December 18, 2023

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

Re: Docket No. FDA-2023-D-2318- "Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence"

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the over 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) is pleased to comment on FDA's draft guidance "Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence."

NORD is a unique federation of non-profit 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 this 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 diagnostics and therapies.

More than 95% of rare diseases do not have any FDA approved treatments. Because many rare diseases lack natural history studies, have limited data on the disease etiology or progression, and affect small patient populations, replicating clinical trials is often not feasible.[1] Therefore, NORD strongly appreciates FDA's efforts to provide guidance on the considerations for using a single adequate and well-controlled clinical investigation and confirmatory evidence to demonstrate effectiveness when two adequate and well-controlled trials are not feasible. Confirmatory evidence and other types of real-world data (RWD) play an increasingly important

[1] Nugent, B., Thomas, A., Bagheri, B., Doi, M., Pepe, S., Welsh, C., & Lee, K. J. (2023, June 2). *Confirmatory Evidence of Effectiveness Used to Support Non-Oncologic Rare Disease Novel Drug Marketing Application Approvals, CY 2020-2022*. FDA. https://www.fda.gov/science-research/fda-science-forum/confirmatory-evidence-effectiveness-used-support-non-oncologic-rare-disease-novel-drug-marketing

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role in rare disease drug development.[2] For instance, in a study conducted by FDA on sources of evidence used in recent new drug approvals for non-oncologic rare disease indications, 32 out of 40 approvals used one adequate well-controlled (AWC) trial and confirmatory evidence (CE).[3] Rare disease drug development faces unique data and trial design challenges and the need for more targeted guidance specific to alternative trial designs for small, rare populations is well-recognized.[4] 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 granular and practical guidance specific to drug development for rare diseases

As mentioned above and explicitly called out in the draft guidance, rare disease drug development programs often rely on one AWC and CE for a variety of logistical and practical reasons.[5] However, uncertainty about what CE will be acceptable to FDA or how it can be used successfully to support rare disease drug development programs often leads to costly delays and may even jeopardize the drug development program. CE for rare diseases faces unique challenges, and the ways in which it can complement evidence from AWCs differs for rare vs. more common diseases. Yet, the draft guidance currently does not discuss these challenges or how they may impact the applicability of these designs for orphan products.[6] As a result, the unique challenges encountered when leveraging confirmatory evidence to supplement one adequate well-controlled trial in rare disease drug development are not considered nor addressed sufficiently in the guidance. For instance, page 10 of the draft guidance discusses leveraging

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[2] Nugent, B., Thomas, A., Bagheri, B., Doi, M., Pepe, S., Welsh, C., & Lee, K. J. (2023, June 2). *Confirmatory Evidence of Effectiveness Used to Support Non-Oncologic Rare Disease Novel Drug Marketing Application Approvals, CY 2020-2022*. FDA. https://www.fda.gov/science-research/fda-science-forum/confirmatory-evidence-effectiveness-used-support-non-oncologic-rare-disease-novel-drug-marketing

[3] Nugent, B., Thomas, A., Bagheri, B., Doi, M., Pepe, S., Welsh, C., & Lee, K. J. (2023, June 2). *Confirmatory Evidence of Effectiveness Used to Support Non-Oncologic Rare Disease Novel Drug Marketing Application Approvals, CY 2020-2022*. FDA. https://www.fda.gov/science-research/fda-science-forum/confirmatory-evidence-effectiveness-used-support-non-oncologic-rare-disease-novel-drug-marketing

[4] Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development; Field MJ, Boat TF, editors. Rare Diseases and Orphan Products: Accelerating Research and Development. Washington (DC): National Academies Press (US); 2010. 3, Regulatory Framework for Drugs for Rare Diseases. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK56185/

[5] Nugent, B., Thomas, A., Bagheri, B., Doi, M., Pepe, S., Welsh, C., & Lee, K. J. (2023, June 2). *Confirmatory Evidence of Effectiveness Used to Support Non-Oncologic Rare Disease Novel Drug Marketing Application Approvals, CY 2020-2022*. FDA. https://www.fda.gov/science-research/fda-science-forum/confirmatory-evidence-effectiveness-used-support-non-oncologic-rare-disease-novel-drug-marketing

[6] Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Oncology Center of Excellence, & Office of the Commissioner. (2023, September). *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence*. U.S. Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-one-adequate-and-well-controlled-clinical

natural history studies and RWD/real-world evidence (RWE) to substantiate AWC trials but is lacking any specific reference to using these mechanisms for rare diseases which often experience unique RWD challenges (e.g., the lack of disease-specific ICD-10 codes), and despite the central role of CE in rare disease drug development.[7]

Recommendation 2: Provide additional guidance and best practices to ensure product development plans based on one AWC trial plus CE are set up for success

To ensure the effectiveness of this guidance, there is an urgent need to compile best practices and case studies for how the rare disease community can successfully leverage CE, and what role patient advocacy groups and other key stakeholders can play at each step of the drug development process in generating this data.

Natural history studies are among the most widely used types of data for CEs in rare disease drug approvals, according to FDA, together with mechanistic evidence, data from additional clinical studies, and other types of CEs.[8] For rare diseases, patient advocacy groups often play a key role in conducting such natural history studies. In fact, according to a recent survey, almost 80% of rare disease advocacy groups are engaged in research, with 53% contributing to patient registries, 73% contributing to natural history studies, as well as 80% being engaged in clinical trials.[9] Yet, according to a soon-to-be published NORD membership survey, as many as 57% of patient advocacy groups struggle with engaging in federal policy and advocacy for their disease state and most would benefit greatly from more guidance and best practices. To name just one recent example, in February 2023, the FDA approved the first product to treat Friedreich's ataxia using CE in addition to a single AWC trial.[10] Given the small patient population for Friedreich's ataxia, completing a second well-controlled trial was deemed to be not feasible, and natural

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[7] Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Oncology Center of Excellence, & Office of the Commissioner. (2023, September). *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence*. U.S. Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-one-adequate-and-well-controlled-clinical

[8] Nugent, B., Thomas, A., Bagheri, B., Doi, M., Pepe, S., Welsh, C., & Lee, K. J. (2023, June 2). Confirmatory Evidence of Effectiveness Used to Support Non-Oncologic Rare Disease Novel Drug Marketing Application Approvals, CY 2020-2022. FDA. https://www.fda.gov/science-research/fda-science-forum/confirmatory-evidence-effectiveness-used-support-non-oncologic-rare-disease-novel-drug-marketing

[9] Patterson AM, O'Boyle M, VanNoy GE, Dies KA. Emerging roles and opportunities for rare disease patient advocacy groups. Ther Adv Rare Dis. 2023 Apr 24;4:26330040231164425. doi: 10.1177/26330040231164425. PMID: 37197559; PMCID: PMC10184204.

[10] *First medication to treat Friedreich's ataxia approved on rare disease day!* Friedreich's Ataxia Research Alliance. (2023, June 9). https://www.curefa.org/news-press-releases/first-medication-to-treat-friedreich-s-ataxia-approved-on-rare-disease-day

history data provided vital insights, ultimately allowing the drug sponsor to leverage data collected through open-label extensions as CE.[11]

Patient advocacy groups are by no means the only stakeholders that would benefit from such a best practices document. The draft guidance mentions drug sponsors should meet with FDA early and often when considering using one AWC trial with CE but provides little in terms of concrete guidance. While NORD appreciates FDA's call for engaging early and often in the drug development process, more is needed from FDA to ensure drug sponsors, in particular those new to orphan drug development, understand how to effectively engage with FDA and which questions to ask specifically on CE. Ideally, FDA should provide guidance on best practices before, during, and after submission of an Investigational New Drug (IND) application, throughout the New Drug Application (NDA) or Biologics License Application (BLA) review, as well as throughout the product life cycle including fulfillment of any Postmarketing Requirements (PMR), and Postmarketing Commitments (PMC).

Recommendation 3: Given the importance of CE to many aspects of rare disease drug development, provide relevant cross references to pertinent information in other guidance's to ensure consistency

The recommendations provided in this draft guidance are closely linked to, and at times build upon, recommendations in other FDA guidance documents.[12,13,14] As the agency's thinking on various issues evolves it may have ripple effects that reverberate through multiple guidance documents. Where more specific and relevant guidance for rare diseases is available from other guidance documents, it would be beneficial to provide an explicit reference (and summarize the pertinent information that is referenced). For example, explicitly referencing and discussing the "Rare diseases: Natural history studies for drug development" draft guidance from March 2019 in the natural history section of this draft guidance (along with a summary of issues associated with natural history studies) would be beneficial for rare disease drug development. Moreover, where multiple guidance documents may seemingly contradict each other, it will be important to

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[11] *First medication to treat Friedreich's ataxia approved on rare disease day!* Friedreich's Ataxia Research Alliance. (2023, June 9). https://www.curefa.org/news-press-releases/first-medication-to-treat-friedreich-s-ataxia-approved-on-rare-disease-day

[12] Center for Drug Evaluation and Research. (2019, March). Rare diseases: Natural history studies for drug development. U.S. Food and Drug Administration. Retrieved May 2, 2023, from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development

[13] *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

[14] Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, & Oncology Center of Excellence. (2023, February). *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products*. U.S. Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products

clarify the relationship among the guidance documents and how the Agency's thinking on the issue may have evolved over time. FDA has done so successfully in other guidance documents. For example, in the draft guidance "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products", FDA notes in footnote 8 how FDA's current thinking has changed from a previous draft guidance published in 2019, and indicates that when final, that guidance will be current with FDA.[15]

NORD again thanks FDA for the opportunity to provide comments on this important draft guidance, and we look forward to continuing the dialogue around confirmatory evidence, 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,

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[15] Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, & Oncology Center of Excellence. (2023, February). *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products*. U.S. Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products