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Approval Re: Docket No. FDA-2024-D-3334 for "Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway Guidance for Industry"

Dear Drs. Corrigan-Curay, Marks, and Pazdur,

On behalf of the more than 30 million Americans living with one of the over 10,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the U.S. Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency's draft guidance, "Accelerated Approval and Considerations for Determining Whether a Confirmatory Trials is Underway Guidance for Industry."

With a more than 40-year history, NORD is the leading and longest-standing patient advocacy organization for the estimated 1-in-10 Americans living with a rare disease. An independent 501(c)(3) nonprofit, NORD is dedicated to individuals with rare diseases and the organizations that serve them. NORD, along with its more than 355 patient organization members, is committed to improving the health and well-being of people with rare diseases by driving advances in care, research, and policy. NORD believes that all individuals with a rare disease should have access to high quality, affordable health care that is best suited to meet their medical needs.

NORD thanks the FDA for the opportunity to comment on this draft guidance. This document supports more timely evidence development while maintaining important flexibilities for rare disease products in accordance with provisions of the FDA Omnibus Reform Act (FDORA), passed as part of the Consolidated Appropriations Act of 2023 (P.L. 117-328). In addition, NORD appreciates this guidance is additive to the draft guidance "Expedited Program for Serious Conditions — Accelerated Approval of Drugs and

Biologics Guidance for Industry,"[1] as together these draft guidances further strengthen the accelerated approval pathway.

Accelerated approval is an essential regulatory mechanism for ensuring that patients with serious and life-threatening conditions, particularly those with rare diseases, can access effective and potentially lifesaving therapies as quickly as possible.[2] Given the nature of rare diseases— which are often characterized by small, heterogenous patient populations with limited knowledge of natural history — this pathway allows for timely patient access to critical therapies that may otherwise face insurmountable hurdles with more traditional clinical trial approaches.

Rare Disease Considerations Should Inform FDA's Approach to Confirmatory Trials

NORD appreciates the clarification provided in the draft guidance regarding the expectation that confirmatory trials be underway prior to granting accelerated approval, except in limited circumstances. This requirement enhances the Agency's ability to make faster, data-driven decisions while maintaining necessary flexibilities, which is particularly important for rare diseases where non-traditional trial designs and smaller patient populations require a more adaptable regulatory approach.

Significantly, the draft guidance acknowledges the "unique challenges with initiating post-approval confirmatory trials prior to approval" for rare disease accelerated approval drugs. The draft guidance also critically recognizes that, for "drugs intended to treat some rare diseases, especially those with very small populations with high unmet need… if appropriate justification is provided, FDA may not require that the confirmatory trial is 'underway' prior to accelerated approval." NORD urges the Agency to undertake outreach and education through the Rare Disease Innovation Hub, in conjunction with the Oncology Center of Excellence, to discuss and clarify its intent, and share illustrative examples, with patients and investigators on these important policies.

NORD additionally thanks the FDA for acknowledging that certain rare disease products may leverage natural history data where appropriate and that this may potentially reduce enrollment challenges for confirmatory trials. Delays in confirmatory trial enrollment are one of the key reasons trial completion dates are missed.[3,4] Enrollment challenges can have several distinct root causes, which each may warrant their own solutions.[5] For example, small patient populations combined with population heterogeneity seen in many rare diseases can also result in heterogeneous clinical trial enrollment,[6] which can make it difficult to pinpoint clinical effects. Studying sub-populations (or verifying clinical

[1] Center for Drug Evaluation and Research, Center for Biologics and Research, & Oncology Center of Excellence. (2024, December). Expedited program for serious conditions. U.S. Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/accelerated-approval-expedited-program-serious-conditions

[2] NORD, Temkin, E. & Trihn, J. FDA's Accelerated Approval Pathway: A Rare Disease Perspective. https://rarediseases.org/wpcontent/uploads/2022/10/NRD-2182-Policy-Report_Accelerated-Approval_FNL.pdf

[3] Health and Human Services (2022, September 29). *Delays in Confirmatory Trials for Drug Applications Granted FDA's Accelerated Approval Raise Concerns*. Office of Inspector General. Retrieved May 15, 2023, from https://oig.hhs.gov/oei/reports/OEI-01-21-00401.asp

[4] NORD, Temkin, E. & Trihn, J. FDA's Accelerated Approval Pathway: A Rare Disease Perspective. https://rarediseases.org/wp-content/uploads/2022/10/NRD-2182-Policy-Report_Accelerated-Approval_FNL.pdf

[5] Id.

[6] U.S. Food & Drug Admin., Rare Diseases at FDA, https://www.fda.gov/patients/rare-diseases-fda (last updated Nov. 21, 2024).

benefits in sub-populations) can be exceedingly difficult.[7] In addition, a lack of available patients to be enrolled in a clinical trial can undermine the sponsor's ability to power the study and reach statistical significance.[8] Given these unique considerations, it is critical not only to emphasize the importance of early discussions between regulators and drug sponsors, but also for the Agency to ensure adequate resources and touch points exist for sponsors and regulators in order to support feasible confirmatory trial designs.

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NORD again thanks FDA for the opportunity to provide comments on this important draft guidance. The accelerated approval pathway is a critical tool that upholds the FDA's rigorous standards while ensuring that safe and effective treatments are available to rare disease patients in a timely manner. We look forward to further opportunities to engage in ongoing dialogue around efforts to strengthen the accelerated approval pathway while maintaining necessary regulatory flexibilities for products intended to treat rare disease patients.

For questions regarding NORD or the above comments, please contact Victoria Gemme, Director of Policy and Regulatory Affairs at vgemme@rarediseases.org or Hayley Mason, Policy Analyst, at hmason@rarediseases.org.

Sincerely,

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[7] U.S. Food & Drug Admin., Report: Complex Issues in Developing Drugs and Biological Products for Rare Diseases and Accelerating the Development of Therapies for Pediatric Rare Diseases 23 (July 2014), https://www.fda.gov/media/89051/download.

[8] See Aya Mitani & Sebastien Haneuse, Small Data Challenges of Studying Rare Diseases, JAMA Network Open (Mar. 23, 2020), https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2763223.