Patrizia Cavazzoni, M.D.
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10001 New Hampshire Ave
Silver Spring, MD 20903

July 17, 2023

Re: Docket No. FDA-2005-D-0460 for "Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act"

Dear Dr. Cavazzoni,

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(NORD) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency's draft guidance, "Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act."

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.

Of the more than 30 million individuals in the United States living with rare diseases,[1] as many as half are children, and approximately 30 percent of children with rare diseases will not reach their fifth birthday.[2] Only 5 percent of rare diseases have an FDA approved treatment.[3] Even where approved orphan products are available, pediatric labeling is often missing. For instance, according to FDA's August 2019 report entitled "Pediatric Labeling of Orphan Drugs," almost 40 percent (127 of 348) of orphan indications approved from January 1999 – August 2018 that warranted pediatric labeling were incompletely labeled, with 81 having no pediatric information and 46 missing some pediatric information.[4] Although some progress has been made since, significant pediatric labeling gaps remain.

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[1] U.S. Government Accountability. (2021, October 18). *Rare diseases: Although Limited, available evidence suggests medical and other costs can be substantial*. Rare Diseases: Although Limited, Available Evidence Suggests Medical and Other Costs Can Be Substantial | U.S. GAO. https://www.gao.gov/products/gao-22-104235

[2] Fleming, S. (2020, February 29). One in three children with a rare disease won't live to see their fifth birthday. ThePrint. https://theprint.in/science/one-in-three-children-with-a-rare-disease-wont-live-to-see-their-fifth-birthday/372994/

[3] U.S. Department of Health and Human Services. (2023, March 21). Rare disease day at NIH 2023: Putting hope into action. National Center for Advancing Translational Sciences. https://ncats.nih.gov/pubs/features/rare-disease-day-at-NIH-2023-putting-hope-into-action#:~:text=Of%20the%20more%20than%2010%2C000,(FDA)%E2%80%93approved%20treatments.

[4] Department of Health and Human Services, Food and Drug Administration. Pediatric Labeling of Orphan Drugs Report to Congress. Table 5. https://www.fda.gov/media/130060/download, downloaded on November 13, 2019.

As these statistics show, pediatric studies remain vital for our community given the large number of rare diseases impacting children. Without proper labeling for pediatric patients, providers are too often left without adequate information regarding the safety, proper dosage, and effectiveness of the product.[5] When providers need to prescribe a drug without proper pediatric labeling, they often have to extrapolate the appropriate dosage for the patient, and must advise parents that a drug has not yet been deemed safe for children.[6] This creates both potential safety and effectiveness challenges, and risks undermining the family's trust in the therapy.

At the same time, developing therapies for rare diseases is uniquely challenging. Pediatric studies can be significantly more complex to plan and implement than for other diseases. Therefore, certain regulatory requirements that are appropriate for more common diseases must be adapted to the rare disease context. NORD appreciates FDA's longstanding regulatory as well as Congress' legislative intent to avoid creating undue barriers for rare disease drug development. In line with this long-standing intent, for some orphan drugs, temporary or permanent exemptions from some study requirements including in some cases certain pediatric studies may be needed to adequately support continued drug development efforts.

NORD appreciates FDA's efforts to provide additional guidance to industry on the development of pediatric studies, including considerations for navigating the requirements of Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA).

Orphan Drugs with PREA requirements should remain BPCA eligible

BPCA[7] and PREA of 2003[8] are complementary landmark pieces of legislation designed to improve information about how to use therapeutics safely and effectively in children while recognizing the unique challenges of orphan drug development. PREA and BPCA together provide incentives, flexibility, and accountability for the development of pediatric drugs. As a result of the over 800 labeling changes to include pediatric information, more drugs, including several key orphan products, today are marketed for use in pediatric patients with proper labeling, dosage, and safety information. [9] In addition, BPCA requirements for enhanced adverse events reporting has greatly expanded the availability of real-world safety data.[10]

NORD recognizes the foundational impact of these labeling changes on pediatric medicine and agrees with FDA's goal to leverage the limited BPCA funding to maximize the available pediatric labeling information. However, in the draft guidance, FDA asserts that upon finalization, "FDA does not expect to issue WRs solely for studies or planned studies that are required under PREA."[11] This strong departure from previous practice may be warranted in many cases. However, the unique challenges of orphan drug development continue to make pediatric studies in rare diseases more complex, and NORD encourages

[5] FDA. Pediatric Labeling Changes. https://www.fda.gov/science-research/pediatrics/pediatric-labeling-changes. Accessed on July 5, 2023.

[6] Boyle, P. (2022, June 21). The wish of pediatricians: More medications deemed safe for kids. AAMC. https://www.aamc.org/news/wish-pediatricians-more-medications-deemed-safe-kids

[7] P.L. 107-109

[8] P.L. 108-155

[9] FDA. Pediatric Labeling Changes. https://www.fda.gov/science-research/pediatrics/pediatric-labeling-changes. Accessed on July 5, 2023.

[10] NIH. (2008). Regulatory framework - addressing the barriers to pediatric drug ... NIH National Library of Medicine. https://www.ncbi.nlm.nih.gov/books/NBK3997/

[11] Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. (May 2023). Retrieved July 11, 2023 from https://www.fda.gov/media/168201/download

FDA to reconsider this policy change for those select orphan products that are subject to PREA requirements. Since orphan drugs are often updated for safety labeling in pediatric populations, collecting data is particularly difficult due to clinical trial enrollment issues and safety considerations.[12] By allowing BPCA to issue Written Requests (WR) to orphan products that fall under PREA requirements, drug sponsors of these orphan products will continue to have access to this important program to study pediatric labeling to determine safety, efficacy, and proper dosage. This will help increase the number of orphan products that have complete pediatric labeling, which is vital to the safety of the pediatric population. At the same time, the policy will help ensure that the development of orphan drug that fall under PREA requirements is not unnecessarily hindered.

Continue to Prioritize Pediatric Labeling for Orphan Drugs without Unduly Delaying Development

It is deeply concerning that as of 2019, roughly one-third of all orphan products had inadequate pediatric labeling and one-fourth failed to contain any pediatric labeling at all. Ensuring that pediatric patients, their families, and their providers have the information they need to make safe and effective treatment decisions is of utmost concern. Without adequate labeling for children, health care providers and caregivers are put in the difficult position of guessing whether and how much of a drug to provide. This could have dangerous consequences for children.

Given the unique challenges of rare disease drug development, the right mix of incentives is vital to close this labeling gap while continuing to create an environment conducive to bringing orphan products to market. As outlined above, the BPCA creates vital incentives that have proven key for closing rare disease labeling gaps and we urge FDA to continue to prioritize orphan drugs in the BPCA. In addition, NORD urges FDA to consider what tools, pilot programs, and additional guidance the agency can provide sponsors to further risk rare disease drug development and reduce the burden associated with pediatric studies for rare diseases.

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

Sincerely,

Hayley Mason, MPA
Policy Analyst
National Organization for Rare Disorders

[12] Fan, M., Chan, A.Y.L., Yan, V.K.C. et al. Postmarketing safety of orphan drugs: a longitudinal analysis of the US Food and Drug Administration database between 1999 and 2018. Orphanet J Rare Dis 17, 3 (2022). https://doi.org/10.1186/s13023-021-02166-9