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April 14, 2023

Meena Seshamani, MD, PhD
Deputy Administrator
Center for Medicare & Medicaid Services (CMS)
Hubert H. Humphrey Building
200 Independence Avenue SW
Washington, DC 20201

Sent via electronic mail

Re: Comments on *Medicare Drug Price Negotiation Program: Initial Memorandum, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026*

Dear Dr. Seshamani:

The EveryLife Foundation for Rare Diseases appreciates the opportunity to comment on the March 15, 2023 initial memorandum on the Medicare Drug Price Negotiation Program (MDPNP). The EveryLife Foundation was founded to empower the rare disease patient community and focuses on a range of public policy issues at both the federal and state levels. Ensuring every person with a rare disease or condition can obtain affordable access to any medication approved by the Food and Drug Administration (FDA) is a top priority.

The Foundation recognizes and appreciates the intent behind the prescription drug negotiation program established by the Inflation Reduction Act. We understand the frustration Congress and most Americans have with the high costs of prescription medications. But we also recognize that multiple factors contribute to the costs of prescription drugs and believe an effective solution will be informed by understanding the systemic cost drivers that impact the entire healthcare system as opposed to disproportionately focusing on any single sector. We urge policymakers to recognize the transformational impact many prescription medications have had on countless American lives, including the lives of those suffering from a rare disease or disorder, as well as their role in reducing or preventing costs in other areas of healthcare, such as inpatient admissions, as well immeasurable life years saved.

The EveryLife Foundation appreciates the opportunity to provide feedback on the implementation of the MDPNP. We recognize CMS was not required to solicit public input in this phase of implementation; however, the patient community remains concerned with the limited opportunities offered for stakeholder feedback given the timelines outlined in the March 15th guidance. We join with other patient advocacy organizations in calling for CMS to utilize official notice and comment opportunities as the MDPNP implementation continues.

Earlier this year, the rare disease community commemorated the 40th anniversary of the enactment of the Orphan Drug Act (ODA) into law. Before the ODA became law, there was little biopharmaceutical interest in developing medications for rare diseases. In the four decades since its enactment, the FDA has issued more than 1,100 orphan designated approvals to treat rare diseases and disorders. This is unquestionably a success story, but that work is far from finished. The stark reality is that even 40 years after the ODA, 95% of all rare diseases and disorders lack any FDA-approved treatment. And while the ODA turned a once barren landscape into a vibrant ecosystem, developing treatments for rare diseases remains a highly challenging pursuit.

We appreciate that Congress recognized, at least partially, the challenges associated with rare disease therapy development by excluding a product that is approved to treat a single rare disease or condition from the Medicare negotiations. While we believe that the exemption, as written, is too narrow, we are especially concerned that the interpretation of this exemption as laid out in the March 15th guidance is even more restrictive than Congress intended and will have a serious negative impact on any industry incentives to evaluate a potential second, third or further application of a rare disease drug to another disease or condition.

As a rare disease-focused organization, we are particularly concerned about the lack of opportunity to provide input into the criteria for determining eligible products for the initial price applicability year of 2026. Given the implications of the criteria for determining eligibility of some orphan products on the highly sensitive rare disease therapeutic development ecosystem, we have provided comments and requests for clarification for the agency'sconsideration.

Additionally, our comments focus on the following areas:

- **Orphan drug designated approvals vs designations when determining eligibility**
- **Broadening and Clarifying the Definition of Unmet Need**
- **Methods for Determining Clinical Benefit - Process for Identifying Therapeutic Alternatives, Comparators, Exclusion of QALYs, Patient Experience Data**
- **Communication and Engagement Throughout the MDPNP**
- **Ensure Timely Access to Therapies**
- **Beneficiary Outreach and Protections**
- **Implement a Robust Monitoring Program**

Application of the Orphan Drug Exemption – Clarifications to Preserve Orphan Drug Incentives

CMS should consider orphan drug designated approvals vs designations when determining eligibility

As CMS knows, seeking and receiving orphan designation for a candidate therapy is not the same as submitting an application for a therapy's approval. The former process typically occurs relatively early in the product development process, typically many years if not longer before any possible approval is granted. We urge CMS to explicitly state that a drug with an orphan designation will not lose its orphan drug exclusion simply if it applies for and receives a designation for a second orphan medication. In addition, we urge FDA and CMS to establish a clearly defined process for FDA to share updates with CMS on both designations and eventual approvals. Given the risks of therapy development, including in exploring the repurposing of a drug approved to treat one condition for efficacy in treating another condition, simply obtaining an orphan designation should not result in any changes to an orphan exclusion. We already know there is widespread off-label use of drugs to treat rare conditions and are

concerned that loss of the orphan drug exclusion upon granting of a designation rather than approval would only further exacerbate this problem. Therefore, we urge CMS to clarify this point and further clarify that the orphan drug exclusion under current law would only be lost if FDA approves the same drug for treating a second disease or condition.

CMS should clearly articulate how it will address rare disease drugs within the letter of the current law

We appreciate the point in the memorandum that *"CMS will use the FDA Orphan product designation database and approvals on the FDA website"* and urge further clarification of this intent. Clarity on how CMS plans to implement the orphan exclusion, including by explicitly stating how it will interpret the requirement that all approvals be within one disease area, is highly encouraged. With the advancements in personalized medicine, there has been an increase in drug development for specific mutations or subtypes of disease. We believe CMS should act within their authority under the law to clarify they will consider separate approvals for different mutations or subtypes of one disease as still eligible for the orphan drug exemption. Without this clarity there will likely be diminished willingness to invest in the additional clinical research necessary to demonstrate effectiveness for other components of the patient population, leaving healthcare professionals, patients, and payers without the evidence they need to make informed decisions about appropriate use.

There are several examples of approved products and those in the pipeline that demonstrate the importance of preserving the exemption if all approvals are within mutations or subtypes of one disease. For example, Kalydeco received its original orphan designation in 2006 and its first approval in 2012. The original approved label was for one CFTR mutation (G551D) for patients 6 years and above. Over the next ten years, it received ten additional approvals, addressing 37 unique gene mutations on the CFTR gene that can cause cystic fibrosis. With each successive approval, more and more patients, who once had few to no treatment options, were able to benefit from this first in class innovative treatment with the confidence that the drug was appropriate for them. Ongoing efforts to develop therapies for diseases like ALS, MPS and other genetic diseases may face similar trajectories; and if not clarified, CMS risks negatively impacting the likelihood of these programs reaching the full range of potential eligible patients.

CMS should identify potential impacts related to changes in formulation

We urge CMS to clarify how the agency will address a potential situation in which a sponsor puts forward a new formulation that is clinically superior compared to the original formulation. The first-generation unity recognizes that first generation therapies may often be limited in their overall efficacy. But it is our hope that through further research, development, and exploration, product developers will produce more efficacious second, third, and subsequent generation treatments, including superior formulations of a first-generation product. We urge CMS to articulate how, for the purposes of IRA implementation, it plans to treat instances in which it determines that a new formulation warrants a product's designation as a new molecular entity.

CMS should address combination therapies involving one or more rare diseases:

We encourage CMS to state how the agency will address medications that are a combination of two products. For example, if one of the two products is approved to treat a second orphan drug, how would that impact the exclusion for the combination product?

Factors Relevant to the Determination of Maximum Fair Price

Broadening and Clarifying the Definition of Unmet Need

Though we appreciate the guidance defined an unmet need as "treating a disease or conditions in cases where very limited or no other treatment options exist," we urge CMS to clarify how it defines *limited treatment options* and how it will determine unmet need overall. A too narrow definition runs the risk of disincentivizing further therapy development in a space that still requires additional treatment at the risk of not meeting the unmet need exemption. Often within the rare disease space, drugs will be approved that only address one aspect of a condition or one specific mutation that can cause the disease or may be intended to slow disease progression but is not curative. A too narrow definition that does not take into account how treatments are utilized runs the risk of stunting interest in finding new and better treatments for the community.

Methods for Determining Clinical Benefit - Process for Identifying Therapeutic Alternatives, Comparators, Exclusion of QALYs, Patient Experience Data

We appreciate CMS's thoughtful considerations on the identification of therapeutic alternatives and the several points raised related to our rare disease community's priorities.

With respect to the identification of *Indications for the Selected Drug and Therapeutic Alternatives for Each Indication (60.3.1),* CMS has stated that therapeutic alternatives for each indication of the selected drug will be considered. CMS has further stated that *it "considered evaluating non-pharmaceutical therapeutic alternatives; however, for initial price applicability year 2026, the agency plans to only consider therapeutic alternatives that are covered Part D or Part B drugs or biologics. CMS believes that pharmaceutical therapeutic alternatives will be the most analogous alternatives to the selected drug when considering treatment effect and price differentials."* We concur that pharmaceutical alternatives are most appropriate comparators of the selected drugs and urge CMS to make permanent the consideration of only pharmaceutical therapeutic alternatives. In addition, we ask CMS to not consider *drugs* approved for each indication to be appropriate comparators to *biologics* within the same indication.

Related to the analysis of *Selected Drugs with Therapeutic Alternative(s) (60.3.3),* we are appreciative of CMS' emphases on the products' outcomes and safety profiles.

We applaud CMS' exclusion of metrics that treat extending the life of any individual as lower value than the life of another individual; this includes QALYs when used in association with life extension. Evidence that values extending the lives of some as less than extending the lives of others, whether based on disability status, age, diagnosis, demographic, or special populations, is unethical. We appreciate that CMS is seeking input on what other measures should also be considered inappropriate, and equally as important, which measures should be considered appropriate for use.

In addition to the outcomes listed by CMS for consideration (safety, efficacy, health outcomes, intermediate outcomes, surrogate endpoints, patient-reported outcomes), we suggest that CMS consider measures that are seen as beneficial to patients and caregivers[1]. Those include measures that capture direct medical costs, especially out-of-pocket costs; non-medical costs to patients and families, effects on future costs, and work loss and absenteeism. The National Economic Burden of Rare Disease Study estimated the overall annual economic burden of rare disease in 2019 exceeded $966 billion in the United States. Of the total economic burden, the largest costs were indirect costs from productivity losses at $437 billion, direct medical costs at $418 billion and non-medical and uncovered healthcare costs of $111 billion absorbed directly by families living with rare diseases. Aside from absenteeism, inpatient care was the biggest expense, accounting for nearly 15% of the overall economic burden while prescription medication and administration costs accounted for about 10% and outpatient care for about 6%. Meaningful assessments of product affordability must focus on more than just one aspect of the overall health care system[2].

As the science of Patient-Focused Drug Development has evolved beyond the regulatory ecosystem, several organizations and initiatives have served as leaders within this space. To that end, CMS should work closely with patient communities, as well as partners such as the Innovation and Value Initiative (IVI), the National Health Council (NHC), the Institute for Gene Therapies (IGT), PAVE (the Patient Driven Values in Healthcare Evaluation) within the University of Maryland School of Pharmacy, and other leaders within this space who are leading innovative, patient-centered valuation efforts.

Communication and Engagement Throughout the MDPNP

We appreciate the agency's interest in creating a useful public explanation for the negotiated MFP. There is a great deal at stake for the rare disease community and a clear understanding of what factors were considered in determining the MFP is necessary to guide ongoing stakeholder engagement and clarity to the investment community that catalyzes most rare disease therapy development. As communities, we have evolved our engagement within the neighboring product development and regulatory ecosystems and have developed processes that enable engagement, patient experience data inclusion, and transparency.

While fewer than 5% of the more than 10,000 rare diseases have any FDA-approved disease-modifying therapies, we are grateful for recent breakthroughs that have extended the life expectancies of once-fatal conditions and we are optimistic about the research that is ongoing to develop treatments for additional conditions. For more than a decade, the rare disease patient community has played a significant role in the paradigm shifts and statutory changes that have occurred with respect to the inclusion of patients and patient experience data within clinical trial design, product development, and regulatory review.

As collaborative stakeholders, we have experienced a tremendous evolution of patient engagement and related areas since their infancy in PDUFA V – through their continued development via the 21st Century Cures Act and PDUFA VI -- and now their continued maturation in the implementation of PDUFA VII today. In this time, the landscape has shifted for the rare disease community. We've seen a deepened engagement and understanding of the patient perspective via numerous approaches such as through the evolution of Patient Focused Drug Development that facilitated new levels of transparency and engagement between regulatory agencies and relevant stakeholders around the integration of patient experience data within the regulatory review.

As a positive byproduct of these engagements, the CDER-issued series of guidance documents for conducting patient-focused drug development have been critical tools in providing stakeholders with practices for

- collecting comprehensive and representative input;
- methods to identify what is important to patients;
- selecting, developing, or modifying fit-for-purpose clinical outcome assessment; and,
- incorporating clinical outcomes assessments into endpoints for regulatory decision-making.

In addition, FDA's issuance of numerous other guidances has been critical to our pipeline as it has informed the inclusion of patient experience data within clinical trial and patient-focused product development activities for drugs, cell- and gene-based therapies, diagnostics, and medical devices.

We encourage CMS to leverage the lessons learned throughout the evolution of patient focused drug development experiences in the regulatory environment as it proceeds with MDPNP implementation, including the proposed communication and transparency restrictions and in the required public explanation.

Gag Period Implications

Frequent and open communication before, during, and after the negotiation process is paramount to establishing public trust in the process and to informing the evolution of a program that constitutes a significant change in how drug prices are determined. Unfortunately, the restrictions proposed in Section 40.2.2 are likely to result in decreased transparency and reduced ability to understand and address the lessons learned in each negotiation process. While we understand and appreciate the need to protect the confidentiality of certain proprietary business information, imposing what amounts to a "gag order" on manufacturers is counterproductive. We encourage CMS to adapt the intended communication restrictions to prohibit sharing of only the most sensitive proprietary information and to abandon plans to place blanket restrictions on the sharing of information exchanged during the negotiation process. We hope CMS leverages its experience on how to communicate agency interactions and sensitive information within the regulatory environment to inform a final plan for what information will be restricted.

Content for Public MFP Explanation

To be an effective engagement tool, we encourage CMS to consider the following elements:

- Stakeholder groups who were engaged during negotiation
- Whether patient experience data (PED) and real-world evidence (RWE) was submitted during the negotiation process
- If patient experience data (PED) and real-world evidence (RWE) was considered in determining the MFP
- If submitted information was not considered to be relevant, publish a discussion of the rationale including what limited the agency's ability to consider the submitted information
- Which metrics were used to evaluate clinical benefit
- Which outcome measures were considered when selecting therapeutic alternatives
- Criteria used to determine unmet need

The final public explanation must be easy to navigate and while much of the requested information is technical in nature, we encourage CMS to provide an appropriate short summary that will enable patients to understand the process that was used to determine the MFP and what they can expect to experience when obtaining their negotiated product. Additionally, while we recognize CMS is not statutorily required to publish the public explanation prior to March 1st of the year prior to the IPAY, we urge the agency to consider moving up this timeline to ensure that the information obtained in the explanation can be used by stakeholders to inform the submission of information for the selected products in the next IPAY.

Ensure Timely Access to Therapies

We appreciate that the law requires payers to include products selected for the MDPNP on the plan formulary. Rare disease patients are facing an onslaught of restrictive coverage policies, high cost-sharing requirements, and burdensome utilization management strategies. While the requirement to include the negotiated product on the formulary is a step in the right direction, we urge CMS to provide additional clarity on the parameters for coverage of negotiated products. Such parameters should seek to provide fair access to negotiated products and limit the potential for payers to arbitrarily implement restrictive utilization management practices as a reaction to increased liability because of the Part D redesign component of the IRA or as a reaction to the required coverage. It is also essential that CMS clarify that plans should not place additional utilization management restrictions on non-negotiated therapeutic alternatives solely due to their negotiation status.

Beneficiary Outreach and Protections

The MDPNP represents a significant technical change to how some drug prices are set, however much of this process is occurring outside of the view of the average Medicare beneficiary. We believe it is important for CMS to consider previous learnings from large scale program implementation efforts, such as the implementation of the durable medical equipment competitive bidding program, when designing beneficiary education and protection efforts. For example, we appreciate the intention to establish a toll-free number and email as mentioned in section 90.2; however, without sufficient public awareness and understanding of what eligible individuals are entitled to and the complaint mechanisms that exist, these resources will go under-utilized. We suggest that CMS consider identifying opportunities to include clear and accessible information about access to the MFP for negotiated products and complaint mechanisms in highly visible locations that don't rely on a beneficiary seeking out said information online or a third party remembering to provide such information. Considerations could include placement on leaflets provided by retail pharmacies with each prescription, along with additional placements in patient portals, relevant healthcare professional locations and community settings.

Implement a Robust Monitoring Program

The rare disease therapeutic development ecosystem is highly sensitive to changes in policy and the underlying incentives that drive investment in high-risk and high unmet need communities. For this reason, the Rare Disease Community Statement on Drug Pricing Policy Priorities recommends that rare disease therapies are excluded from policy experiments or demonstrations that significantly alter how prices are set until or unless it is proven that the changes do not threaten patient access and medical innovation. Given the limited nature of the exclusion for orphan drugs in the MDPNP, active monitoring

of a broad range of metrics to monitor the impact of the program on the rare disease ecosystem is paramount.

Specifically, we suggest CMS establish procedures to monitor the following metrics:

- Increases in launch price trends
- Growth in the use of utilization management strategies
- Trends in the approval of new indications for approved orphan designated products
- Increased time between completion of phase 3 clinical trials and FDA filing for follow on indications of approved orphan designated products
- Trends in the approval of new formulations of approved products
- Shifts away from investment in drug development programs for rare diseases that primarily affect Medicare beneficiaries
- Reliance on off-label use of therapies

Actions CMS can take to Support Orphan Drug Development

Beyond clearly articulating how the agency plans to interpret the statutory language and preventing any overly narrow approach to implementation, we appreciate CMS' interest (as stated in section 30.1.1) in other actions it could take to support orphan drug development. With that in mind, and recognizing these actions are outside of the scope of the current MDPNP, we offer the following points for the agency's consideration.

- **Support early dialogue between payers and rare disease developers/ manufacturers**: The FDA has long operated a program that provides medical device manufacturers with the opportunity to engage with payers early in the development process to obtain payer feedback that may inform clinical evaluation and other decisions. The intent is to maximize the likelihood of favorable coverage policies upon a product's market clearance. The EveryLife Foundation sees tremendous value in this approach and believes FDA and CMS should institute a similar program focused on rare disease therapy development which falls under the authority of CDER and CBER. Through a rare disease early payer engagement program, CMS and FDA can jointly establish a process to enable voluntary early dialogue between rare disease product manufacturers and payers – including Medicare and Medicaid. Through such interactions, we would hope that payers could provide invaluable inputs, including thoughts on trial design and data needs they will want to see to support a positive coverage decision. These interactions would also help manufacturers educate payers about specific rare diseases and conditions as well as the impact an approved therapy would have on the patient population. Given the potential significant benefits associated with an early payer engagement program, we urge CMS to work with FDA to launch such an initiative in the near-term.

- **Support development of diagnosis codes for rare diseases and disorders.** The diagnostic odyssey is the term used to describe the often multi-year period – and the rounds of medical appointments, tests, and other procedures – that patients with rare disease must often navigate just to receive an accurate diagnosis. One of the challenges associated with this process is the lack of ICD-10 codes for rare diseases and conditions. CMS, along with the Centers for Disease Control and Prevention (CDC) plays an important role in this process by staffing the ICD-10 Coordination and Maintenance Committee, which handles requests for new or updated codes. Some rare disease communities have been successful in navigating the process to successfully

develop codes for their disease or condition, but the vast majority of rare diseases lack any such codes. We would encourage CMS to work with the CDC to identify and implement improvements to facilitate the promulgation of additional rare disease codes. Specifically, we would encourage them to work on resource guides to help patient communities and researchers understand and navigate this process. In addition, convening a dedicated meeting or meetings of the committee each year focused on rare disease applications should be considered. Ultimately, by establishing more diagnostic codes for rare diseases, CMS can help shorten the diagnostic odyssey and could also help enhance understanding of a rare disease's natural history.

- **Do not Undermine FDA approvals and create additional impediments to coverage.** The Foundation is concerned about actions CMS has taken that have hindered program beneficiary access to FDA-approved medications, demonstrated most clearly in the agency's actions regarding novel therapies for Alzheimer's disease. While Alzheimer's is not a rare disease, we are troubled by the actions that have cast dispersion on the validity of an approval pathway created by Congress and of high importance to rare disease stakeholders. Limitations in natural history data associated with many rare diseases necessitate the use of a validated surrogate endpoint. We recognize the concerns regarding how the approval pathways have at times been used and the desire of policymakers to address these gaps. But, we are very concerned about actions that threaten to undermine the pathway overall and the ramifications such actions may have for those developing therapies to treat rare conditions and, most importantly, the patients who stand to benefit. We urge CMS to clearly recognize and communicate the value of the Accelerated Approval pathway which has been so successfully applied for patient unmet needs in common and rare cancers and to prevent from taking any actions that undermine drugs approved via this pathway. Specifically, we urge you to ensure that any rare disease therapy approved under Accelerated Approval be fully covered by programs under your authority.

- **Innovate in Utilization Management Strategies**
  In rare diseases, time is a precious commodity. Extensive diagnostic odysseys often lead to diagnoses of rapidly progressive diseases with limited life expectancies. Utilization management techniques create unnecessary hurdles to critical and time-sensitive treatment interventions, yielding irreversible disease progression and catastrophic healthcare costs.

  In 2021, 94% of prior authorization requests were approved, but of the over 2 million requests that were denied, only 11% were appealed with only 80% of those being successfully appealed. The data aligns with the stories we consistently hear from rare disease patients[3]. We urge CMS to partner with CMMI to explore innovative ideas to radically change the use of prior authorization policies, especially for vulnerable populations including those with rare diseases. Gold carding programs, shortened response times, and creating a pathway to eliminate prior authorization for certain drugs are among the many ideas that would help to limit the amount of prior authorization requests submitted for vital treatments and services.

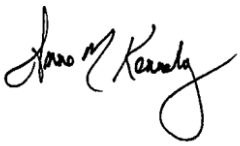
Conclusion

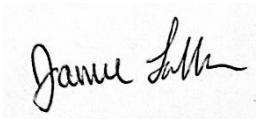
Lowering the cost of health care, including prescription drug therapies, is an important goal that warrants thoughtful insight on how best to develop policies that will ensure the lowering of costs while

limiting potential negative unintended consequences. Policies that are implemented without consideration of the impact on incentives for rare disease research and development will mean lives will be lost and unnecessary suffering will be extended. We appreciate CMS's thoughtful process to ensure that the proposed negotiation process does not harm the same patients it is intending to help.

Thank you for the opportunity to provide comments on how the proposed negotiation process could impact the rare disease community and potential avenues to ensure that rare disease therapy development is not harmed through that process; the EveryLife Foundation and our partners are eager to engage with you. Please contact Jamie Sullivan, Senior Director of Policy at jsullivan@everylifefoundation.org if we can provide any additional information to inform your process.

Sincerely,





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Citations

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2. OJRD-D-21-00823R1 The National Economic Burden of Rare Disease in United States in 2019 Wenya Yang; Inna Cintina; Anne Pariser; Elisabeth Oehrlein; Jamie Sullivan; Annie Kennedy Orphanet Journal of Rare Diseases
3. https://www.kff.org/medicare/issue-brief/over-35-million-prior-authorization-requests-were-submitted-to-medicare-advantage-plans-in-2021/