions against using cost to determine a selected drug's therapeutic alternative(s). Rather, during selection of therapeutic alternatives, we encourage CMS to:

- Publicly communicate proposed therapeutic alternatives and permit feedback from manufacturers, clinicians with specific expertise in the treating the disease, patients and caregivers, and other stakeholders before proceeding with comparative effectiveness analyses that inform the initial offer.
- Include patient preferences and priorities that inform shared decision-making between appropriate treatment options.<sup>33</sup>
- Invite manufacturers to proactively present clinical information focused on the relative clinical benefit of their products compared to therapeutic alternatives during the process of comparator selection and give manufacturers the opportunity to respond to CMS' choices of therapeutic alternatives (which would also require advanced notice from CMS on which alternatives they will consider). Broad stakeholder engagement, including opportunities for technical input throughout the assessment and clear rules for manufacturer communication of evidence, have been identified as important steps in high-quality value assessment.<sup>34</sup> Early manufacturer communication is also consistent with practices employed by state Medicaid agencies, other federal agencies and commercial payers.
- Seek input from clinicians with specific expertise in treating the indication of the selected drug to define appropriate therapeutic alternatives among Medicare patient sub-populations, including patients with multiple comorbidities and varying levels of disease severity.<sup>35</sup> There is a long history of guidance to gain this information,<sup>36</sup> and

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<sup>32</sup> National Health Council. A Dialogue on Patient-Centered Value Assessment: Overcoming Barriers to Amplify the Patient Voice. December 2018. Available from: <https://www.nationalhealthcouncil.org/dialogue-patient-centered-value-assessmentovercoming-barriers-amplify-patient-voice>

<sup>33</sup> Schmidt T, Valuck T, Riposo J, et al. Impact of Shared Decision-Making and Patient Decision Aids on Health Care Cost and Utilization in the US: A Systematic Review. *J Clin Pathways*. 2022;8(8):33-43. doi:10.25270/jcp.2022.12.0

<sup>34</sup> Sorenson C, Lavezzari G, Daniel G, Burkholder R, Boutin M, Pezalla E, Sanders G, McClellan M. Advancing Value Assessment in the United States: A Multistakeholder Perspective. *Value Health*. 2017 Feb;20(2):299-307. doi: 10.1016/j.jval.2016.11.030.

<sup>35</sup> Drummond M, Schwartz JS, Jansson B, Luce BR, Neumann BR, Seibert U, Sullivan SD. Key Principles for the Improved Conduct of Health Technology Assessments for Resource Allocation Decisions. *International Journal of Technology Assessment in Health Care*. 2008. 24:3:250.; Luce BR, Drummond MF, Dubois RW, Neumann PJ, Jönsson B, Siebert U, Schwartz JS. Principles for planning and conducting comparative effectiveness research. *J Comp Eff Res*. 2012 Sep;1(5):431-40

<sup>36</sup> Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ*. 1999 Feb 27;318(7183):593-6.

NIH's National Center for Advancing Translational Sciences provides tools to help elicit valuable information from practicing clinicians.<sup>37</sup>

- Limit the choice of therapeutic alternative to drugs and biologics with FDA-approved indications and exclude off-label use from being compared to FDA-approved indications of selected drugs.

### C. Prioritize Patient and Caregiver Input

Patients' and caregivers' view of the drugs they take and the benefits they receive is essential to understanding "the full range of clinical and patient-centered outcomes",<sup>38</sup> as PCORI stated in their recent multi-stakeholder research initiative. The centrality of direct patient input is echoed in best practices for comparative effectiveness research and value assessment that underpin the concept that the price of pharmaceuticals should be based on the value they provide to patients, caregivers, healthcare systems, and society. Value encompasses the balance of benefits and costs experienced by patients and society over time. There are a multitude of specific benefits that constitute "value," from reducing mortality and improving patient functioning, quality of life, and productivity to outcome equity and societal value of scientific innovation, among others.<sup>39</sup>

Measures of "indirect costs" such as patient productivity, caregiver time, and treatment burden (such as travel times for repeated hospitalization) are very important to patients and their families but are often poorly captured in administrative claims databases. This misalignment between patient concerns and priorities surrounding the impact of a disease or its treatment and the outcomes data collected in research and care is well documented.<sup>40</sup> As stewards of the Medicare program accountable to the health of people with Medicare, CMS should include these issues throughout discussions with patients and patient groups and seek and utilize observational studies or real-world evidence that includes these outcomes.

Systematically and rigorously incorporating patient perspectives on the value of selected drugs is essential to ensure that patients have a voice in decisions that affect their health and wellbeing.<sup>41</sup> We are mindful of the federal prohibition on CMS's use of QALYs in coverage and reimbursement decisions. We also emphasize that direct engagement with patients identifies the measures of treatment benefit that patients and their families value, and therefore can avoid the potentially discriminatory nature of aggregate and limited measures such as the QALY. Thus, CMS should take tangible steps to capture the patient voice with validity and

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<sup>37</sup> NIH National Center for Advancing Translational Sciences. Toolkit for Creating Clinical Care Guidelines:

<https://toolkit.ncats.nih.gov/module/after-fda-approval/creating-clinical-care-guidelines/guideline-development-process/>

<sup>38</sup> Patient-Centered Outcomes Research Institute (PCORI). Landscape Review and Summary of Patient and Stakeholder Perspectives on Value in Health and Health Care. <https://www.pcori.org/resources/landscape-review-and-summary-patient-and-stakeholder-perspectives-value-health-and-health-care>

<sup>39</sup> Neumann PJ, Garrison LP, Willke RJ. The History and Future of the "ISPOR Value Flower": Addressing Limitations of Conventional Cost-Effectiveness Analysis. *Value Health*. 2022 Apr;25(4):558-565.

<sup>40</sup> Perfetto, E.M., Oehrlein, E.M., Love, T.R. et al. Patient-Centered Core Impact Sets: What They are and Why We Need Them. *Patient* 15, 619–627 (2022). <https://doi.org/10.1007/s40271-022-00583-x>

<sup>41</sup> Oortwijn W, Husereau D, Abelson J, et al. Designing and Implementing Deliberative Processes for Health Technology Assessment: A Good Practices Report of a Joint HTAi/ISPOR Task Force. *Int J Technol Assess Health Care*. 2022;38(1).



fidelity, engaging with patient groups directly to understand their perspective on the value of different pharmaceuticals at the following stages of the negotiation process:

### 1. Defining Unmet Need

The Guidance states that CMS intends to define unmet medical need “as treating a disease or condition in cases where very limited or no other treatment options exist.” This definition is substantially narrower than definitions of unmet need found in the peer-reviewed literature and promulgated by FDA as well as international agencies.

First, the CMS definition incorporates only one of ten elements of unmet medical need identified in a published scoping review (i.e., number of available treatments), an approach considered inadequate in published multi-stakeholder discussions.<sup>42</sup> The CMS definition of unmet need excludes remaining morbidity from alternative treatments, severity and burden of the disease, and size of the population, among other elements; by excluding treatments that address remaining morbidity from alternative treatments from the definition of unmet need, CMS ignores the considerable value of incremental innovation to patients.

Second, it significantly narrows FDA’s definition of unmet need, as outlined in its guidance for expedited programs. The FDA includes in its definition of unmet need improved efficacy, reduced toxicity and/or potential drug-drug interactions, and improvements in other benefits such as adherence.<sup>43</sup> Notably, the FDA definition of unmet need also highlights conditions for which there is significant heterogeneity in response to existing treatment options. Patients may respond differently to available treatment options due to pharmacologic differences, genetic risk, or social determinants of health, creating unmet need despite existing treatments.<sup>44</sup>

Finally, the CMS definition is even narrower than some international practices, which often evaluate unmet need in the context of broader concepts of novelty. These novel considerations include new methods of administration and dosing schedules as well as provision of benefits not captured in conventional measures of health gain (e.g., caregiver benefit, equity, and patient dignity).<sup>45</sup>

We believe assessments of unmet medical need should go beyond simply identifying the number of treatment alternatives in a therapeutic area and encourage CMS to expand their definition of unmet medical need to include a multifaceted definition informed by the patient perspective. Rigorous methods can be used to elicit consensus from clinician experts and have

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<sup>42</sup> Vreman RA, Heikkinen I, Schuurman A, et al. Unmet Medical Need: An Introduction to Definitions and Stakeholder Perceptions. *Value in Health*. 2019;22(11):1275-1282. doi:10.1016/j.jval.2019.07.007

<sup>43</sup> Food and Drug Administration. Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics. U.S. Department of Health and Human Services. May 2014. Silver Spring, MD. Available at: <https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf>

<sup>44</sup> National Pharmaceutical Council. The Myth of Average: Why Individual Patient Differences Matter. 2022. Washington, DC. Available at: [https://www.npcnow.org/sites/default/files/2022-01/The\\_Myth\\_of\\_Average\\_01.2022.pdf](https://www.npcnow.org/sites/default/files/2022-01/The_Myth_of_Average_01.2022.pdf)

<sup>45</sup> Synnott PG, Voehler D, Enright DE, Kowal S, Ollendorf DA. The Value of New: Consideration of Product Novelty in Health Technology Assessments of Pharmaceuticals. *Appl Health Econ Health Policy*. 2023 Mar;21(2):305-314. doi: 10.1007/s40258-022-00779-0. Epub 2022 Dec 19. PMID: 36529826

been used to identify unmet medical needs to achieve optimal treatment goals throughout the natural history of a disease.<sup>46</sup> These methods have identified patient-centered unmet needs, including patient quality of life, poor adherence, severe stages of a disease that are hard to treat, and patient preferred routes of administration.<sup>47</sup> Failure to capture the value of treatments that address patient-centered unmet needs disincentivizes innovations that meet those needs, in turn exacerbating disparities in health outcomes among patients receiving treatments less effective in their subgroups and/or unaligned with their preferences.

## 2. Selecting alternatives

As discussed above, the choice of comparator is the fundamental driver of any value assessment and its implications for patients and caregivers. Accordingly, patient preferences and priorities that inform shared decision-making between appropriate treatment options should be incorporated into CMS's process for selecting treatment alternatives.<sup>48</sup> Prioritizing the patient voice in defining unmet medical need promotes patient access to not only *any* treatment alternative but *satisfactory* and *appropriate* treatment options aligned with patient preferences.<sup>49</sup>

## 3. Determining clinical benefit

We encourage CMS to make use of resources to capture the patient's voice when selecting outcomes for evaluation of relative clinical benefit and to emphasize patient-centered benefits throughout its evaluation process. People with Medicare may prioritize different outcomes, such as symptom relief, improved quality of life, or indirect benefits such as caregiver burden, compared to clinical outcomes like survival or disease progression.<sup>50</sup> Subgroups of people with Medicare may also have different priorities. Our research has identified heterogeneous patient preferences for both treatment characteristics and outcomes,<sup>51</sup> demonstrating the benefits associated with novel drugs and formulations that provide patients and providers with preference-aligned treatment options. Accordingly, patient preferences regarding the benefits and risks of a product, its available dosage forms, and any innovative delivery systems should be included early in the assessment. Patient preference information can inform many aspects of evaluation of benefit in value assessment, including defining what benefits are most important to patients, selecting measures to quantify benefits, and supplementing health state

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<sup>46</sup> Danese S, Allez M, Van Bodegraven AA, et al. Unmet Medical Needs in Ulcerative Colitis: An Expert Group Consensus. *Digestive Diseases*. 2019;37(4):266-283. doi:10.1159/000496739

<sup>47</sup> Danese S, Allez M, Van Bodegraven AA, et al. Unmet Medical Needs in Ulcerative Colitis: An Expert Group Consensus. *Digestive Diseases*. 2019;37(4):266-283. doi:10.1159/000496739

<sup>48</sup> Schmidt T, Valuck T, Riposo J, et al. Impact of Shared Decision-Making and Patient Decision Aids on Health Care Cost and Utilization in the US: A Systematic Review. *J Clin Pathways*. 2022;8(8):33-43. doi:10.25270/jcp.2022.12.0

<sup>49</sup> Zhang K, Kumar G, Skedgel C. Towards a New Understanding of Unmet Medical Need. *Appl Health Econ Health Policy*. 2021;19(6):785-788. doi:10.1007/s40258-021-00655-3

<sup>50</sup> Ciarametaro M, Buelt L, Dubois RW. Getting Value Right: The Case For Indirect Benefits. Published online 2020. doi:10.1377/forefront.20200310.267867

<sup>51</sup> Hollin IL, González JM, Buelt L, Ciarametaro M, Dubois RW. Do Patient Preferences Align With Value Frameworks? A Discrete-Choice Experiment of Patients With Breast Cancer. *MDM Policy & Practice*. 2020;5(1). doi:10.1177/2381468320928012

utilities.<sup>52</sup> The FDA has created useful backgrounders and issued guidance on collection and use of patient preference information.<sup>53</sup>

In evaluating relative clinical benefit, we encourage CMS to consider patient-reported outcomes that are complete, comprehensive, and fit for purpose, as opposed to limited, QALY utility-based approaches, including QALYs in or outside of a life-extension context.<sup>54</sup> Fit-for-purpose tools may include disease-specific measures in addition to overarching measures, as well as other outcomes that are meaningful to patients, including productivity, treatment and caregiver burden, and downstream healthcare utilization. Societal benefits, including scientific spillover, limiting the fear and risk of contagion for infectious diseases, and increasing equity have also been recognized as important elements of value.<sup>55</sup>

Comprehensive approaches to measuring patient-centered value, including incorporation of factors beyond effectiveness and side effects, will result in more meaningful comparisons.<sup>56</sup> Multi-criteria decision analysis (MCDA) is widely recognized and accepted methodology to aggregating different dimensions of value for patient-centered value assessment.<sup>57</sup> Importantly, MCDA addresses many of concerns of discrimination against disabled and elderly patient that are inherent in utility-based QALYs. While MCDA has important advantages over CEA and other non-consensus methods, it is simply one input to payer decision-making.

CMS has a longstanding commitment to beneficiary engagement. By engaging with patients through surveys, advisory panels, and other forms of direct engagement, CMS can ensure that they are receiving comprehensive and representative information directly from patients to better inform CMS evaluations. We also encourage CMS to emphasize its commitment to patient engagement by including, in its initial offer and price justification, how the patient experience was considered in the evaluation of unmet need, selection of treatment alternatives, and evaluation of clinical benefit.

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<sup>52</sup> Marsh K, de Bekker-Grob E, Cook N, Collacott H, Danyliv A. How to integrate evidence from patient preference studies into health technology assessment: a critical review and recommendations. *International Journal of Technology Assessment in Health Care*. 2021;37(1).

<sup>53</sup> FDA. Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities Questions and Answers Guidance for Industry and Review Staff.; 2018. Available at: <https://www.fda.gov/media/133620/download>

<sup>54</sup> Brown J, Cryer DR. Is the QALY Fit for Purpose? *Am J Accountable Care*. 2021;9(2):8-13.

<sup>55</sup> Lakdawalla DN, Doshi JA, Garrison LP Jr, Phelps CE, Basu A, Danzon PM. Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report [3]. *Value Health*. 2018 Feb;21(2):131-139. doi: 10.1016/j.jval.2017.12.007.

<sup>56</sup> Westrich K, Lisabeth Buelt M. *Current Landscape: Value Assessment Frameworks*. Washington, DC: National Pharmaceutical Council; 2016.

<sup>57</sup> National Pharmaceutical Council. *Multi-Criteria Decision Analysis: Can It Help Make Value Assessment More Patient Centered?* 2020. Washington, DC. Available at: <https://www.npcnow.org/sites/default/files/media/2020mcda-roundtable-nhc-npc-whitepaper-final.pdf>; Mendola ND, Oehrlein E, Perfetto EM, Westrich K, McQueen RB. Stakeholder perception of pharmaceutical value: A multicriteria decision analysis pilot case study for value assessment in the United States. *J Manag Care Spec Pharm*. 2022 Oct;28(10):1190-1196.

## II. **(Section 110) Part D Formulary Inclusion of Selected Drugs**

The IRA requires Part D plan sponsors to include on their formularies drugs for which an MFP is available. However, the perverse incentives that remain in the ecosystem could be exacerbated because the MFP process will occur concurrently with Part D redesign; more so if selected drugs are in competitive classes and may be priced below the ceiling price. This could lead to adverse tiering impacting patient copayments and/or formulary-driven switching, increased utilization management, or other reductions in beneficiary access thwarting the intent of the MFP process and undermining the competition that has made Medicare Part D a success.

Experts have already warned that the intersection of MFP and Part D redesign provisions are likely to increase formulary exclusions.<sup>58</sup> CMS should provide additional guidance about how to ensure selected and non-selected treatments are included in Part D formularies. CMS should also consider the risk of Medicare Prescription Drug Plans (PDPs) penalizing selected drugs compared to non-selected drugs in the same therapeutic class with adverse tiering or overly burdensome utilization management. CMS should also redefine Part D negotiated price to include all manufacturer price concessions, which would put less pressure on plan sponsors in the catastrophic phase of the benefit and decrease beneficiary coinsurance for both selected and non-selected drugs.

NPC and others will be closely monitoring changes to patient access as a result of IRA and encourages the agency to pay close attention to decreased access or discriminatory behavior.

## III. **General Comments**

### A. *Adjusting the preliminary price downward for existing patents and exclusivities*

In section 60.3.4, Consideration of Manufacturer-Specific Data, the Guidance specifies that the agency intends to “*consider the length of the available patents and exclusivities before the selected drug may no longer be single source. For example, if the selected drug has patents and exclusivities that will last for a number of years, CMS may consider adjusting the preliminary price downward.*” The IRA statute establishes an applicable percentage of non-FAMP ceiling price based on the length of time since a selected drug was approved. Because that formula already factors in historical exclusivity periods, adjusting the price downward represents a double counting not expressly permitted in the statute.

NPC disagrees with CMS’ proposal to adjust the preliminary price downward for selected drugs that have existing patents and exclusivities, including Orphan Drug Exclusivity and Pediatric Exclusivity. Patents and regulatory exclusivity are critical mechanisms to accelerate innovation and incentivize research and development for both existing and emerging products, particularly

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<sup>58</sup> Kelly C. Medicare Part D Redesign Could Expand Rebate-Driven Formulary Exclusions in Program. The Pink Sheet. January 26, 2023. <https://pink.pharmaintelligence.informa.com/PS147634/Medicare-Part-D-Redesign-Could-Expand-Rebate-Driven-Formulary-Exclusions-In-Program>

when addressing unmet needs in orphan and pediatric populations.<sup>59</sup> Accordingly, this proposal will hinder innovation in areas where vital momentum to develop clinically important therapies has increased over time.

Orphan drug development has accelerated over the past four decades, resulting in more novel treatments for patients with rare diseases, particularly in the therapeutic areas of oncology, neurology, and infectious disease.<sup>60</sup> Pediatric research has also grown considerably, with nearly all drugs granted exclusivity for pediatric research receiving new pediatric labeling, most often a new or expanded pediatric indication.<sup>61</sup>

## B. Orphan drug development

Though CMS published Section 30 of the guidance as final, we are encouraged that the agency *“is considering whether there are additional actions CMS can take in its implementation of the Negotiation Program to best support orphan drug development.”* People with rare diseases face significantly higher health care costs,<sup>62</sup> and these patients and their families highly value the current and future treatments that meet their needs. Furthermore, the small patient populations for which orphan drugs are indicated are highly sensitive to changes in the research and development landscape, and the companies that develop orphan drugs are additionally highly sensitive to changes in the reimbursement landscape – especially those that threaten their ability to bring new orphan treatment to market and conduct post-approval research and development.

As such, we encourage CMS to broadly interpret the discretion provided by the IRA statute to exclude orphan drugs from negotiation and when determining the number of designations and indications that exempt an orphan product from selection. For example,

- CMS should incorporate the definition in the Orphan Drug Act and exclude from negotiation a drug intended to treat a condition affecting fewer than 200,000 persons in the United States. CMS’s too-narrow orphan drug exclusion jeopardizes the development of rare disease therapies that treat fewer than 200,000 patients across multiple indications.
- CMS should support orphan drug development by clarifying that for orphan drugs the 7- or 11-year period that must elapse before a drug can be considered for negotiation begins upon the date that the orphan drug exclusion no longer applies.

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<sup>59</sup> Grabowski HG, DiMasi JA, Long G. The roles of patents and research and development incentives in biopharmaceutical innovation. *Health Aff (Millwood)*. 2015 Feb;34(2):302-10. doi: 10.1377/hlthaff.2014.1047.

<sup>60</sup> Miller, K.L., Fermaglich, L.J. & Maynard, J. Using four decades of FDA orphan drug designations to describe trends in rare disease drug development: substantial growth seen in development of drugs for rare oncologic, neurologic, and pediatric-onset diseases. *Orphanet J Rare Dis* **16**, 265 (2021). <https://doi.org/10.1186/s13023-021-01901-6>

<sup>61</sup> Wharton GT, Murphy MD, Avant D, et al. Impact of Pediatric Exclusivity on Drug Labeling and Demonstrations of Efficacy. *Pediatrics* 2014 Aug;134(2):e512-8. doi: 10.1542/peds.2013-2987. Epub 2014 Jul 14

<sup>62</sup> Tisdale, A., Cutillo, C.M., Nathan, R. *et al.* The IDeaS initiative: pilot study to assess the impact of rare diseases on patients and healthcare systems. *Orphanet J Rare Dis* **16**, 429 (2021). <https://doi.org/10.1186/s13023-021-02061-3>

### C. Application of MFP across dosage forms and strengths

NPC appreciates that CMS is seeking comments under section 60.5 on approaches to the application of the MFP across dosage forms and strengths that could accurately and fairly compensate manufacturers and other entities. As stated earlier in this document, our research demonstrates how novel formulations provide patients and providers with treatment options that account for heterogeneous patient preferences<sup>63</sup> and promote medication adherence through reduced regimen complexity.<sup>64</sup> Given the documented value of dosage form innovation on patient-centered care and outcomes, NPC encourages CMS to incorporate the value of novel formulations in its price determination and negotiation process.


We also recommend that CMS provide more clarity in the calculation of 30-day equivalent supplies. The use of loading doses, weight-based dosing, and severity-based dosing are common clinical practices that result in the amount of medicine being used by one patient being different than that used by others. This is yet another reason why CMS should consult with manufacturers early and often in its process, and openly communicate important information such as the agency's estimation of a 30-day equivalent supply and how that compares with actual use across the Medicare population.

NPC is disappointed that CMS chose a broad and sweeping approach to defining qualifying single-source drugs in Section 30 and did not invite stakeholder feedback on that process. The definition ignores the value of novel formulations and delivery systems, which should be considered at the selection phase of the process not the MFP application phase.

### IV. **Conclusion**

The National Pharmaceutical Council appreciates the opportunity to submit comments in response to this Guidance and looks forward to additional opportunities to engage with CMS as it implements the Medicare Drug Price Negotiation Program. Please contact me at [john.obrien@npcnow.org](mailto:john.obrien@npcnow.org) or (202) 827-2080 if we may provide any additional information.

Sincerely,



John Michael O'Brien, PharmD, MPH  
President & Chief Executive Officer

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<sup>63</sup> Hollin IL, González JM, Buelt L, Ciarametaro M, Dubois RW. Do Patient Preferences Align With Value Frameworks? A Discrete-Choice Experiment of Patients With Breast Cancer. *MDM Policy & Practice*. 2020;5(1). doi:[10.1177/2381468320928012](https://doi.org/10.1177/2381468320928012)

<sup>64</sup> Wertheimer AI, Santella TM, Finestone AJ, Levy RA. Drug delivery systems improve pharmaceutical profile and facilitate medication adherence. *Adv Ther*. 2005 Nov-Dec;22(6):559-77. doi: 10.1007/BF02849950.