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Docket No. FDA-2023-D-0110-0001- "Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics Guidance for Industry"

Dear Dr. Pazdur,

On behalf of the more than 25 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(NORD) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency's draft guidance, "Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics Guidance for Industry."

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.

Rare disease patients need robust evidence to trust in the safety and effectiveness of FDA-approved therapies, and time is of the essence. Since more than 90% of rare diseases do not have an FDA approved treatment, NORD appreciates FDA's efforts to provide guidance on the considerations for using accelerated approval to support oncology therapeutics. In fact, this guidance, once finalized, will likely have far-reaching impacts on rare disease drug development well beyond oncology products.

The accelerated approval pathway has been and continues to be vital to rare disease patients.[1] For example, among 252 FDA-approved novel orphan drugs and indications approved from 2008 to 2021, about a quarter were approved through the accelerated approval pathway.[2] In fact, orphan drugs accounted for 85% of all novel drugs approved through the accelerated approval pathway during this time period.[3] Similarly, oncology indications consistently account for more than 50% of drugs approved

[1] 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

[2] Monge AN, Sigelman DW, Temple RJ, Chahal HS. Use of US Food and Drug Administration Expedited Drug Development and Review Programs by Orphan and Nonorphan Novel Drugs Approved From 2008 to 2021. JAMA Netw Open. 2022;5(11):e2239336. doi:10.1001/jamanetworkopen.2022.39336

[3] Monge AN, Sigelman DW, Temple RJ, Chahal HS. Use of US Food and Drug Administration Expedited Drug Development and Review Programs by Orphan and Nonorphan Novel Drugs Approved From 2008 to 2021. JAMA Netw Open. 2022;5(11):e2239336. doi:10.1001/jamanetworkopen.2022.39336

through the accelerated approval pathway.[4] As a 2011 study of oncology drugs demonstrates, drugs receiving accelerated approval are available to patients years earlier – at a median 3.9 years faster than oncology drugs that receive traditional approval.[5] Nearly all accelerated approval drugs are ultimately able to confirm clinical benefit and are eventually converted to traditional approvals. For instance, more than three out of four drugs that received accelerated approval from 1992 to 2016 have already been successfully converted to traditional approvals.[6] In fact, only about 10 percent of the 278 accelerated approval drugs approved from 1992 to now are currently past their original confirmatory trial completion date.[7] Among these 'late' drugs, more than half are less than a year past their confirmatory trial date and only four drugs are five or more years late.[8] As these data show, the accelerated approval pathway has had tremendous positive impacts on rare disease patients.

This guidance will complement and amplify other efforts to further strengthen the accelerated approval pathway, including provisions in the Food and Drug Omnibus Reform Act of 2022 (FDORA) directing FDA to implement changes to ensure more drugs meet their target date for confirmatory trial completion. For instance, moving forward, FDA will have greater authorities to require drug companies to begin enrollment in their confirmatory studies before being granted accelerated approval.[9] Similarly, thanks to FDORA it will be easier for FDA to withdraw drugs that fail to demonstrate clinical benefit, and a new FDA council will help improve transparency and alignment across centers and review divisions.[10] Once finalized, this guidance will be an important step forward in ensuring the accelerated approval pathway continues to be a powerful tool for rare disease drug development.

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 concrete guidance and best practices for effective confirmatory trial enrollment, including strategies for overcoming common issues leading to enrollment challenges. Delays in confirmatory trail enrollment are one of the key reasons confirmatory trial dates are missed.[11,12] NORD recognizes that these enrollment challenges can have several distinct root causes, which each may

[4] https://www.fda.gov/drugs/resources-information-approved-drugs/ongoing-cancer-accelerated-approvals

[5] Johnson, J., Ning, Y., Farrell, A. , Justice, R., Keegan, P., Pazdur, R.,, Accelerated Approval of Oncology Products: The Food and Drug Administration Experience, *JNCI: Journal of the National Cancer Institute*, Volume 103, Issue 8, 20 April 2011, Pages 636–644, https://doi.org/10.1093/jnci/djr062

[6] Stengel, K., Zalewski, Z., West, M., Gustafson, K., & Nell, A. (2022, January 4). *Understanding the History and Use of the Accelerated Approval Pathway*. Retrieved May 11, 2023, from https://avalere.com/insights/understanding-the-history-and-use-of-the-accelerated-approval-pathway#:~:text=In%20a%20review%20of%20accelerated,9.5%20years%20without%20confirmatory%20evidence

[7] 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

[8] 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

[9] Lupkin, S. (2023, March 3). *FDA has new leverage over companies looking for a quicker drug approval*. Retrieved May 15, 2023, from https://www.npr.org/sections/health-shots/2023/03/03/1160702899/fda-enforcement-drug-approval-manufacturer-promises#:~:text=Changes%20to%20the%20accelerated%20approval,accelerated%20approval%20to%20the%20drug.

[10] Lupkin, S. (2023, March 3). *FDA has new leverage over companies looking for a quicker drug approval*. Retrieved May 15, 2023, from https://www.npr.org/sections/health-shots/2023/03/03/1160702899/fda-enforcement-drug-approval-manufacturer-promises#:~:text=Changes%20to%20the%20accelerated%20approval,accelerated%20approval%20to%20the%20drug.

[11] 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

[12] 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

warrant their own solutions.[13] As outlined in the draft guidance on page 4, transitioning confirmatory trials into earlier disease stages or population subgroups that do not have ready access to the approved drug can help overcome enrollment challenges that stem from a lack of incentives to participate in a confirmatory trial once a drug is approved and available outside of the confines of the trial; however, this approach may not always be feasible, and it may not be the only – or at times most appropriate – approach. For instance, efforts to modernize and decentralize trials can reduce the burden and hence disincentives weighing against trial participation. At the same time, patients face increasing barriers to coverage and reimbursement of drugs approved through the accelerated approval pathway. [14,15] This makes life-saving drugs essentially unaffordable for too many patients and threatens to undermine the integrity and intent of the accelerated approval pathway. To close any remaining post-market data gaps, creative solutions can help leverage confirmatory trials to meet both FDA's and payers' data needs and help overcome the practical access barriers our patients too often face. If done effectively, such approaches may also potentially have positive impacts on confirmatory trial enrollment.

On the other hand, enrollment challenges stemming from disruptions to clinical care (e.g., during the COVID pandemic), from a lack of access to diagnostics and difficulty locating eligible patients, from limited understanding and potentially incomplete assumptions about disease epidemiology and progression, from the need to repeatedly revise trial protocols as new evidence emerges, or from any other potential root cause may need other approaches and may or may not be easily addressed by the limited number of strategies outlined in the draft guidance.

Specifically, given the importance of effective confirmatory trial enrollment, and the history of challenges drug sponsors have navigated to overcome these challenges, FDA should:

- Summarize, analyze, and make publicly available granular data on the root causes that have led to enrollment challenges for confirmatory trials in the past, as well as strategies that have proven successful for overcoming these challenges.
- Provide additional guidance and oversight to ensure drug sponsors emphasize and highlight enrollment strategies, challenges, and progress in the semi-annual progress reports drug sponsors must submit under the new FDORA requirements to improve transparency and foster the collection of lessons learned.
- Organize workshops, listening sessions, and/or research projects to identify best practices for effective confirmatory trial enrollment.

Recommendation 2: Provide more-nuanced guidance on the effective and efficient use of single-arm trials and other external controls using real-world evidence.

NORD appreciates that the draft guidance acknowledges the importance of single-arm trials for accelerated approval drugs, particularly for diseases that have small populations, scarce data, and limited natural history studies. While traditional randomized, double-blinded, placebo-controlled trials are the

[13] 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

[14] Oregon Health Authority, 2022-2027 Medicaid 1115 Demonstration Application, (February 18, 2022), https://www.oregon.gov/oha/HSD/Medicaid-Policy/Documents/2022-2027-Waiver-Application-Final.pdf

[15] Centers for Medicare & Medicaid Services, Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N), (January 11, 2022), https://www.cms.gov/medicare-coverage-database/view/ncacal-decisionmemo.aspx?proposed=Y&NCAId=305

gold standard for clinical evidence of safety and effectiveness, they are not always feasible or ethical in rare disease drug development.[16] 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.[17] Similarly, another study found that 116 FDA approvals between 2019 and 2021 leveraged real-world evidence, most notably external control arms.[18]

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. At the same time, 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. In addition, the limited patient populations and financial realities of rare disease drug development generally make repeating a fatally flawed study impossible. This is particularly true for accelerated approval drugs given the added complexity introduced by surrogate or intermediate clinical endpoints and the need to validate clinical benefit post-approval.

Appropriately designing and conducting clinical studies the first time, whether for traditional or accelerated approval, is often a matter of life and death for our patients. FDA's accelerated approval guidance will play a critical role in facilitating well-designed studies. NORD also recognizes that FDA recently released a draft guidance specific to the use of external controls.[19] NORD appreciated the opportunity to provide extensive comments on that guidance, given the vital importance of external controls to our rare disease community.[20] Many of the same recommendations NORD provided in response to that guidance also apply here. Moreover, FDA must carefully ensure alignment and cohesion among the multiple guidance documents relevant to the use of external control arms in pivotal trials supporting traditional and accelerated approval. Given the importance of well-designed rare disease trials with external control arms in the accelerated approval context, specific recommendations for this accelerated approval guidance include:

- Clearly identify other relevant FDA guidance documents, including the external control arm guidance, in the final guidance document and provide a detailed overview of how these guidance documents relate to each other
- Provide more detailed guidance on how to appropriately develop pivotal trials and, as appropriate, confirmatory trials for rare diseases with external control arms that are supporting accelerated approvals.

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[16] *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

[17] 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.

[18] 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.

[19] 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

[20] https://rarediseases.org/wp-content/uploads/2023/05/NORD-comments-on-Considerations-for-the-Design-and-Conduct-of-Externally-Controlled-Trials-for-Drug-and-Biological-Products-Guidance-for-Industry-FINAL.pdf

- Develop and publish best practices and lessons learned to provide examples of successful (and potentially unsuccessful) uses of external control arms for accelerated approvals, including the potential combination of external control arms with other data sources.

Recommendation 3: Provide more guidance for the validation of surrogate or intermediate clinical endpoints in rare diseases and the intersections with the RDEA pilot program.

Since its creation 1992, after the HIV/AIDS epidemic drastically altered the landscape for drug development, accelerated approvals rely on surrogate or intermediate clinical endpoints that are 'reasonably likely' to predict clinical benefit but so far lack final validation.[21] In the rare disease space, surrogate and intermediary endpoints tend to play a particularly key role in drug development. On the other hand, developing and validating such novel endpoints is often particularly challenging given the unique complexities of rare disease drug development, including the limited patient populations, scarcity of natural history data, heterogeneity of disease manifestation, and incompletely understood epidemiology and disease pathology.

As mentioned previously, given the importance and complexity of the accelerated approval pathway, this guidance is likely to impact rare disease drug development far beyond the oncology space. Surrogate or intermediate endpoint validation is critical to accelerated approval and given the success of accelerated approval for oncology products, important lessons from the oncology space can likely be learned and translated into other rare disease drug development areas.

Recognizing the unique challenges of endpoint validation across rare diseases, Congress, as part of FDORA tasked FDA with establishing the Rare Disease Endpoint Advancement (RDEA) Pilot Program to promote the development and use of novel efficacy endpoints.[22] In fact, on June 7-8, 2023, FDA will fulfill the first RDEA commitment by partnering with Duke University to host the "Duke-Margolis Center for Health Policy RDEA Public Workshop" to disseminate information regarding novel efficacy endpoint development for drugs that treat rare diseases.[23] This provides unique opportunities for alignment, and to develop lessons learned and best practices to provide greater clarity on how to best validate surrogate or intermediate endpoints for rare diseases to confirm clinical benefit of accelerated approval drugs and streamline the future drug development process.

Specifically, given the importance of endpoint validation for successful conversion of accelerated approval products to full approvals, FDA should:

- Expand the discussion of new endpoints in the draft guidance, with a focus on best practices and lessons learned for endpoint selection and validation in rare disease pivotal trials and confirmatory studies.
- Provide greater clarity about the intersection between the RDEA pilot and this accelerated approval guidance, as well as other agency initiatives around accelerated approval reform.

[21] The Centers for Disease Control and Prevention ("CDC") published its first report on HIV/AIDS in 1981. See James W. Curran & Harold W. Jaffe, AIDS: The Early Years and CDC's Response, 60 Morbidity & Mortality Weekly Rep. 64 (Oct. 7, 2011), available at https://www.cdc.gov/mmwr/preview/ mmwrhtml/su6004a11.htm.

[22] https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/rdea-pilot-program-2023-public-workshop-06072023

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

- Work closely with the RDEA program to ensure the workshops, guidance documents, mechanisms, and other resources developed as part of the pilot will be tailored to, and effective for, accelerated approvals to treat rare diseases.

Recommendation 4: Create an education campaign to demonstrate the history and efficiency of accelerated approval drugs

Patient advocacy groups, academic researchers, and small biotech companies in the pre-revenue phase play an outsized role in research and data collection including patient-led disease registries and clinical trial designs. It is vitally important that these stakeholders understand the accelerated approval pathway and how it differs from traditional approval, including FDA's current standards on what is "reasonably likely" to predict clinical benefit. These groups must have realistic expectations about data to support the accelerated approval pathway and be equipped with the information and tools needed to collect regulatory-grade data. These groups need additional outreach to effectively understand and leverage FDA's guidance documents. Many of these stakeholders do not have ample experience interacting with FDA review divisions; they often lack awareness of the need to engage early, lack the understanding of FDA organizational structures to identify the appropriate contacts, and often do not have the tools and knowledge to engage effectively. In fact, in NORD's recent membership survey, 21% of queried patient advocacy groups identified guidance for how to request a meeting with FDA as a key gap and 23% wanted guidance on how to prepare for a meeting with FDA. As a result, critical rare disease stakeholder groups are unlikely to consult with the relevant FDA division early and often proactively and effectively in the drug development process, increasing the risk of externally controlled studies and data that ultimately fail to meet FDA's regulatory standards.

FDA's LEADER 3-D program provides one meaningful and timely avenue to create awareness and disseminate the relevant information to this stakeholder group. However, combining a variety of approaches, based on successful existing programs, will likely be most successful. For instance, on April 13, 2023, representatives from the FDA and the Reagan-Udall Foundation partnered to discuss in a webinar the draft external control arm guidance and were able to clarify various questions on how to use external controls and best mitigate confounding and bias.[24,25] Hosting webinars like these, and leveraging opportunities such as the upcoming webinar with Duke University on the RDEA pilot, can be vital to meaningfully engage these stakeholders in the accelerated approval discussion. NORD strongly encourages the Agency to engage rare disease patients, providers, and academic researchers more proactively on accelerated approval by hosting webinars, workshops, and partnering with trusted advocacy organizations and other government agencies to cover topics to give better guidance on the use of this approval process.

Specifically, given the complexity of the topic and importance of patient education about accelerated approval, FDA should develop educational materials that address:

- The benefits, mechanisms, and best practices of early engagement with FDA in rare disease drug development, including early considerations for accelerated vs. traditional approval;

[24] *Real-world evidence Webinar series: Considerations for the design and conduct of externally controlled trials for drug and Biological Products Draft Guidance for Industry*. Reagan-Udall Foundation. (2023). Retrieved April 28, 2023, from https://reaganudall.org/news-and-events/events/real-world-evidence-webinar-series-considerations-design-and-conduct

[25] *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance for Industry*. Food and Drug Administration. (2023, February). Retrieved April 28, 2023, from https://www.fda.gov/media/164960/download

- The history, current uses, and best practices of accelerated approval;
- Considerations and best practices for the collection and use of single-arm trials and other RWE/RWD in rare disease drug development, with specific focus on accelerated approvals; and
- Considerations and mechanisms to increase the recruitment and timely completion of confirmatory trials.

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

Sincerely,

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