VIA ELECTRONIC DELIVERY to: IRARebateandNegotiation@cms.hhs.gov

April 14, 2023

The Honorable Chiquita Brooks-LaSure
Administrator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Baltimore, MD 21244–1850

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

Dear Administrator Brooks-LaSure:

With the Centers for Medicare & Medicaid Services' (CMS') issuance of its initial set of guidance on implementation of the Inflation Reduction Act of 2022 (IRA), it has become increasingly clear that (a) the IRA has the potential to exact unintended, but catastrophic, consequences for patients with extremely rare conditions; and (b) CMS may not have a sufficient understanding of our communities' unique challenges to steer its policies in a "do no harm" direction. Haystack Project, therefore, appreciates the opportunity to submit its comments on CMS' Initial Guidance.

Haystack Project is a 501(c)(3) non-profit organization enabling rare and ultra-rare (20,000 or fewer US patients) disease patient advocacy organizations to coordinate and focus efforts that highlight and address systemic reimbursement obstacles to patient access. Our core mission is to evolve health care payment and delivery systems with an eye toward spurring innovation and quality in care toward effective, accessible treatment options for all Americans. We strive to amplify the patient and caregiver voice in these disease states where unmet need is high and treatment delays and inadequacies can be catastrophic.

Our comments to the Initial Guidance briefly outline the inherent differences in commercial realities between the treatments our patient and caregivers rely upon and/or hope for and those that address more common diseases and conditions. We also identify specific provisions within the Initial Guidance likely to have unintended consequences for our patient populations as well as actions CMS can take to minimize those consequences.

We ask that CMS fully consider our comments and that it also give Haystack Project and its member organizations the opportunity to meet with IRA-implementation staff and leadership to articulate our concerns in greater detail so that we may work together to protect access to necessary treatments for all patients, regardless of the rarity of their condition(s).

Background: Individuals with Rare and Ultra-Rare Conditions will be Disproportionately Impacted by the IRA's Potential to Deter Innovation.

Although countless lives have been improved or saved by new therapies enabled by Congress' set of incentives for orphan drugs, significant unmet need predominates in extremely rare conditions and rare cancers:

- Of the approximately 7,000 rare diseases identified to date, 95% have no FDA-approved treatment option.
- 80% of rare diseases are genetic in origin, and present throughout a person's life, even if symptoms are not immediately apparent.
- Diagnosing a patient with a rare disorder is usually a multi-year process involving a series of primary care clinicians, specialists, and diagnostic testing regimens – extreme rarity of a disorder compounds the resources required for diagnosis. Patients often progress to more serious and more costly disease states by the time they receive a diagnosis.
- If a diagnosed condition has no FDA-approved option, treatment often involves off-label use of existing products.
- Approximately half of identified rare diseases do not have a disease-specific advocacy network or organization supporting research and development, and lack of disease-specific natural history severely complicates research toward new, targeted treatments.

Patients suffering from rare diseases that are currently untreatable have maintained hope that the incentives toward innovation, coupled with increased scientific understanding of disease mechanisms, would stimulate progress toward treatment and, eventually, a cure. The economic calculation of unmet patient need balanced against research and development costs, projected risk, and population-based revenue estimates must be accompanied by an analysis of whether it is possible to successfully clear reimbursement mechanisms and hurdles that may tip the scales for or against pursuing a specific drug candidate for an orphan indication. For patient populations approaching the 200,000 orphan disease limit, current incentives have proven to be sufficiently robust to mitigate clinical trial and reimbursement risks. As affected populations dwindle below 20,000 or even into and below the hundreds, the balance can be far more tenuous, and risks or uncertainties can discourage the investor interest required to take promising therapeutic candidates from bench to market.

Patients with rare and ultra-rare conditions as well as rare cancers rely on payers and society in general to lay a strong foundation that gives investors a level of comfort that the costs of research and development can be recouped, either through the price of the new drug, its use in other patient populations, or both. Without this, there is little reason for us to hope they will invest their limited resources in advancing the treatments we need.

Haystack Project and its member organizations have focused on educating stakeholders and shaping health policy to address longstanding challenges to treatment access and innovation. We have engaged with CMS through comments on CMMI model proposals, implementation and refinement of the Medicare Quality Payment Program (QPP) and the Affordable Care Act, as well as throughout annual rulemaking cycles refining policies under Medicare Parts A, B, C and D. In 2019, Haystack Project expressed its increasing concerns that health reform efforts initiated to decrease health care costs would fail to consider our patient communities:

> We are concerned that drug-pricing reforms will all but close the narrow window for commercial viability of ultra-rare disease treatments. Our sincere hope is that a greater understanding of our experiences will enable pragmatic solutions to existing problems and guide future health system refinements that take our unique needs into account.

Since enactment of the IRA, Haystack Project membership has continued to grow – both in numbers (nearly doubling to 150 ultra-rare disease advocacy organizations) and in the acute sense of urgency on the need to be heard, prioritized and accounted for in the policy decisions shaping treatment access and product development for the foreseeable future. We recognize that the IRA offers financial relief to our patient communities in (1) capping Part D out-of-pocket costs and (2) enabling a "smoothing" mechanism so that patients can spread their out-of-pocket costs over the year. We expect that these Part D refinements will reduce financial stress on patients and their families so that more patients can base their treatment decisions on medical need rather than financial resources.

Unfortunately, the drug price negotiation program presents significant threats to the fragile balance that has historically enabled researchers, manufacturers, and investors to capture an adequate return on investment for

targeted treatments in small population diseases and rare cancers. Haystack Project expects that the drug price negotiation program will marginally reduce healthcare costs for patients with relatively common conditions. The vast majority of ultra-rare disease and rare cancer patients - who routinely hit the out-of-pocket cap in Part D - will not experience any benefit from CMS' drug price negotiation. That is not to say that the program will have no impact on our patients. Haystack Project's community of patients and caregivers fear that unless CMS implements the drug price negotiation program with proactive and intentional consideration of the complex set of incentives and risks inherent to developing treatments in the ultra-rare disease space, the scales will inextricably tip away from innovation.

We ask that CMS:

- Engage in meaningful dialogue with Haystack Project and other patient organizations to identify innovative approaches to accommodate challenges associated with developing rare and ultra-rare disease treatments, including through CMMI and CMS' general demonstration authority.

- Expand the window for stakeholder feedback on the Initial Guidance, and in particular, consider implications for rare diseases.

- Identify 'qualifying single source drug' by NDA/BLA.
- implement the orphan drug exemption to maintain incentives for rare disease drug development and expansion of labeled indications for existing therapies

    - Work with patient and other stakeholders to ensure that access to orphan drugs is not impeded by diversity of rare conditions for which a treatment is safe and effective.
    - Implement a transparent process for manufacturers to submit evidence demonstrating that a particular product is eligible for the orphan drug exception.
    - Identify orphan drug designations for a particular product at the time of selection, not the date on which the product achieved one or more of its FDA approvals.

- Apply the small biotech exception with minimal burden to manufacturers.

Haystack Project urges CMS to expand the window for stakeholder feedback on the Initial Guidance.

Haystack Project engages its member organizations by analyzing and educating its members on new policy proposals likely to impact treatment access and innovation. This enables our commuities to contribute general feedback as well as specific examples of how a new policy might impact patients. The Initial Guidance contains a complex set of interconnected proposals and mechanisms that require thorough analysis, substantial knowledge of the drug and biologics manufacturing industry, and significant time to ascertain and convey its impacts to non-industry stakeholders. The 30-day comment period was far too short to enable Haystack Project to collect specific, meaningful input from our member organizations and incorporate the feedback into a comprehensive comment.

In addition, CMS' decision to broadly define ‚qualifying single source drug' for negotiation eligibility purposes was unexpected. Haystack Project had anticipated that CMS would identify negotiation-eligible drugs on the basis of NDA/BLA approvals. This decision will shape the IRA drug price negotiation program to negate existing incentives for securing approvals in small population conditions and burden industry stakeholders in a manner not likely contemplated within the statute. The repercussions from CMS' decision are likely far-reaching and, we believe, warrant a level of consideration that cannot be accomplished without stakeholder feedback. We urge CMS to reverse its finalization of Section 30 of the Initial Guidance and solicit additional stakeholder comments on the entirety of the guidance.

CMS Should Reconsider its Definition of Qualifying Single Source Drug

Haystack Project was both surprised and disappointed that CMS' Initial Guidance finalized a definition of qualifying single source drug that looks to active moiety or active ingredient rather than NDA/BLA. We had expected that CMS would look to the statutory language and its referance to products as negotiation-eligible if the product was approved under an NDA/BLA and seven/eleven years have elapsed since such approval. Under CMS' definition, it would be possible to render a drug eligible for which an NDA is approved, for example, 2 years before a product with the same active moiety/ingredient is selected for negotiation. Under any reading of the plain language of the IRA, the product would not be negotiation-eligible.

We have significant concerns that CMS' approach to identifying products eligible for negotiation (and to which any Maximum Fair Price (MFP) would be applied) maximizes the extent to which the IRA's drug price negotiation program will hinder research and development toward expanded labels for existing treatments. Individuals with relatively common conditions will likely maintain access to promising therapies developed for other conditions based on compendia listings for off-label uses. Off-label treatments for extremely small population conditions are rarely included in the various compendia relied upon for Part D coverage, and patient access is completely foreclosed. In fact, Haystack Project has heard from several patient groups that treatments within the standard of care for their ultra-rare condition fall outside the Part D benefit. Unless CMS retracts its determination to include all NDAs/BLAs for a product as a singular qualifying single source drug for negotiation purposes, our patients have little hope that manufacturers be able to justify investing in NDA/BLA approvals for ultra-rare uses of existing treatments.

In addition to the concerns described above, Haystack Project expects that CMS' definition of qualifying single source drug will place burdens on manufacturers that Congress did not consider in drafting the IRA. We note that CMS' set of examples on application of the qualifying single source drug definition included scenarios with multiple NDAs and multiple manufacturers. The Initial Guidance contemplates requiring the primary manufacturer (NDA/BLA holder) to assume full responsibility and liability for participation in the negotiation process, submission of complete, accurate information and access to the MFP.

Agreements between manufacturers are generally based on contracts negotiated and executed before the parties perform any manufacturing, distribution, and/or marketing activities. They outline the duties and responsibilities of the various parties based on the laws and regulations in place at the time of contract execution and may provide for amendment based on specified legal or regulatory changes. Neither the IRA nor CMS' Initial Guidance provide for any mechanism through which a primary manufacturer can secure information or performance from a secondary manufacturer. While CMS might assume that manufacturers can contract with each other to accommodate the IRA requirements, the substantial liability and potential monetary penalties placed on primary manufacturers negates the potential for a level playing field between the parties. We expect that CMS will face legal challenges to this provision of its Initial Guidance and urge the Agency to take a more pragmatic approach. Identifying negotiation-eligible products by NDA/BLA will preserve incentives for research and development of new uses for existing products, and minimize the potential that manufacturers will be responsible for activities over which they have no control.

The Orphan Drug Exclusion Should be Implemented to Maintain Incentives for Developing New Treatments in Rare Conditions and Expanding Labeled Indications of Existing Therapies

Haystack Project appreciates that CMS recognizes the need to protect access to orphan drugs currently available as well as innovations that have yet to be developed. We fully support CMS' determination to qualify drugs for the exclusion based on whether approved indications are within a single designation. Unfortunately, the policy on defining a qualifying single source drug by active moiety/ingredient discussed above will likely reduce manufacturer interest in pursuing multiple indications within or beyond a single designation.

When the IRA was enacted, our member organizations voiced significant concerns that the narrow exception for orphan drugs would introduce a new set of considerations to deter pursuit of FDA approval for multiple uses of promising new therapies. Drug and biotech manufacturers already face considerable pressures to fulfill their legal

obligations to shareholders while maintaining their commitment to improve care for the patient communities they serve. The landscape envisioned under CMS' Initial Guidance increases the tension between those interests. For example, it would be difficult to make a financial case for investing in clinical studies toward approval of an ultra-rare indication outside a product's original orphan designation unless the financial consequences of losing eligibility for the orphan drug exception were outweighed by projected revenue from a new indication. The smaller the population, the less likely it is that the manufacturer could justify investing in the research needed for FDA approval. Any decision to rely on off-label use (for cancer uses and indications likely to be included in compendia) would be more likely driven by math than an intent to game the system. CMS, patients, and manufacturers can and should be aligned on incentivizing (or at least not discouraging) research that maximizes access to innovations across indications through a demonstration of safety and efficacy sufficient to garner FDA approval.

Patients with ultra-rare conditions and rare cancers are particularly concerned that:

- Manufacturers will face pressures to focus on an orphan indication with the largest patient population.

- Research and development programs confirming clinical benefit for accelerated approval treatments may be halted and indications withdrawn if those indications fall outside a single orphan drug designation. We note that on April 6, 2023, AbbVie and Johnson & Johnson announced withdraw of the accelerated approvals for Imbruvica (ibrutinib) in mantle cell lymphoma (MCL) and marginal zone lymphoma (MZL). Patients with these rare cancers will have only one BTK inhibitor available to treat their disease.

- Pressures to focus on larger-population orphan designations/indications could delay product approval and increase initial research and development costs. The BTK inhibitor described above was approved for MCL a year before receiving approval in chronic lymphocytic leukemia (CLL).

- The IRA's chilling effect on research and development will fall disproportionately on patients with ultra-rare diseases and rare cancers.

- Investors and shareholders will seek to ensure that initial price points for newly-approved drugs are sufficient to recoup research and development costs and achieve a profit margin from successful innovations.

Once again, we appreciate that CMS has limited discretion in implementing the orphan drug exclusion and that the Agency seeks stakeholder feedback on how it might implement the IRA drug price negotiation program without detering access and innovation in rare diseases. We urge CMS to:

- Work with patient and industry stakeholders to remove the single orphan designation requirement from the IRA orphan drug exception.

    - The existing statutory language will severely chill research and development to secure approval for ultra-rare disease uses of existing orphan drugs.
    - The set of compendia used to determine whether a use is medically accepted (and, therefore, a covered Part D drug) tend not to include off-label uses in ultra-rare conditions.
    - Ultra-rare patients can find that treatments that are part of the standard of care are not within the Part D benefit ***for patients like them*** simply because their condition is too rare to catch the attention of drug compendia listings.

- Identify qualifying single source drugs by NDA/BLA (as more fully outlined in the preceding section).

- Engage in meaningful dialogue with Haystack Project and other patient-centered organizations to preserve the balance in incentives and risks that has spurred innovation in rare and ultra-rare disease treatments, including through CMMI and CMS' general demonstration authority.

- Implement a transparent process for manufacturers to submit evidence demonstrating that a particular product is eligible for the orphan drug exclusion.

- Identify orphan drug designations for a particular product at the time of selection, not the date on which the product achieved one or more of its FDA approvals.

The Small Biotech Drug Exception should be Applied with Minimal Burden to Manufacturers.

Haystack Project understands that CMS has been charged with implementing the Inflation Reduction Act provisions related to price negotiation, including the small biotech exception, as Congress directed. In our comments to the Information Collection Request associated with the Small Biotech Drug Exception, we asked that CMS to exercise its implementation discretion to minimize the IRA's potential to disrupt the fragile balance between risk and reward that has fueled hope for new treatments within our patient communities. We reiterate our recommendation that CMS provide stakeholders with greater clarity on the process it will use to determine eligibility for the small biotech drug exception, including that the Agency:

- Ensure that manufacturers know how and when they will be informed of CMS' receipt of a submission and determinations on completeness and eligibility for the exception. CMS' communication could be by email, letter, or other mechanism, but it is essential that manufacturers know what they are looking for and when to look for it.

- Provide a substantive response to submissions when it determines that a small biotech manufacturer's drug is ineligible for the exception. The response should be sufficiently detailed to enable manufacturers to provide any data or other information that may refute a negative CMS determination.

- Implement a dispute resolution process that manufacturers can understand and utilize in the event of a negative determination.

- Accept manufacturer submissions through a dedicated email "inbox." Haystack understands that CMS envisions developing an HPMS tool that manufacturers would use to submit information on the Small Biotech Exception ICR form. Unfortunately, creating new processes within short implementation timeframes increases the likelihood for delays, errors, and inadvertent inclusion or exclusion of information. Emailed submissions with automated receipt response will give manufacturers confidence that the information they intended to send was received.

- Maintain open lines of communication between specific CMS personnel making determinations on small biotech drug exception eligibility and manufacturers submitting information to qualify their drugs. Our patient and caregiver communities know all too well that the decisions on our access to treatments are often made within closed processes that do not include our participation. The IRA implementation processes are new to industry, patients, and CMS, and are therefore vulnerable to miscommunications, inadvertent submission errors, and other missteps that could prove dispositive. A clear and open line of communication between CMS staff and manufacturers can avoid unintended delays and erroneous determinations.

- Streamline continuing eligibility for the small biotech drug exception. Under the IRA, a drug determined to be eligible for the exception would lose its eligibility only if the manufacturer is acquired by a manufacturer that does not qualify for the exception. We urge CMS to apply the exception to drugs for each year upon receipt of a simple statement certifying that the manufacturer has not been acquired by another entity. A new eligibility submission should only be required when an acquisition has occurred, and the new manufacturer seeks to qualify for the exception.

- Allow for small biotech drug exception submissions in each year for which the exception is applicable. This will permit companies that failed to fully submit required information within the timeframe allowed to secure the exception for the drugs it was intended to benefit.

- Furnish a material response to submissions indicating whether the submission was successful. The response should (as noted above) provide a clear and substantive rationale for CMS' decision if the Agency determines that the drug is ineligible for the small biotech drug exception.

Haystack Project has previously expressed its concern that CMS' ICR and the explanations accompanying it did not fully implement the IRA small biotech drug exception. We urge CMS to modify its "form" for small biotech drug exception qualification to fully comply with the statutory two-pronged "test" conferring eligibility when drugs meet ***either*** prong. This means that a drug would be eligible for negotiation applicable to Part D drugs if it meets either the 1%/80% test on Part D expenditures or the 1%/80% test on Part B expenditures.

Conclusion

Haystack Project appreciates the opportunity to submit feedback on the Initial Guidance toward implementing the drug price negotiation program within the IRA. Our member organizations have significant concerns that the decisions CMS makes within the next several months could determine the set of new treatment options in ultra-rare conditions and rare cancers for the foreseeable future. More importantly, the decisions likely to have the greatest impact are being made without a meaningful engagement and dialogue between CMS and the rare and ultra-rare disease community.

We would appreciate the opportunity to meet with IRA implementation staff and leadership to further discuss the concerns within our communities and possible mechanisms to address them, such as:

- Including patient-centered value considerations within the negotiation process.
- Ensuring that the importance of a particular treatment in a rare or ultra-rare condition is not lost within the context of its use in a relatively common condition with multiple available treatment options (i.e., averaging benefit across uses marginalizes the health care needs of ultra-rare patients).
- Incorporating value-based payment arrangements into the drug price negotiation process.
- Developing mechanisms to encourage (carrots rather than sticks) manufacturers to apply discounts throughout a product's lifecycle – not just for Medicare patients after the product has been selected for negotiation.
- Additional ideas within our member organizations to foster innovation and treatment access for patients with ultra-rare conditions and rare cancers.

Once again, we thank you for your consideration of our comments and look forward to a substantive discussion to ensure that all Medicare beneficiaries have access to the treatments they need. In the meantime, if you have any questions, please contact our policy consultant M Kay Scanlan, JD at 410.504.2324.

Very truly yours,

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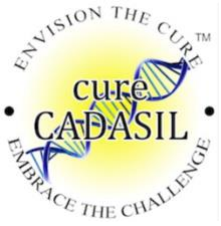
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