October 10, 2023

Dr. Richard Pazdur, MD
Director
Oncology Center of Excellence (OCE)
U.S. Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20903

Re: Docket No. FDA-2022-D-2629-0002- "Postmarketing Approaches to Obtain Data on Populations Underrepresented in Clinical Trials for Drugs and Biological Products"

Dear Dr. Pazdur,

On behalf of the more than 30 million Americans living with one of the over 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency's draft guidance, "Postmarketing Approaches to Obtain Data on Populations Underrepresented in Clinical Trials for Drugs and Biological Products."

NORD is a unique federation of non-profits and health organizations dedicated to improving the health and well-being of people with rare diseases by driving advances in care, research, and policy. 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. Since that time, NORD has been advancing rare disease research and funding to support the development of effective treatments and cures; raising awareness and addressing key knowledge gaps; and advocating for policies that support the availability of and access to safe and effective therapies.

NORD agrees with FDA's statement on page 1 of the guidance that pre-market clinical trials should enroll diverse patient populations including adequate representation from historically underserved communities. NORD also recognizes that, when despite the sponsor's best efforts, these populations are not adequately captured in pre-market trials, information from post-market setting can be useful in supplementing safety and effectiveness information for underrepresented patient populations.

For several reasons, clinical trials are often particularly difficult to conduct for rare diseases. For instance, the often small and geographically dispersed patient populations make enrollment for rare disease trials disproportionately time consuming and resource intensive. Far too often, rare disease patients must travel long distances to participate in clinical trials and face financial barriers, which can negatively impact trial recruitment and retention, and further complicate diversity efforts as patients from historically underserved communities tend to be disproportionately impacted by these challenges. Due to these challenges, clinical trials for rare diseases in particular have historically not been representative of the entire community, and as rare diseases can affect each person differently, there are exacerbated knowledge gaps regarding how they appear in minority populations.[1] Collecting post-market information

[1] U.S. Department of Health and Human Services. (2023, April 24). *Diversity and inclusion in clinical trials*. National Institute of Minority Health and Health Disparities. https://www.nimhd.nih.gov/resources/understanding-health-disparities/diversity-and-inclusion-in-clinical-trials.html#:~:text=People%20may%20experience%20the%20same,can%20benefit%20from%20scientific%20advances.

to supplement data on a drug's safety and effectiveness for underrepresented populations can identify different safety or efficacy profiles across subparts of the patient population, and can hold vital clues about the disease and lead to new therapeutic breakthroughs.

Over 95% of the more than 7,000 known rare diseases do not have any FDA approved treatment. This makes post-market data collection to supplement data on historically underrepresented populations even more essential for rare disease drug development programs that have progressed too far to reasonably address these data limitations pre-market, in particular for rare disease patients that lack any other treatment options. NORD thanks the Agency for drafting this guidance to help drug sponsors effectively collect post-market data on underrepresented populations to ensure the safety and effectiveness of drugs on the market.

NORD is pleased to offer specific recommendations below for how to maximize the impact of this draft guidance, informed by our 40 years of experience working constructively with all key stakeholders to help bring more rare disease therapies to more patients more quickly.

Recommendation 1: Provide more nuanced guidance on the effective and efficient use of post-market studies to close key data gaps about the safety and/or effectiveness of a product for historically underrepresented population groups.

NORD appreciates that the draft guidance acknowledges the importance and potential appropriateness of a variety of study designs (including single-arm trials, randomized trials, real-world data, and meta-analysis) for post-market data collection. This flexibility in study design is particularly important for diseases that have small populations, scarce data, and limited natural history studies. While traditional randomized, double-blinded, placebo-controlled trials are the gold standard for clinical evidence of safety and effectiveness, they are not always feasible or ethical in rare disease drug development.[2] For instance, a study analyzing approvals from 1999 to 2014 showed FDA approved as many as 60 new indications based on data other than randomized controlled trials.[3] Similarly, another study found that 116 FDA approvals between 2019 and 2021 leveraged real-world evidence, most notably external control arms.[4]

The unique challenges associated with rare disease research complicate both traditional randomized, double-blinded, placebo-controlled trials, as well as alternative research approaches, including single-arm trials, real-world data sources, and meta-analyses. For instance, most rare diseases lack disease-specific ICD-10 codes, making it difficult to identify patients for clinical trials and gather Real World Data (RWD) and Real World Evidence (RWE) to use in alternative research approaches.[5] Without ICD-10 codes for specific rare diseases, providers will only be able to report codes that describe symptoms but not

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[2] *Rare diseases: Common issues in drug development guidance for industry*. Food and Drug Administration. (2019, February). Retrieved April 28, 2023, from https://www.fda.gov/media/120091/download

[3] Hatswell AJ, Baio G, Berlin JA, Irs A, Freemantle N. Regulatory approval of pharmaceuticals without a randomised controlled study: analysis of EMA and FDA approvals 1999-2014. BMJ Open. 2016 Jun 30;6(6):e011666. doi: 10.1136/bmjopen-2016-011666. PMID: 27363818; PMCID: PMC4932294.

[4] Purpura, C., Garry, E., Honig, N., Case, A., & Rassen, J. (2022). *The role of real-world evidence in FDA-approved new drug and Biologics License Applications*. Clinical pharmacology and therapeutics. Retrieved April 28, 2023, from https://pubmed.ncbi.nlm.nih.gov/34726771/#:~:text=Finally%2C%20we%20qualified%20FDA's%20documented,evidence%20of%20safety%20or%20effectiveness.

[5] *June 2023 - World Health Organization*. World Health Organization. (2023, June). https://cdn.who.int/media/docs/default-source/classification/icd/icd-10/icd-10-to-meddra-mapping-conventions.pdf?sfvrsn=1b36c13b_1

the rare disease, thus not allowing for researchers to access symptoms and manifestations under the specific diagnosis.[6] More detailed guidance on how to overcome these challenges in post-market studies specific to historically underserved populations would be tremendously helpful to ensure the studies are in fact fit for purpose.

Nothing is more devastating to the rare disease community than dedicating considerable time and resources to a rare disease study only to find its flawed design and/or execution compromises the interpretability of the data to a point where it is inadequate to serve its regulatory purpose. This remains true for post-market requirements, in particular given the financial realities of rare many rare diseases. In fact, the limited patient populations and financial realities of rare disease drug development generally make repeating a seriously flawed study impossible and any resources unnecessarily dedicated to overly burdensome post-market data collection efforts may impede future rare disease research efforts into the same and other diseases.

Along those lines, NORD recognizes that FDA recently released several related draft guidance documents, including those specific to the use of external controls. Given the importance of well-designed rare disease studies, specific recommendations to enhance the effectiveness of pre- and post-market data collection on individuals from historically underrepresented communities should be incorporated into the following guidances:

- Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics Guidance for Industry[7]
- Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance for Industry[8]
- Decentralized Clinical Trials for Drugs, Biological Products, and Devices[9]

For this reason, FDA must carefully ensure alignment and cohesion among the multiple guidance documents relevant to the use of post-market data collection on underrepresented populations.

In addition, NORD urges the Agency to provide more detailed and tangible guidance on how to appropriately integrate pre- and post-market data collection – including for coverage and reimbursement issues - into ongoing rare disease drug development programs to appropriately incentivize rare disease drug development.

In addition, we urge the agency to develop and publish best practices and lessons learned to provide examples of successful (and potentially unsuccessful) pre- and post-market data collection on safety and effectiveness in historically underserved populations, including through a variety of study designs spanning randomized trials to single-arm trials and RWE.

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[6] Luxner, L. (2019, February 5). *ICD-10 codes, "really important" to rare disease patients, soon up...* Pompe Disease News. https://pompediseasenews.com/news/icd-10-codes-really-important-to-rare-disease-patients-soon-up-for-fresh-consideration/#:~:text=%E2%80%9CFor%20one%2C%20it%20helps%20define,but%20not%20the%20underlying%20disease.

[7] Oncology Center of Excellence. (March 2023). Retrieved October 5, 2023 from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-considerations-support-accelerated-approval-oncology-therapeutics

[8] Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, & Oncology Center of Excellence. (January 2023). Retrieved May 24, 2023 from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products

[9] Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health & Oncology Center of Excellence. (May 2023). Retrieved October 3, 2023 from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/decentralized-clinical-trials-drugs-biological-products-and-devices

Similarly, CMS has prioritized trial diversity and appropriate representation for issues such as coverage with evidence generation and national coverage decisions in their draft guidance titled, "CMS National Coverage Analysis Evidence Review and Coverage with Evidence Development." Better alignment between FDA and CMS on practical strategies and best practices to increase recruitment and retention of diverse populations will be key to ensure timely access to innovative therapies.

Recommendation 2: While post-market data collection has a role, in particular for rare diseases, appropriate representation should be part of any rare disease drug development program from the start. Provide additional guidance to help sponsors meet pre-market trial diversity goals and ensure post-market data collection is not abused as a substitute for appropriate pre-market efforts to ensure clinical trials accurately represent the whole patient population.

Recommendation 2a: Make pre-market clinical trials more accessible and equitable for the entire patient population. Ensuring that clinical trials appropriately represent the intended patient populations is a priority for NORD and we thank the FDA Commissioner, Dr. Califf, for acknowledging the need for clinical trials to be more representative of the patient population.[10] While collecting post-market data can help ensure the safety and efficacy of products for specific population subgroups after a clinical trial is conducted, it is imperative to ensure that historically underrepresented populations are taken into consideration from the very beginning of the drug development process. Post-market data collection should never be an excuse for a lack of sponsor efforts to collect appropriate data pre-market.

Patients from historically underserved populations are consistently underrepresented in clinical trials, to the detriment of everyone involved. Broadly, clinical trial participation for the Latino/Hispanic population in the United States remains low at 11%, despite constituting 18% of the population in the United States.[11] Increasing access to a more diverse population is a particularly critically important issue for rare diseases given the limited patient populations, geographic dispersion, and heterogenous disease manifestation. For instance, in a recent study published by the Foundation for Sarcoidosis Research, researchers found that in the analyzed rare disease trials, Black participants constituted only 9% of clinical trial participants, whereas white participate constituted 70% of participants.[12] In the case of sarcoidosis, Black women in particular are three times more likely to receive a sarcoidosis diagnosis in their lifetimes with mortality rates 12 times higher than those of white patients with sarcoidosis.[13] Despite having more diagnoses and worse outcomes, sarcoidosis drugs are being produced from trials that are not representative of its patient population.[14]

Many disparities hinder the participation of historically underserved populations in clinical trials, including structural racism, mistrust in clinical research and financial and logistical barriers to participation. Research has shown that historically underserved populations are more likely to participate in clinical trials if they:

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[10] Office of the Commissioner. (2023). *FDA takes additional steps to advance decentralized clinical trials*. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-takes-additional-steps-advance-decentralized-clinical-trials

[11] Day, J. A. (2023, May 1). *Why it's vital that all people - including people of color - take part in Clinical Research Studies: Johns Hopkins Division of Gastroenterology and Hepatology*. Johns Hopkins Medicine. https://www.hopkinsmedicine.org/research/understanding-clinical-trials/poc-and-clinical-trials.html

[12] Foundation for Sarcoidosis Research. (2023). *Advancing clinical trial equity for black patients with sarcoidosis*. Foundation for Sarcoidosis Research. https://www.stopsarcoidosis.org/wp-content/uploads/FSR-Clinical-Trial-Diversity-White-Paper-FINAL.pdf

[13] *Id*.

[14] *Id.*

- Are asked to participate in the trial by a trusted healthcare provider or community leader;
- Are given information on how the trial benefits them or their community;
- Receive support for clinical trial participation, including financial support to cover travel expenses and lodging, and flexible appointment times to minimize disruptions to work and caregiving obligations; and/or
- Hear the experiences of other patients who are part of the clinical trial.[15]

Equitable access to clinical trials and equitable enrollment of trial participants from historically underserved communities requires deliberate planning and strong community partnerships to achieve. Sponsors will require additional guidance and support to ensure historically underserved communities, patients with disabilities, and patients with limited financial abilities have equitable access to clinical trials.

Recommendation 2b: Promote the use of decentralized clinical trial designs to ensure equitable access to pre- and post-market studies

In May 2023, FDA released the draft guidance titled, "Decentralized Clinical Trials for Drugs, Biological Products, and Devices," which provided recommendations for sponsors regarding the implementation of decentralized clinical trials.[16] In response to this draft guidance, NORD provided extensive comments on the successes of decentralized clinical trials and ensuring that these efforts from the COVID-19 era are made permanent.[17] These types of trial designs have the potential to increase diversity and participation by bringing trials to the patient's home or community-ultimately making participation faster, easier, and more equitable by decreasing access barriers for historically underrepresented communities.

While conducting pre- and post-market studies in a decentralized manner can be an effective way to bring these studies into communities, efforts should be put in place to ensure that potential participants are made aware of the studies and their benefits, given financial support, and reach participants with language barriers.

NORD again thanks FDA for the opportunity to provide comments on this important draft guidance, and we look forward to continuing the dialogue around decentralized clinical trials, as well as other strategies to bring safe and effective rare disease drugs quickly and effectively to market. For questions regarding NORD or the above comments, please contact Hayley Mason, Policy Analyst, at hmason@rarediseases.org

Sincerely,

Hayley Mason

Hayley Mason, MPA
Policy Analyst
National Organization for Rare Disorders

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[15] *Id.*

[16] Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health & Oncology Center of Excellence. (May 2023). Retrieved October 3, 2023 from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/decentralized-clinical-trials-drugs-biological-products-and-devices

[17] Retrieved from https://rarediseases.org/wp-content/uploads/2023/08/NORD-Comments-on-Decentralized-Clinical-Trials-080123.pdf