April 14, 2023

The Honorable Chiquita Brooks-LaSure
Administrator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
200 Independence Avenue SW
Washington, DC 20201

Meena Seshamani, M.D., Ph.D.
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Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, Maryland 21244-1850

Dear Administrator Brooks-LaSure and Dr. Seshamani,

On behalf of the more than 25 million Americans living with one or more of the over 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the Centers for Medicare and Medicaid Services (CMS) for their extensive engagement with the rare disease community around implementation of the Inflation Reduction Act (IRA). NORD appreciates this opportunity to provide comments on the draft guidance 'Medicare Drug Price Negotiation Program: Initial Memorandum, Implementation of Sections 1191- 1198 of the Social Security Act for Initial Price Applicability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,' hereafter referred to as the "Negotiation Program" guidance.

NORD is a unique federation of non-profits and health organizations dedicated to improving the health and well-being of people living with rare diseases. NORD was founded 40 years ago, after the passage of the Orphan Drug Act (ODA), to formalize the coalition of patient advocacy groups that were instrumental in passing that landmark law. Our mission has always been and continues to be to improve the health and well-being of people with rare diseases by driving advances in care, research, and policy.

NORD appreciates CMS' willingness in the Negotiation Program guidance (Section 30.1.1) to consider additional actions to "best support orphan drug development" and is pleased to submit these comments to help CMS make good on its commitment to the rare disease community. These comments are intended to supplement and expand on the April 14th comment letter submitted by NORD and 100 other patient advocacy organizations that support rare disease patients (available in the appendix).

For many Americans living with a rare disease, out of pocket prescription drug costs create significant financial barriers and hinder patient access to needed therapies. Key provisions in the IRA, including the $2,000 annual and amortized monthly caps on out-of-pocket costs for Medicare Part D beneficiaries, as well as expanded eligibility for financial assistance for low-income beneficiaries, ensure that more rare disease patients on Medicare will be able to afford the life-altering therapies they need. Robust patient education, particularly about the opt-in requirement to the smoothing mechanism, will be critical to ensuring patients have access to and benefit from these provisions of the IRA. While outside the scope of this guidance, NORD would welcome the opportunity to partner with CMS to help educate the rare disease community as IRA-authorized benefits become available to Medicare beneficiaries at the appropriate time.

As implemented under the draft guidance, however, the Negotiation Program may adversely impact rare disease drug development. Before the Orphan Drug Act was enacted in 1983, fewer than 40 Food and Drug Administration (FDA) approved therapies were available to treat rare diseases.[1] Thanks to the ODA, rare disease therapies now consistently account for more than half of FDA approvals for new molecular entities.[2] Still, more than 90% of the more than 7,000 known rare diseases do not have an FDA approved treatment, making continued investment in rare disease research and innovation critical to the rare disease community.[3] The section 1192(e)(3) exclusion for orphan drugs approved to treat a single rare disease could help sustain this innovation, as will the broader exclusion for "low spend" drugs with less than $200 million in annual Medicare spending. However, the small patient populations and medical complexity associated with rare diseases create unique challenges to drug development. These small population sizes and complex, heterogenous disease manifestations also result in a more limited availability of data on issues such as clinical benefit and therapeutic alternatives, making it more difficult to determine a fair negotiated price for drugs that treat rare diseases compared to other therapies. Therefore, NORD appreciates the opportunity to highlight additional ways that CMS, consistent with the statute, can further support rare disease drug development in implementing the Negotiation Program.

Successful Negotiation Program implementation hinges on a careful balance between greater affordability and maintaining appropriate incentives for continued rare disease drug development. NORD urges CMS to address four areas of concern in future guidance:

1. Actively engage patients and create opportunities to provide meaningful data and insights;
2. Ensure rare disease patients have access to the negotiated therapies;
3. Further clarify the scope and timing of the orphan drug exclusion; and
4. Begin tracking the impact of the IRA on innovation and patient outcomes now.

Specifically, CMS should take the following steps to support rare disease patients and families:

1. Expand and strengthen data collection and engagement opportunities to ensure patients can meaningfully contribute their unique insights on the negotiated drug and its alternatives.

NORD commends CMS' efforts to consider data on clinical benefit, therapeutic alternatives, and unmet medical need in the negotiation process and to incorporate relevant patient and provider perspectives. NORD thanks CMS for recognizing, in section 60 of the draft guidance, the unique and nuanced value orphan drugs can bring to specific subsets of the patient population, including those with few or no therapeutic alternatives. The agency's stated objective to assess value in an indication-specific manner, including some off-label uses, is critical for CMS to fully understand and account for the complex treatment trade-offs and unmet needs that exist within the rare disease patient community.

Moreover, we are encouraged that the draft guidance explicitly recognizes the value of patient experience data, including its nuances, in section 60.3.3, and that not all patients are necessarily sharing the same

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[1] Orphan Drugs In The United States: An Examination of Patents and Orphan Drug Exclusivity (2021): available at https://rarediseases.org/wp-content/uploads/2022/10/NORD-Avalere-Report-2021_FNL-1.pdf; accessed 4/2023

[2] New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products; available at: https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products; accessed 4/2023

[3] Larkindale J, Betourne A, Borens A, Boulanger V, Theurer Crider V, Gavin P, Burton J, Liwski R, Romero K, Walls R, Barrett JS. Innovations in Therapy Development for Rare Diseases Through the Rare Disease Cures Accelerator-Data and Analytics Platform. Ther Innov Regul Sci. 2022 Sep;56(5):768-776. doi: 10.1007/s43441-022-00408-x.

views and experiences. For instance, the science of patient engagement has long recognized that patient experience data may reflect differences depending on disease progression or a patient's cultural, geographic, and socio-economic background. While we are grateful CMS recognizes the value of patient experience data, we strongly encourage CMS to expand the opportunities and strengthen the processes for providing such input to the agency as part of the negotiation process.

NORD is concerned that CMS' proposed approach would make it essentially impossible for patients and providers to submit meaningful data. CMS plans to largely rely on voluntary, public data submissions, on very short timelines, without meaningful data standardization, using complicated forms written at too-advanced reading levels and through hard-to-navigate processes that are neither intuitive nor patient-friendly. Patients will either not become aware of data collection efforts in time, or struggle to navigate the complex submission process. In addition, the required attestations are worded in a way that will likely discourage many patients from submitting data. To the extent patients will feel compelled to submit data containing Personal Identifiable Information (PII) and Personal Health Information (PHI), the data collection also raises privacy concerns.

Moreover, NORD foresees challenges in aggregating and analyzing individual patient and provider experience data submitted through this process. The data will be collected without a sampling frame and likely not representative while the collection method essentially makes it impossible to determine or account for such inherent biases in the data. In addition, the lack of standardized questions and scientific rigor will likely render this data largely anecdotal. This would contrast sharply with appropriate qualitative and/or quantitative research methodologies that would collect information in a scientifically rigorous and reproducible manner. A good example of such rigorous approaches is data collected through the FDA's patient-focused drug development (PFDD) meetings or patient surveys. Specifically, FDA's "Patient-Focused Drug Development: Collecting Comprehensive and Representative Input" guidance[4] provides detailed and tangible advice on operationalizing and standardizing data collection and data management in ways that are feasible for the rare disease patient community.

CMS will have to refine its proposed approach to incorporate meaningful external data sources. CMS plans to supplement the aforementioned data submitted by the public with relevant published data retrievable through literature searches. Unfortunately, for many rare diseases, data relevant to determine a negotiated drug's clinical benefit, therapeutic alternatives, or unmet medical need does not currently exist in peer-reviewed journals or consensus treatment guidelines. Additionally, the lack of disease-specific International Classification of Disease (ICD-10) codes for most rare diseases makes Real-World Data (RWD) sources such as Electronic Health Records (EHRs) or medical claims data largely infeasible for many rare diseases. This is a recognized challenge within rare diseases.

FDA's Voice of the Patient (VOIP) reports are designed to address this data scarcity and are critical to patient-focused drug development by assembling meaningful information on how patients evaluate therapeutic alternatives or characterize the unmet need and clinical benefit of alternatives. However, these data are not indexed in a way that would clearly find them in a traditional literature search. CMS should consider all relevant data collected as part of the FDA approval process in the negotiation process. Moreover, patient and provider engagement will be critical to ensure CMS is aware of and able to leverage all other available and relevant data sources regardless of how they are indexed.

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[4] FDA GFI: Patient-Focused Drug Development: Collecting Comprehensive and Representative Input; available at https://www.fda.gov/media/139088/download; accessed 4/2023

CMS will consequently have to collect data on treatment alternatives, clinical benefits, and unmet medical need for rare diseases *de novo,* including from patients, caregivers, and providers. Patients and caregivers have key insights on issues such as determining the value of a therapy and how it compares to potential alternate treatment options. Rare disease patients are often uniquely positioned to share the challenges associated with unmet medical needs - when there are no or very few options available to treat their condition - and the benefits to themselves, their families, and the community from a safe and effective therapy. Patient experience data will be particularly important given CMS' desire to evaluate drug prices on an indication-specific level including certain off-label uses, which are common in the rare disease space albeit notoriously hard to study.[5] Because published data to assess these specific uses remain scarce, patients and providers are often the best experts from which to elicit such information related to rare disease treatments.

For the reasons outlined above, NORD urges CMS to:

a. Simplify and streamline the data submission process for patients, caregivers, and providers to eliminate barriers to their providing the requested information. This should include pre-testing the forms, attestations, and instructions with representatives of the relevant community to ensure they are clearly understood and easy to navigate, including by individuals with visual and other impairments. Because this data submission is voluntary and not subject to the 30-day statutory data submission timeline for mandatory manufacturer-provided data, CMS should work with the patient community to establish feasible timelines that will be workable for the community. FDA listening sessions, PFDD meetings, and other FDA-led initiatives routinely collect meaningful patient experience data in ways that works for rare disease patients and families and can serve as another valuable guide and resource for CMS, including all applicable attestations and data protections.

b. Clarify what information the agency is seeking from patients to allow data standardization and aggregation. The short time for submitting data makes it imperative to provide detailed instructions as early as possible, before the negotiation period begins, to facilitate and streamline the collection and submission of meaningful data. Clarifying the key data elements ahead of time will also empower patient advocacy groups and other important stakeholders to proactively collect and collate relevant information in a way that is scientifically rigorous and representative of the relevant patient community.

c. Organize CMS-led patient listening sessions specific to selected drugs to collect representative data within the different drug indications to inform CMS' initial offer for a negotiated drug. In planning for these sessions, CMS should use FDA patient listening sessions as a roadmap and work closely with the various impacted patient communities to develop a representative and meaningful data collection effort. For instance, while we appreciate why CMS intends to only focus on pharmaceutical alternatives and to primarily consider alternatives in the same drug class, we recognize non-pharmaceutical options such as surgery are often the only viable alternative for our patient populations and that therapeutic alternatives in other drug classes and with other mechanisms of actions may in fact be the most appropriate alternatives for some of our patients. Engaging the patient community in planning the listening sessions will help ensure that these alternatives are appropriately considered. Close collaboration with FDA will enable CMS to benefit from FDA's relevant best practices and extensive experience.

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[5] Fung A, Yue X, Wigle PR, Guo JJ. Off-label medication use in rare pediatric diseases in the United States. Intractable Rare Dis Res. 2021 Nov;10(4):238-245. doi: 10.5582/irdr.2021.01104. PMID: 34877235; PMCID: PMC8630459.

d. Include consistent and granular summaries of the data and assumptions on which each negotiation was based, including patient experience data. We urge CMS to report a detailed and standardized summary of the data relied upon in the negotiation process including the therapeutic alternatives, clinical benefit, off-label use, and unmet need for each indication and the data sources relied upon. CMS should further break out the use of patient experience data and patient-reported outcomes; list data identified by CMS through literature searches and guideline review; and identify primary data, such as claims, electronic health record (EHR), or other real-world-evidence, generated and collated by CMS. This level of transparency will be important to create consistency and trust in the negotiation process. Clearly breaking out the use of different data sources will also motivate the creation of valuable data sources including patient experience data for future negotiation years. In fact, much of the data for rare diseases collected through this process will be unique and have value beyond this specific negotiation process.

2. Give negotiated drugs a preferred place on the formulary and minimize utilization burdens to ensure patients have ready access to the negotiated drugs.

NORD supports section 1860D-4(b)(3)(I) of the Social Security Act which will require Medicare Part D negotiated drugs to be included on Part D plan formularies. However, we encourage CMS to take additional steps to ensure rare disease patients benefit from reduced out-of-pocket expenses associated with better formulary tier placement and to better assure their timely access to negotiated drugs through reduced utilization management processes.

Often, rare disease drugs are placed on the non-preferred or specialty tiers of Medicare Part D plan formularies, resulting in significant out-of-pocket costs and access delays. For instance, a study published in the America Journal of Managed Care (AJMC) in 2020 found "on average, 85% of orphan drugs on a [Medicare Part D] formulary were placed on its highest cost-sharing tier."[6] Similarly, a KFF analysis of 2023 Medicare Part D plans found that in 12 of the 16 the national prescription drug plans, coinsurance amounts for non-preferred drugs range from 40% to 50%, showing similar trends as in previous plan years.[7] Moreover, 44% of these plans' enrollees will face coinsurance ranging from 15% to 25% for preferred brands[8], meaning less predictable and often higher out of pocket costs for patients compared to flat copays. KFF also found that the median coinsurance for drugs on the specialty tier was 25%.[9]

Another common source of treatment delays or denials for rare disease patients is related to prior authorization and step therapy. NORD believes health care providers, in partnership with their patients, are best positioned to choose the right therapy to treat the often-complex health care challenges faced by those with a rare disease. Yet, a 2020 study found that a staggering 76% of orphan drugs on Medicare Part D formularies were subject to prior authorization.[10] Similarly, a 2021 study[11] found that nearly 40

[6] Yehia, F., Segal, J.B. Predictors of Orphan Drug Coverage Restrictions in Medicare Part D. 2020 Sep; AJMC 26(09); accessible at https://www.ajmc.com/view/predictors-of-orphan-drug-coverage-restrictions-in-medicare-part-d
[7] Kaiser Family Foundation (KFF): Medicare Part D: A First Look at Medicare Drug Plans in 20203; available at: https://www.kff.org/medicare/issue-brief/medicare-part-d-a-first-look-at-medicare-drug-plans-in-2023/'; accessed 4/2023
[8] Kaiser Family Foundation (KFF): Medicare Part D: A First Look at Medicare Drug Plans in 20203; available at: https://www.kff.org/medicare/issue-brief/medicare-part-d-a-first-look-at-medicare-drug-plans-in-2023/'; accessed 4/2023
[9] Ibid.
[10] Yehia, F., Segal, J.B. Predictors of Orphan Drug Coverage Restrictions in Medicare Part D. 2020 Sep; AJMC 26(09); accessible at https://www.ajmc.com/view/predictors-of-orphan-drug-coverage-restrictions-in-medicare-part-d
[11] Lenahan, K.L., Nichols, D.E., Gertler, R.M., Chambers, J.D.: Variations in Use and Content of Prescription Drug Step Therapy Protocols, Within and Across health Plans. 2021, Nov; Health Affairs 40(11); https://doi.org/10.1377/hlthaff.2021.00822; available at https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2021.00822

percent of the specialty drugs offered within the 17 largest commercial health plans included step therapy in the drug coverage plan. Additionally, 55.6 percent of the step therapy protocols were found to be more stringent than clinical guidelines,[12] delaying timely patient access to appropriate care.[13]

From CMS' perspective, negotiated drugs will have been appropriately valued and therefore, we encourage CMS to:

a. Require that a negotiated drug be placed on a higher formulary tier to improve patient access through further reduced patient out-of-pocket costs. While the $2,000 annual out-of-pocket cap and the smoothing mechanism to spread a patient's out-of-pocket costs out over the plan year will be tremendously helpful to Medicare patients living with a rare disease, coinsurance makes it more difficult for patients to predict their out-of-pocket expenditures. Requiring a negotiated drug's placement on formulary tiers that typically have copays instead of coinsurance can assist patients with both planning for prescription drug expenses and their ability to pay for their medications at the time they need them.

b. Significantly reduce or eliminate step therapy and prior authorization barriers in Medicare Part B and Medicare Part D for negotiated drugs. To further ensure timely access to these drugs, NORD urges CMS to include utilization management protections for negotiated drugs that have been determined by CMS to be appropriately priced. In the 2024 Medicare Advantage and Part D Final Rule (CMS-4201-F) released on April 5, 2023, and effective for the CY 2024 plan year, CMS will require "an approval granted through prior authorization processes must be valid for as long as medically necessary to avoid disruptions in care in accordance with applicable coverage criteria, the patient's medical history, and the treating provider's recommendation, and that plans provide a minimum 90-day transition period when an enrollee who is currently undergoing an active course of treatment switches to a new MA plan."[14] NORD encourages the adoption of these or similar requirements for negotiated drugs offered on traditional Medicare Part D plan formularies as well.

3. Ensure CMS' interpretation of the orphan drug exclusion protects vital incentives for rare disease drug development

While the IRA includes a limited exclusion for orphan drugs that only treat one rare disease from drug price negotiation, NORD is greatly concerned with the potential impact of CMS' proposed interpretation of the exclusion on future innovation in rare disease drug development. Today, about 60 percent of all orphan drugs have a single FDA-approved indication, whereas only about 20 percent are FDA-approved for both orphan and non-orphan indications.[15] Among the drugs that only have orphan indications, fewer than a quarter have more than one FDA-approved indication and fewer than 10 percent have three or more approved indications.[16] Similarly, among the drugs that have both orphan and non-orphan indications, less than 20 percent have 3 or more orphan indications. This indicates that to date, relatively few orphan drugs have been successfully developed for more than one disease.

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[12] Ibid.
[13] Ibid.
[14] Centers for Medicare & Medicaid Services (CMS); RIN 0938-AU96 Medicare Program; Contract Year 2024 Policy and Technical Changes to the Medicare Advantage Program, Medicare Prescription Drug Benefit Program, Medicare Cost Plan Program, and Programs of All-Inclusive Care for the Elderly; available at https://public-inspection.federalregister.gov/2023-07115.pdf; accessed 4/2023
[15] IQVIA: Orphan Drugs in the United States. 2020; Dec; available at: https://rarediseases.org/wp-content/uploads/2022/10/orphan-drugs-in-the-united-states-NRD-2020.pdf; accessed 4/2023
[16] Ibid.

Still, developing already-approved therapies to treat additional rare diseases is a critical strategy to address the rare disease community's significant unmet need because these drugs have already proven to be safe for humans. In fact, according to a recent analysis, over 3,000 unique drugs have been FDA-designated as rare disease drugs and studied, with about a quarter of these drugs being designated for more than one rare disease.[17] Serial innovation and the investigation and development of multiple rare disease indications of use is an increasingly important dimension of orphan drug development, making the preservation of incentives to further develop drugs to treat additional orphan diseases after they have entered the market particularly important.

NORD also recognizes that relatively few orphan-only drugs will meet the annual revenue threshold of $200,000,000 in combined expenditures under Medicare Parts B and D to make a drug negotiation-eligible. However, due to the complexity and long timeline from initial drug discovery and early research and development to FDA approval, drug sponsors are making decisions today that will impact their investments and drug development pipeline for decades to come. Remaining uncertainty about if, when, and how rare disease drugs will become negotiation eligible creates real business risks that work as strong disincentives to develop drugs for the limited populations impacted by rare diseases. Therefore, as part of the negotiation process, NORD urges CMS to make clear that research and development efforts in support of innovative therapies that help address unmet needs will be treated favorably in the price negotiation process.

We thank CMS for clarifying in the draft guidance that an orphan drug with multiple FDA-approved indications within the scope of an orphan drug designation for one rare disease (i.e., multiple indications tied to one orphan designation as shown in **Example 1**) remains excluded from negotiation. As a result, drug sponsors will consequently not be discouraged or penalized for further developing a rare disease drug for new sub-populations, such as children, or specific disease subtypes.

Example 1 - Orphan drug with one designation & multiple associated approved indications; CMS already clarified this is excluded from negotiation; this example was selected to be illustrative while reflecting common trends in orphan drug approvals.

Drug 1 (one designation, multiple FDA-approved indications)

Designations		**FDA Approved Indications**	
Disease	**Year**	**Year**	**Population**
Rare Disease A	2014	2015 2016 1018 2022	12 years and older 6 years and older 2 years and older 1 year and older

However, NORD is gravely concerned that CMS' interpretation of the orphan drug exclusion might contravene the intent of the ODA by discouraging drug sponsors from developing their drug for additional rare diseases. Specifically, CMS' interpretation of the IRA makes drugs eligible for negotiation as soon as they have been designated under section 526 of the Federal Food, Drug, and Cosmetic Act

[17] Miller, KL, Kraft, S, Ipe, A, and Fermaglich, L. Drugs and biologics receiving FDA orphan drug designation: an analysis of the most frequently designated products and their repositioning strategies. Expert Opin Orphan Drugs. 2022 Mar 1;9(11-12):265-272. doi: 10.1080/21678707.2021.2047021.

(FFD&C) for more than one orphan disease – even if the drug is not actually FDA approved (or indicated) to treat more than one of the designated orphan diseases. For instance, consider **Example 2** and the many other rare disease drugs with similar regulatory history; although this drug has been designated for five different rare diseases, it is only FDA approved to treat a single orphan disease.

Example 2: Orphan drug with multiple designations and one FDA-approved indication; CMS should clarify that that this drug will be excluded from negotiation because while it has five designations, it only has one approved indication.

Drug 2 (multiple designations, one FDA-approved indication)

Disease	Designation Year	FDA Approval Year
Rare Disease B	2007	2017
Rare Disease C	2009	-
Rare Disease D	2016	-
Rare Disease E	2018	-
Rare Disease F	2019	-

Designating an orphan drug under section 526 of the FFD&C Act is done early in the drug development process and much earlier than submission of a New Drug Application (NDA) or Biological License Application (BLA). Orphan drug designation is critical to access to ODA incentives such as funding and tax credits for clinical research to help de-risk this phase of drug development. However, an orphan drug designation does not allow the company to market the drug; it is only the first in many steps towards approval and marketing. In fact, FDA's Orphan Drug Designations and Approvals database currently contains 6,445 orphan drug designations (including withdrawn designations) compared to only 1130 approved orphan indications, demonstrating that a vast majority of orphan drug designations do not result in any FDA-approved indications – and therefore are largely irrelevant to the pricing considerations central to the Negotiation Program.[18]

NORD understands that the language of section 1192(e)(3), due to the manner in which it was drafted, is ambiguous and therefore open to CMS interpretation. CMS states that to qualify for the orphan drug exclusion, "the drug or biological drug must (1) be designated as a drug for only one rare disease or condition under section 526 of the FFD&C Act and (2) be approved by the FDA for only one or more indications within such designated rare disease or condition."[19] This two-prong test, embodying two separate and distinct criteria, is a possible interpretation of the statute. But under the canons of legislative drafting, if the congressional authors had intended the two clauses to be read ***independently***, the proper legislative drafting would have structured the two clauses separately and in sequence. Instead, Congress did not separate the clauses, intending them to be read ***together****:* that a drug designated for a given "rare disease or condition" has "only [one] approved indication" or multiple "approved... indications" ***within the scope of that designation*****.** CMS substantiates this plain meaning[20] of the provision in accepting that

[18] US FDA Orphan Drug Designations and Approvals database; available at https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm; accessed 4/2023
[19] Meena Seshamani, Memorandum to Interested Parties: 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, March 15, 2023, at 10-11.
[20] E.g., Sebelius v. Cloer, 569 U.S. ___, No. 12-236, slip op. (May 20, 2013).

an orphan drug with ***multiple*** ("one or more") FDA-approved indications qualifies for the exclusion provided all such approved indications are within the scope of a ***single*** ("only one") ***designation***.

A two-prong test also does not best reflect and advance the purposes and function of the Negotiation Program. The cardinal rule of statutory construction is that the whole statute should be drawn upon as necessary, with its various parts being interpreted within their broader statutory context in a manner that furthers statutory purposes.[21] The proper interpretation of the orphan drug exclusion "in a manner consistent with [the] legislative purposes"[22] of the Negotiation Program preserves an intentionally narrow class of qualifying orphan drugs determined upon the basis of a drug's FDA **approval history** – not on orphan drug designations which have no bearing on, or applicability to, prescription drug marketing or pricing.

In considering the regulatory history for the drug shown in **Example 3,** the approval for Disease H in 2014 should trigger the drug becoming negotiation eligible (assuming it meets the other statutory requirements outlined in the IRA), rather than the Designation for Diseases H or I in 2010, thus preserving vital rare disease research and development incentives. One of the critical "additional actions" that CMS can take to support rare disease research and development would be to revise its guidance to reflect a sound statutory interpretation more fully in line with congressional intent to make an orphan drug negotiation eligible once it has been approved (or indicated) to treat a second disease.

Example 3: Orphan drug with multiple designations and multiple FDA-approved indications; CMS should clarify that an orphan drug with multiple designations and approved indications becomes negotiation eligible when the drug is approved for the second disease (in this example 2014) – NOT upon second designation in 2010.

Drug 3 (multiple designations & multiple FDA-approved indications)

Disease	Designation Year	FDA Approval Year
Rare Disease G	2008	2011
Rare Disease H	2010	2014
Rare Disease I	2010	-
Rare Disease J	2013	-

NORD is also concerned about the potential chilling effect residual uncertainty about CMS's implementation of the orphan drug exclusion will have on rare disease drug development. CMS remains silent as to when orphan drugs that receive FDA approval for a second disease and therefore lose eligibility for the orphan drug exclusion would become negotiation eligible. Qualifying single-source drugs must have been approved at least 7 years and qualifying single-source biologics must have been licensed at least 11 years to qualify, but CMS has not yet clarified if the 7 or 11 years will be counted beginning on the date of the FDA approval for the second disease that made the drug negotiation eligible or based on the first orphan drug approval. CMS should clarify that obtaining additional designations for a small molecule or biologic will not make a drug negotiation eligible until the drug has been approved by

[21] See, e.g., King v. Burwell, No. 14-1158 (4th Cir. July 22, 2014) (various provisions of the Affordable Care Act sufficiently indicate an expectation that tax credits will be available to participants in all health exchanges to cast doubt on whether provision specifically making credits available to participants in state exchanges implicitly denies credits to participants in federal exchanges).
[22] Robert A. Katzman, Judging Statutes 31 (2016), at 10.

FDA for 7 or 11 years to treat the second disease or condition and in doing so, would provide meaningful incentives for continued rare disease drug development.

Considering the **Example 4,** CMS should clarify that – assuming the drug meets the other statutory requirements to become negotiation eligible as outlined in the IRA – the drug would become negotiation-eligible 7 or 11 years from the approval date for Disease O (i.e., in 2026 or 2030, 7 or 11 years from 2019).

Example 4: Orphan drug with multiple designations and multiple FDA-approved indications; CMS should clarify that the statutory period (i.e., 7 or 11 years) before negotiation starts at the approval that made the drug negotiation eligible (in this example 2026 or 2030, 7 or 11 years from 2019) – and <u>not first approval</u> (in this example 2021 or 2026, 7 or 11 years from 2014)

Drug 4 (multiple designations & multiple sequential FDA-approved indications)

Disease	Designation Year	FDA Approval Year
Rare Disease N	2011	2014
Rare Disease O	2016	2019
Rare Disease P	2016	-

For the reasons outlined above, NORD urges CMS to:

a. Clarify that if a drug has been designated under section 526 of the FFD&C Act for a second rare disease <u>but</u> has not been approved under section 505 (c) of the FFD&C Act or licensed under section 351(a) of the PHS for such disease, the drug will remain excluded from negotiation. As outlined above and illustrated in Examples 2 and 3, NORD believes this interpretation is consistent with the statute, maintaining Congressional intent to keep the orphan drug exclusion limited and will help protect the ODA incentives that have proven crucial for rare disease drug development.

b. Clarify that when a previously-excluded orphan drug becomes negotiation-eligible the statutory timeline for negotiation will begin from the time of the approval or licensure that made the drug negotiation-eligible, rather than from the very first approval or licensure in the drug's regulatory history. As outlined above and illustrated in Example 4, this will provide regulatory predictability and ensure continued investments in orphan drug development so that rare disease patients can meaningfully benefit from the price negotiation process.

c. Continue to work closely with FDA on the implementation of the orphan drug exclusion. As outlined above, the negotiation program may impact orphan drug development and as a result FDA in a variety of ways; at the same time, CMS will base regulatory decisions on a history of FDA actions and databases that were not originally designed for these uses. Close alignment between the two agencies will be important to maximize the positive impacts of the negotiation program while minimizing unintended consequences.

4. Begin tracking the impact of the IRA on patient outcomes and innovation now to support a data-driven program evaluation

The IRA will impact patients and the larger healthcare ecosystem in complex and somewhat unpredictable ways; some of these impacts, such as greater affordability of life-altering therapies through out-of-pocket caps, will be unequivocally beneficial, while others, such as the impact on innovation, remain less clear. Some impacts on the healthcare ecosystem may begin long before the first negotiated price takes effect while others may not occur until many years later. Baseline data will be important to track and truly understand the impact of the drug negotiation program and to document its successes and challenges. Now is the time to ensure appropriate IT systems exist and robust data are collected and analyzed to evaluate these impacts today and for years and decades to come. In the rare disease space, data scarcity and limited populations available for study make tracking the impact of the IRA on orphan drugs even more challenging, requiring additional thought and attention be given to the tracking of intended and unintended consequences on rare disease patients.

NORD is concerned additional efforts are needed to meaningfully track IRA impacts on patient outcomes and the healthcare system. The IRA may impact the healthcare ecosystem in complex way. For instance, the new law may increase healthcare utilization and improve medication adherence because out-of-pocket costs are capped, possibly adding years to the life of impacted patients; physician prescribing behavior may be influenced by IRA-associated changes in reimbursement rates under Medicare Part B, with uncertain impacts on overall cost savings and patient costs and outcomes; changing incentives may impact the relative placement of negotiated drugs on formularies; and the healthcare ecosystem may be impacted in a many other ways, some we may not even anticipate, and possibly with wide-reaching ramifications beyond the patients directly utilizing the negotiated Medicare Part B and D drugs.

CMS has long taken a leadership role in developing and reporting quality measures that lead to better-quality healthcare and improved health outcomes through robust, consistent, and data-driven accountability. [23] Many of the lessons learned will be directly applicable and should inform IRA tracking efforts, including selecting metrics that are person-centered and meaningful to patients and caregivers; engaging stakeholders early and often in the measure development process; minimizing the burden associated with measurement; prioritizing outcome-based metrics where possible; and guarding against unintended consequences of measure implementation.[24] In addition, CMS processes for rigorously evaluating metrics against established criteria and gathering robust stakeholder feedback at every step of the measure lifecycle are some of the additional areas where quality measures can inform IRA tracking efforts.[25]

NORD is also concerned additional efforts are needed to meaningfully track IRA impacts on innovation. Drug sponsors make decisions today that will impact the drug pipeline for decades to come. The IRA is likely to ultimately impact these decisions in a myriad of complex, interdependent, and hard-to-predict ways. NORD encourages CMS to work closely with FDA and other public and private-sector experts to establish meaningful metrics and monitor impacts on innovation. Tracking efforts will necessarily be limited by the available data systems and their ability to capture meaningful data, while many key data

[23] CMS: Quality Measures: How they are developed, used, & maintained; available at: https://mmshub.cms.gov/sites/default/files/Guide-Quality-Measures-How-They-Are-Developed-Used-Maintained.pdf; accessed 4/2023
[24] Ibid.
[25] Ibid.

sources to evaluate innovation in early research and development are proprietary and not readily available to the public. Moreover, consensus on appropriate metrics to capture pharmaceutical innovation during early research and development phases is largely lacking.[26] Given these challenges it appears likely that strategies to capture IRA impacts on pharmaceutical innovation will have to consider a relatively broad set of metrics in concert, looking at trends over time and across disease areas and geographic regions.

For the reasons outlined above, NORD urges CMS to:

a. Begin tracking key metrics to monitor and measure impacts on innovation and patient outcomes to ensure baseline data are available and as robust as possible. This will help lay a foundation for future evidence-based assessments of the IRA and draw thought and attention to the issue of data collection and tracking as well as help identify current key data gaps.

b. Engage with CMS quality metrics experts and other measurement experts within CMS, HHS, as well as government-wide and within the private and non-profit sector and issue requests for information (RFI) as applicable to reach agreement on what to measure and how to measure including key performance indicators (KPIs) and the data systems that generate the needed data. This will help lay the foundation for a resilient and sustainable tracking system to rigorously track and measure the impacts, intentional and unintentional, beneficial, and potentially harmful, of the IRA.

We thank CMS again for the opportunity to comment and look forward to working with CMS to ensure rare disease patients can fully participate in and benefit from the Negotiation Program. For questions related to this letter, please contact Heidi Ross, Vice President of Policy and Regulatory Affairs at HRoss@rarediseases.org or Karin Hoelzer, Director of Policy of Regulatory Affairs at KHoelzer@rarediseases.org

Sincerely,

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[26] Deshpande, A., Hood, C., Leach, B., Gutherie, S: Existing indicators to measure the biomedical innovation ecosystem; RAND 2019; available at: https://www.rand.org/content/dam/rand/pubs/working_papers/WR1300/WR1312/RAND_WR1312.pdf; accessed 4/2013