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Re: Docket No. FDA-2024-D-2033 for "Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics Guidance for Industry"

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

On behalf of the estimated 1-in-10 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thanks the U.S. Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency's draft guidance "Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics."

With a more than 40-year history, NORD is the leading and longest-standing patient advocacy group for the more than 30 million 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NORD thanks the FDA for the opportunity to comment on this draft guidance.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). Accelerated approval is an essential regulatory mechanism for ensuring that patients with serious and life-threatening conditions, particularly those with rare diseases, can obtain timely access to effective and potentially lifesaving therapies.[1] Given the nature of rare

[1] 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

diseases— which are often characterized by small, heterogenous patient populations with limited knowledge of natural history available — this pathway allows for patient access to critical therapies that may otherwise face insurmountable hurdles with more traditional clinical trial approaches.

Guidance Reflects Regulatory Flexibilities Critical for Rare Disease Drug Development

NORD thanks the Agency for its recognition of rare disease product needs and relevant regulatory flexibilities as incorporated throughout the draft guidance. Of note, we appreciate that the guidance reinforces the importance of leveraging various types of evidence when more traditional clinical data are limited or not feasible to obtain. As the Agency highlights, with regard to "... data supporting a relationship between the target of the therapy and a surrogate endpoint, particularly certain gene therapies for genetic disorders, FDA may determine that clinical data are not needed based on the strength of the totality of the evidence provided supporting the surrogate endpoint."[2] NORD strongly supports this important statement by the Agency of its flexible authority to determine substantial evidence of efficacy on the basis of a totality of the best available data. To improve patient, investigator, and sponsor understanding of its significance, we encourage FDA to expand upon this important statement of policy by providing a more in-depth discussion of examples or applications of the cited policy.

NORD additionally thanks the FDA for incorporating the Rare Disease Endpoint Advancement (RDEA) Pilot Program in the draft guidance, which further elucidates the value this program can bring to sponsors in the rare disease space. The RDEA Pilot Program provides a much needed additional avenue for sponsors to engage with the FDA early in the development process, allowing for discussions around endpoint selection and development, trial design, and regulatory pathways that can be leveraged to counter the unique challenges experienced in rare disease drug development.[3] Given the elevated role of RDEA with regard to accelerated approval, NORD urges the FDA to expand on the pilot to allow for the active participation of non-sponsor stakeholders, expanding the impact of the pilot by ensuring an appropriate feedback loop and engagement with the National Institutes of Health, and coordinating an expanded program through the FDA's Rare Disease Innovation Hub. Alternatively, we urge the Agency to pursue its expansion under the Prescription Drug User Fee Act VIII reauthorization to ensure there is sufficient support for sponsors of rare disease products.

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. Products receiving accelerated approval are subject to post-marketing requirements to ensure the

[2] 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. Footnote 36, page 10. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/accelerated-approval-expedited-program-serious-conditions

[3] U.S. Food and Drug Administration (2023, April 19). Rare Disease Endpoint Advancement Pilot Program. Retrieved January 22, 2025, from https://www.fda.gov/drugs/development-resources/rare-disease-endpoint-advancement-pilot-program

safety and efficacy profile is confirmed through additional study, and this guidance clarifies FDA's enhanced ability to ensure that such requirements are completed in a timely manner.

However, we note that the recent amendment to the statute clearly states FDA "may" require that "a [confirmatory] study or studies to be underway prior to approval." As with the Agency's approach to granting and withdrawing accelerated approval, it is crucial that FDA retains flexibility in its approach to confirmatory trials for rare disease products. We recommend that the draft guidance be revised to explicitly acknowledge the special challenges of designing and implementing such trials for rare diseases - challenges which frequently delay or even render infeasible the initiation of confirmatory trials prior to approval. We look forward to providing further comments in response to the complementary draft guidance, titled *"Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway,"* which provides greater details on the subject.[4]

Patient Experience Should Guide Sponsor, Agency Decision Making Where Appropriate

NORD is pleased to see inclusion of the statement encouraging sponsors "to incorporate patient perspectives into the design of confirmatory trials, which may enhance recruitment and retention, especially in rare disease populations."[5] NORD has long supported patient involvement in the drug development and regulatory review process, as clinical trials that are developed and reviewed in consultation with patients are much more likely to reflect the needs and desires of the patient population. We encourage FDA to consider issuing additional guidance that may facilitate increased stakeholder understanding and integration of this critical information into the decision-making process for accelerated approval products.

Patient perspectives should also be taken into account during the expedited withdrawal process described in this guidance. The newly described process is an important enhancement to the pathway, as timely withdrawal of therapies that fail to confirm safety and efficacy ensures that the pathway delivers the benefits promised to patients and shields them from unnecessary risks from "dangling" approved drugs. To that end, NORD thanks FDA for language reflecting important FDORA reforms that increase transparency by mandating that more detailed information about accelerated approvals, specifically progress of required postapproval studies, be made available to the public. We urge the FDA to act expeditiously in making such information publicly available.

Patients and caregivers should be part of any discussions that may have implications for transitioning off of products where evidence no longer supports a positive benefit-risk profile. NORD encourages FDA to work closely with rare disease product sponsors and patient communities on how best to address accelerated approval drugs when sponsors are unable to complete confirmatory trials or otherwise are unable to meet the challenges of meeting these essential requirements.

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[4] See: https://www.federalregister.gov/documents/2025/01/07/2024-31527/accelerated-approval-and-considerations-for-determining-whether-a-confirmatory-trial-is-underway

[5] 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. Page 14. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/accelerated-approval-expedited-program-serious-conditions

FDA, CMS Alignment is Essential for Realizing the Benefits of Accelerated Approval

NORD strongly encourages continued and improved collaboration between FDA and the Centers for Medicare and Medicaid Services (CMS) to better ensure timely and appropriate coverage and reimbursement for products approved through the Agency's accelerated approval pathway. Regulatory grade evidence produced for informing FDA decision-making may not always align with the data CMS seeks to inform coverage determinations. Such discrepancies can result in delays for patient access to potentially lifesaving products, undercutting the value to patients of accelerated approval. Interagency collaboration can help proactively address discrepancies in data needs and expectations should they arise between the two bodies.

FDA should additionally continue to prioritize efforts to educate stakeholders about the accelerated approval pathway. The FDA maintains a strong track record of ensuring that therapies receiving accelerated approval meet the same regulatory standards for demonstrating substantial evidence of effectiveness as those receiving traditional approval. The success of the accelerated approval pathway is evidenced not only by high conversion rates to traditional approval, but also by the tangible benefits it has delivered to many rare disease patients who might not otherwise have access to vital treatments. An education campaign focused on how accelerated approval works for rare diseases can enhance transparency and trust among patients, health care providers, payers, and product developers.

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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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