July 2, 2024

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RE: Medicare Drug Price Negotiation Program Draft Guidance

Dear Administrator Brooks-LaSure:

Last year, Haystack Project submitted comments to the Centers for Medicare & Medicaid Services’ (CMS’) initial guidance for initial payment applicability year (IPAY) 2026, cautioning 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.” Once again, we have significant concerns that CMS’ implementation of the Medicare Drug Price Negotiation Program (MDPNP) continues to stray from the patient-centered approach this Administration has committed to take as steward of the Medicare program. CMS’ proposals to expand opportunities for patient engagement are welcome procedural refinements that are, unfortunately, unlikely to resolve the potential for unintended consequences on patient access to existing treatments and development of new rare and ultra-rare disease treatments.

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 for IPAY 2026 emphasized that there are inherent differences in commercial realities between the treatments our patients and caregivers rely upon and those that address more common diseases and conditions. We briefly reiterate those contextual factors that increase the likelihood that the MDPNP will exact unintended consequences on our patient communities. Our primary concern with last year’s guidance was that CMS’ statutory interpretations and implementation policies created very real financial disincentives to investment in ultra-rare indications for new and existing treatments. Rare and ultra-rare disease patients similarly fear that CMS’ pursuit of aggressively low negotiated prices in the initial years of the MDPNP could further disrupt incentive frameworks for development of new rare and ultra-rare treatment options. We ask that CMS take a cautious approach when considering initial offers significantly below the ceiling price in the initial years of the MDPNP and do so only when there is a compelling, patient-centered justification.

Haystack is also concerned that the Draft Guidance for IPAY 2027, taken as a whole, adds a new threat. Specifically, the combination of an expansive view of “qualified single source drug,” the potentially unworkable Primary/Secondary Manufacturer framework, and CMS’ failure to account for supply chain transactions impacting acquisition costs for dispensing entities make the negotiation program a riskier prospect than the statute requires. CMS has faced several lawsuits that challenge the Agency’s implementation policies and statutory interpretations and assert that the penalties for not participating in the MDPNP are coercive. We expect that CMS’ refinement of the processes for manufacturers declining to enter into a negotiation agreement, including mechanisms that would enable manufacturers to avoid imposition of excise tax penalties, were newly incorporated to mitigate the chance that any of the lawsuits challenging the MDPNP would succeed. Haystack Project recognizes that fundamental concepts of “agreement” and “negotiation” assume an element of choice for all parties.

We also doubt that Congress intended to create a Medicare cost-savings program that could ultimately deprive patients covered by the Medicare and Medicaid programs of necessary medications. The lack of legal challenges to the MDPNP from the patient community to date likely reflects both the lack of financial means groups like Haystack have to mount such a challenge and the widely held belief that declining to participate in the negotiation process was not a real option. We may not see a manufacturer decline to participate in negotiation this year, but the possibility is real. Once a manufacturer
withdraws their products from the Medicare and Medicaid programs, it will be too late to prevent the resulting harms to patients.

**Background**

Despite existing incentives for orphan drug development, 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.
- 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.
- Lack of disease-specific natural history severely complicates research toward new, targeted treatments.

The economic calculation of unmet patient need balanced against research and development costs, projected risk, and population-based revenue estimates is complex and often fragile. 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.

Haystack and its member organizations appreciate that the IRA Part D benefit redesign provisions offer significant financial relief to our patient communities. We expect that the Part D out-of-pocket cap 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. Since most ultra-rare disease patients will routinely reach the $2000 out-of-pocket cap within the initial months of the plan year, it is unlikely that they will receive the financial benefits from the MDPNP that individuals with more common conditions treated by less costly drugs receive. Our communities of patients and caregivers fear that unless CMS recognizes the potential impacts the MDPNP might have on rare disease treatment access and innovation, its implementation of the negotiation program will likely disrupt the
balance of incentives and risks inherent to developing new treatments and new uses of existing treatments for ultra-rare conditions.

**CMS’ definition of qualified single source drug is a broad interpretation of the IRA that frustrates Congress’ intent to consider therapeutic alternatives.**

CMS’ MDPNP guidance for IPAY 2026 was drafted as “final” with respect to the decision to broadly define “qualified single source drug” (QSSD) for negotiation eligibility and selection purposes. Haystack appreciates CMS’ stated intent to consider comments on this portion of the Draft Guidance for IPAY 2027. We had previously noted that the definition of QSSD will shape the MDPNP and could negate existing incentives for manufacturers to secure new approvals in small population conditions. In reiterating its intent to maintain its policy of defining QSSD through active moiety or active ingredient, CMS stated that:

> This approach to identifying a potential qualifying single source drug aligns with the requirement in section 1192(d)(3)(B) of the Act to use data aggregated across dosage forms and strengths of the drug, including new formulations of the drug. Consistent with this statutory instruction, this approach is also appropriate because CMS is aware that existing NDA / BLA holders have obtained approval for new dosage forms or different routes of administration of the same active moiety/active ingredient under different NDAs or BLAs.

Haystack once again urges CMS to reconsider this approach. The IRA’s timeline for negotiation eligibility begins at FDA approval of an NDA or BLA, not the manufacturer’s first NDA or BLA approval for an active moiety/active ingredient. Longstanding public policy has, however, favored pursuit of new NDAs/BLAs that enable on-label use of treatments in multiple diseases and conditions, including multiple orphan and/or non-orphan conditions and mixes of orphan NDAs/BLAs with approvals in more common conditions. There are also instances where FDA finds that a manufacturer’s new formulation is sufficiently distinct from the original NDA/BLA that it is, in essence, a new product. By wrapping all treatments with the same active moiety/active ingredient into a single QSSD, CMS fails to distinguish between reducing incentives that deter generic competition and neutralizing incentives that further public policy goals and/or align with FDA processes and determinations.

We remain concerned that defining QSSD by active moiety/active ingredient will have a significant detrimental effect on new approvals of existing drugs, particularly in ultra-rare
diseases for which statutory exclusivity has helped drive research and development. It is unlikely, if not impossible, that a manufacturer could recoup the costs of achieving FDA approval in an ultra-rare follow-on indication for a drug subject to a negotiated price, particularly given the relatively short timeline to renegotiation to a lower price based on a change in status to long monopoly drug.

Moreover, the statute directs CMS to consider the cost of therapeutic alternatives to a selected drug in reaching an initial offer. This makes far less sense within the context of multiple indications in divergent disease states with diverse sets of recommended dosages and alternative therapies. Any calculation based on aggregated and/or weighted costs of therapies that are appropriate for some, but not all, indications would likely fail to reflect the cost of other treatments for any indication.

The examples below illustrate the operational complexities associated with CMS’ QSSD definition and the impact that definition could have on new approvals in ultra-rare conditions:

- Imbruvica provides an example of divergent uses and therapeutic alternatives. Imbruvica’s highest volume of use in Medicare is for Chronic Lymphocytic Leukemia (CLL) but a year before its selection for negotiation, it was approved for pediatric chronic graft versus host disease (cGVHD). This is a very rare indication for which many of the underlying conditions leading to a need for transplant are extremely rare. Imbruvica has lost market share year over year due to competing products within its therapeutic class and is scheduled for renegotiation as a “long monopoly” drug for IPAY 2030. The in-class competition has led to improved alternatives within the BTK inhibitor class for CLL patients. Haystack is concerned that the MDPNP will discourage manufacturers of newer BTK inhibitors from pursuing new approvals in cGVHD given that the high proportion of Medicare patients will drive a short timeline to selection for negotiation followed by relatively rapid selection for renegotiation.

- Gavorestat is an investigational aldose reductase inhibitor that is being studied in two orphan indications, Galactosemia and sorbitol dehydrogenase deficiency (SORD), a recently discovered type of Charcot-Marie-Tooth disease. Future studies are also being considered in PMM2 congenital disorder of glycosylation (PMM2-CDG). These conditions do not fall into a single orphan designation and the product would be ineligible for the MDPNP orphan drug exclusion. A manufacturer could mitigate the risk that the MDPNP might hamper its ability to generate sufficient
revenue to cover research and development and recognize an acceptable return on investment by seeking approval in a single orphan indication, adjusting launch pricing to account for IRA impacts, or both.

- Although introduction of a biosimilar may prevent CMS’ selection of the biologic denosumab, this treatment illustrates the unintended consequences of CMS’ active moiety/active ingredient definition of QSSD. Prolia is administered as 60 mg subcutaneous injection every 6 months for its FDA-approved indication in treating osteoporosis. Denosumab is also approved under the brand name Xgeva for bone metastasis, multiple myeloma (approximately 37,000 cases per year) and in giant cell tumors of the bone (an extremely rare (1 in 1,000,000) predominantly noncancerous condition that destroys the bone). The recommended dose of XGEVA is 120 mg administered as a single subcutaneous injection once every 4 weeks additional 120 mg doses on days 8 and 15 of the first month of therapy. CMS’ definition of QSSD creates problems that make it all but impossible to utilize the statutory process and arrive at any initial offer that reflects the cost of treatment based on therapeutic alternatives for any indication. Differential dosing and extremely divergent therapeutic alternatives are relatively common for products with multiple approvals and especially so when one or more approval is in an ultra-rare condition.

As we stated in comments to the guidance for IPAY 2026, FDA approval is extremely important within the context of ultra-rare conditions. Individuals with relatively common conditions have access to off-label use of promising therapies developed for other conditions based on compendia listings. Off-label treatments for extremely small population conditions are rarely included in the various compendia relied upon for Part D coverage. This means that even if an off-label use is within the standard of care, lack of compendia inclusion places that medically necessary treatment outside the definition of Part D covered drug and patient access is completely foreclosed. Over the years, Haystack has heard from several patient groups that treatments within the standard of care for their ultra-rare condition are simply not covered.

We are also concerned that CMS’ definition leads to complicated Primary/Secondary Manufacturer relationships. It is not uncommon for smaller manufacturers to fund research and development efforts by licensing arrangements providing for exclusive commercialization rights for one or more indications to another manufacturer. These arrangements may, but do not always, provide for the licensing manufacturer to hold the NDA/BLA. Under CMS’ QSSD definition, whether these separate NDAs/BLAs for distinct indications are considered one drug for which negotiation eligibility turns on the date of the
first NDA/BLA will depend solely on whether pre-IRA contract terms provided for the manufacturer with commercialization rights also holds the NDA/BLA. Although it appears that the Draft Guidance would permit the Primary Manufacturer to transfer the NDA/BLA to the Secondary Manufacturer, we believe that CMS’ QSSD definition and delegation of all MDPNP responsibilities and liabilities to the Primary Manufacturer significantly impacts both the value of the NDA/BLA and the relative negotiation positions between the parties.

As noted above, Haystack is concerned that CMS’ approach will not only eviscerate existing incentives for manufacturers to study new, ultra-rare uses of existing drugs, but increase the likelihood that a manufacturer might look at the MDPNP as a whole and determine that withdrawal from Medicare and Medicaid agreements is the better business decision. That possibility is particularly dangerous for our patient communities given the limited set of available therapies to manage ultra-rare disease symptoms or slow disease progression. We firmly believe that CMS can achieve the MDPNP’s goals of lowering prices of high-cost prescription drugs without deterring innovation in rare and ultra-rare diseases or creating unworkable scenarios for manufacturers that have transferred commercialization rights for specific indications to one or more other, unrelated entities.

The Orphan Drug Exclusion should be implemented (or amended) to maintain incentives for developing new treatments in rare conditions and expanding labeled indications of existing therapies.

Haystack recognizes that CMS has limited discretion in implementing the orphan drug exception, and its implementation policy likely reflect its view that the statute requires CMS confirmation of a single orphan designation into which all approved indications fit.

Our member organizations have voiced significant concerns that the IRA’s 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. The smaller the population, the less likely it is that a manufacturer could justify investing in the research needed for FDA approval, particularly when such approval would lead to loss of eligibility for the exception. Our patient communities are particularly concerned that:

- Manufacturers will tend to focus on an orphan designation with the largest patient population, even if studying the product in that population might delay a first approval.
- Research and development programs confirming clinical benefit for accelerated approval treatments may be halted and indications/designations withdrawn if they fall outside a single orphan drug designation.

- Investors and shareholders will pressure manufacturers 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 exception. We believe, however, that CMS could significantly alleviate the concerns expressed by Haystack and other patient advocacy organizations by revising its QSSD definition from the active moiety/active ingredient framework to the NDA/BLA approach outlined above. CMS could comply with the statutory requirement that it aggregate dosage forms, strengths, and formulations for each NDA/BLA.

Finally, we reiterate our request from last year’s comments that CMS 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.

**CMS’ criteria for identifying off-label uses and therapeutic alternatives does not fully account for uses in ultra-rare conditions.**

Haystack remains concerned that CMS’ implementation of the MDPNP fails to consider ultra-rare patients for whom unmet need is a near-universal reality. The Draft Guidance retains the criteria applied in IPAY 2026 with respect to identifying off-label indications. Specifically, CMS will look first to the FDA-approved indications that are not subject to a Part D coverage exclusion and then consider off-label uses that are included in nationally recognized, evidence-based guidelines and listed in CMS-recognized Part D compendia. Since ultra-rare off-label tend not to receive attention from CMS’ set of recognized compendia, CMS will not consider the experience of these patients, the set of therapeutic alternatives available, or any unmet need the selected drug addresses. Although these ultra-rare uses are often rendered non-covered based on the statutory definition of a Part D covered drug, there are instances for which patients receive coverage based on the disease symptoms for which the drug is prescribed. For example, a hypothetical anti-hypertensive product might be the standard of care in a hypothetical ultra-rare condition that leads to severe hypertension. CMS’ set of evidence sources for identifying off-label uses would not reveal the ultra-rare use or that the specific drug is the only product that can manage
hypertension without exacerbating underlying disease symptoms or introducing significant side effects.

CMS’ process for identifying potential therapeutic alternatives introduces a different set of complexities. CMS states that it will look beyond the sources used to identify off-label uses and include clinical guidelines and peer-reviewed studies. To the extent that the drug is not used for a cancer indication, this expansive set of therapeutic alternatives could include treatments that are outside the definition of a Part D covered drug and ineligible for coverage. Haystack and its member organizations are acutely aware that their prescribed medications may be noncovered by Part D due to lack of inclusion in compendia because it impacts their access to treatment. We expect that many stakeholders are unaware of the impact of CMS’ broad interpretation of therapeutic alternatives.

If CMS intends to include noncovered treatments within the set of therapeutic alternatives considered in calculating an initial offer, it should state that intention clearly so that stakeholders have an opportunity to comment. An alternative approach might be to broaden the set of uses of the selected drug CMS considers and, if an ultra-rare use is not included in compendia but is supported by guidelines and/or peer-reviewed studies, the evidence for therapeutic alternatives should similarly not be limited to compendia-listed uses.

**CMS should reconsider its decision to engage in complex, subjective inquiries to confirm that a generic drug or biosimilar is marketed on a bona fide basis.**

Haystack understands that one of the goals of the MDPNP is to shift manufacturer incentives away from behaviors that deter generic competition. We support that goal and believe that robust competition through multiple branded in-class treatments can lead to improved treatment options and introduction of generic competition can reduce drug costs. The IRA seeks to rebalance incentives by exempting products with generic competition from the MDPNP. We urge CMS to apply the exemption in a manner that aligns with the statutory goals of changing manufacturer behaviors. An inquiry into the behavior of unrelated entities that have secured approval to market generic alternatives reduces the extent to which any manufacturer can avoid price negotiation by removing obstacles to generic product development.

CMS has acknowledged that there is no objective measure of bona fide marketing and suggested that it will engage in a holistic inquiry based on the totality of the circumstances. This ambiguous bona fide marketing requirement will inevitably lead to inconsistencies in
any determination on whether introduction of a generic or biosimilar exempts a particular
drug from selection. CMS’ stated intent to continue monitoring marketing activities of a
generic or biosimilar manufacturer to ensure that those activities continue to constitute
bona fide marketing creates an additional layer of unpredictability. We believe that these
activities will require significant time and expertise within the Agency and ultimately
complicate successful MDPNP implementation. We do, however, support CMS’ inquiry into
whether a manufacturer enters into an agreement with a generic competitor to limit the
number of generic or biosimilar units marketed or influence the pricing of a generic or
biosimilar.

**Haystack appreciates CMS’ proposal to expand its stakeholder engagement beyond
the listening sessions conducted for IPAY 2026.**

Haystack has met with CMS to express its concerns with the listening session format for
patient engagement, and we appreciate CMS efforts to enhance opportunities for patients
to contribute to CMS’ decision processes through patient-focused events. In particular, we
support CMS events that are patient-focused and facilitate discussion among speakers
and dialogue between speakers/attendees and CMS staff.

We urge CMS to:

- Leverage relationships with patient advocacy organizations, including Haystack, by
  enabling CMS participation in events organized by these organizations. We expect
  that patient participation and willingness to engage in candid dialogue would be
  more robust when conducted within the familiar context of an advocacy
  organization event.
- Provide clear information on the types of information CMS seeks and how it intends
to use that information in arriving at an initial offer for a selected drug.
- Permit questions from patients and clinicians on the MDPNP generally as well as the
  impact negotiation might have on the patient’s access to and cost of the selected
drug.
- Ensure that patients and clinicians are informed on applicable formulary
  requirements, including limitations on adverse tier placement, step therapy
  protocols, and burdensome prior authorization requirements so they can advocate
  for their access to the selected drug and/or alternative therapies.
Conclusion

Haystack appreciates the opportunity to submit feedback on the Draft Guidance for IPAY 2027. Our member organizations remain concerned that CMS decisions on the initial years of the MDPNP could determine the set of new treatment options in ultra-rare conditions for the foreseeable future.

We would appreciate the opportunity to meet with IRA implementation staff and leadership to further discuss the concerns within our communities so that the MDPNP improves the experience of Medicare beneficiaries with ultra-rare conditions. 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.

Alliance to Cure Cavernous Malformation
Alstrom Syndrome International
Association for Creatine Deficiencies (ACD)
Biomarker Collaborative
CancerCare
Casey's Cure Foundation
CDG CARE
Chondrosarcoma Foundation
Choroideremia Research Foundation
CLL Society
CSNK2A1 Foundation
Cutaneous Lymphoma Foundation
Desmoid Tumor Research Foundation
Dup15q Alliance
Exon 20 Group
Galactosemia Foundation
HealthTree Foundation
Hope for Stomach Cancer
ICAN, International Cancer Advocacy Network
International Foundation for CDKL5 Research
International Pemphigus & Pemphigoid Foundation
International Waldenstrom’s Macroglobulinemia Foundation (IWMF)
MET Crusaders
MitoAction
MLD Foundation