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Re: Docket No. FDA-2024-N-3528-0001 for "Advancing Rare Disease Therapies Through a Food and Drug Administration Rare Disease Innovation Hub"

Dear Dr. Cavazzoni and Dr. Marks:

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 Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency's open docket, "Advancing Rare Disease Therapies Through a Food and Drug Administration Rare Disease Innovation Hub."

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 over 41 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 proudly collaborated with individuals affected by rare diseases, our 350+ member organizations, and our network of 40 Rare Disease Centers of Excellence nationwide to advance rare disease research and funding for the development of effective treatments and cures.

NORD applauds FDA's creation of the Rare Disease Innovation Hub (Hub), as opposed to establishing a Rare Disease Center of Excellence, as we believe the Hub will provide the right organizational structure to support effective, transparent and patient-centric regulatory decision-making, and enhance collaboration internally between FDA centers, as well as externally with the broader rare disease community. We appreciate how Agency leadership, in discussing the purpose of the Hub, have appropriately emphasized the critical role of patients and caregivers needs in the anticipated operations of the Hub.

To achieve these shared goals, NORD believes the Hub should initially focus on three key priorities:

1. Improving communication between the rare disease community and FDA;
2. Strengthening alignment internally between CDER and CBER, as well as the Center for Devices and Radiological Health (CDRH) and better explaining the rationale behind differences in decision-making; and
3. Utilizing learnings from past activities and establishing new ways to support meaningful patient group, academic investigator, and small biotech input, including developing tools and approaches that can be leveraged across drug candidates and diseases to support patient access to safe and effective therapies.

To make tangible progress on these priorities and improve the health outcomes for individuals living with one of the 95% of rare diseases that lack an FDA-approved treatment, **NORD proposes the following concepts be integrated into the strategic plan for the Hub, many of which can be implemented or facilitated through NORD, our robust Rare Disease Centers of Excellence (RD CoE) network and patient member organizations.**

NORD urges the Hub to prioritize the following items:

- **Ensuring Patient Representation in FDA's RDI Hub.** The Hub should include standing mechanisms for patient- and clinician-focused dialogue, including creation of a standing advisory council (not an advisory committee) to advise the Hub's director and *ex officio* CDER and CBER directors.

- **Rare Disease Academic Regulatory Assistance.** In fulfillment of unmet needs identified by FDA leadership, our 350+ member organizations, and the RD CoEs, and consistent with NASEM's September recommendation (2-3),[1] the Hub should establish an academic researcher assistance program to provide "investigator-initiated" IND assistance, training, timely feedback, and a structure for continued mutual engagement and learning. FDA and NORD's RD CoEs have both noted the lack of experience, need for training, and importance of engagement with FDA for new RD investigators. Like CDER and CBER's Small Business & Industry Assistance (SBIA) programs and CDRH's DICE program, an assistance program geared to rare disease academic investigators could redress knowledge and experiential gaps, and provide a platform for constructive outreach and dialogue.

  Additionally, RD CoEs have noted the critical value of early FDA engagement and feedback for pre-IND investigators on enabling studies and subsequently on acceptable clinical trial design, outcomes, endpoints and enrollments for RD pivotal trials, particularly for very rare diseases. A program focused on supporting academic researchers could render development process less error-prone for RD first time and small sponsors/investigators, from enabling preclinical studies, to streamlining 'entry' to FDA on compassionate use/treatment INDs.

- **Annual Rare Disease Regulatory Science Meeting.** In fulfillment of NASEM's September report recommendation (4-3),[2] NORD recommends the Hub convene an annual meeting to review new advances in regulatory science (pre-clinical, clinical, and platform technologies), iterate on innovative study design and methods, advance CBER/CDER alignment on COAs/other endpoints and consider other uses of alternative and confirmatory data for regulatory decision making. Invited participants should include EMA and other global regulators, NIH and NCATS, NORD's RD CoEs, industry groups, other rare disease patient groups, and the broad stakeholder community, including NORD's sister organization and collaborator, EURORDIS.

[1] National Academies of Sciences, Engineering, and Medicine. 2024. Regulatory Processes for Rare Disease Drugs in the United States and European Union: Flexibilities and Collaborative Opportunities. Washington, DC: The National Academies Press. https://doi.org/10.17226/27968.

[2] National Academies of Sciences, Engineering, and Medicine. 2024. Regulatory Processes for Rare Disease Drugs in the United States and European Union: Flexibilities and Collaborative Opportunities. Washington, DC: The National Academies Press. https://doi.org/10.17226/27968.

- **Sustaining Rare Disease Diagnostic Innovation.** CDER and CBER should integrate CDRH into the Hub to support sustained engagement with rare disease clinicians and laboratorians. For example, the implications of FDA's Laboratory Developed Tests (LDT) final rule[3] are significant for rare disease clinicians and patients, so identifying development gaps as well as training on new regulatory requirements is critical and should be done in conjunction with the Hub. NORD and the NORD RD CoE are already convening regular technical discussions with CDRH Office of In Vitro Diagnostics (OHT7) but should include Hub staff and maintain these discussions as an important, ongoing Agency workstream. Ensuring devices and diagnostics are safe and valid is important, but must take into account the unique nature of devices and diagnostics used to diagnose, treat and care for those living with a rare disease.

- **FDA RWD/RWE Partnership with NORD and Other Rare Disease Stakeholders.** To fulfill identified absence of streamlined venues to support leveraging diverse and decentralized sources of rare disease RWD data, the Hub should collaborate with NORD, our RD CoEs investigators and our member organizations on development and appropriate use of fit-for-purpose RWE/RWD. This should include identifying and sharing rare disease specific case studies, exemplars and best practices in the application of FDA PFDD-generated outcomes, reports, and recommendations, and use and validation of innovative methods to capture patient experience. These best practices and lessons learned specifically for the use of RWE/RWD in rare diseases must then be used to supplement existing guidance.

  The NORD IAMRARE® program was built by NORD with extensive input from FDA, NIH, patients, and could effectively support this effort as well. IAMRARE currently holds 41 active registry/natural history studies, including 16,455 consented participants representing 140+ rare diseases, with 28 more IAMRARE® registries in active development. Data visualization tools provide real-time de-identified data, and sub-studies encourage multi stakeholder collaboration and minimize community fragmentation. Additionally, NORD developed a software (API) tool to facilitate sharing of data to external repositories, such as C-Path's RDCA-DAP, and NORD recently co-led an effort with CDISC to create a CDISC Rare Disease Therapeutic Area User Guide, all of which can be leveraged to support robust and appropriate utilization of RWE/RWD for regulatory decision making.

- **Facilitate Robust Patient Access to Safe and Effective Therapies through Appropriate Data Collection.** NORD urges FDA to work with the Centers for Medicare and Medicaid Services (CMS), insurers, patients, clinicians and other stakeholders to standardize data collection, including the use of RWD data and data from post-market commitments to enable robust coverage policies by payers. For many in our community, FDA approval of a therapy represents a huge milestone, but it is just one of many barriers to affordable access to that treatment. Appropriate and intentional collaboration on necessary data elements by payers, including CMS, with the Hub can support patient access to life-altering therapies and treatments.

[3] U.S. Food and Drug Administration. (2024, May 6). *Medical Devices; Laboratory Developed Tests*. Federal Register / Vol. 89, No. 88 / Monday, May 6, 2024 / Rules and Regulations . https://www.govinfo.gov/content/pkg/FR-2024-05-06/pdf/2024-08935.pdf

- **Data element standardization for long-term cell and gene therapy follow-up from 10- and 15-year long post-market commitments**. Patient registries are an essential tool to conduct long-term follow up for safety, as well as to collect data on long-term clinical efficacy and durability, including for patients who were not part of pre-licensure trials. A centralized and harmonized set of interoperable patient registry data elements (collectively referred to as 'GT registry-of-registries solution') could help make long-term follow up more cost-effective, efficient, easier, and sustainable.

  NORD recommends establishing a Hub-based rare disease community-sponsor-clinician-FDA-payer working group to assess current gene therapy registries and data elements, develop consensus findings on "registry-of-registries" approach, pilot projects (workplans, deliverables, and funding), and facilitate implementation of common 'floor' for registry data elements. Ideally, this would help establish a harmonized set of data standards for use in outcomes-based payment agreements that would remain largely unaffected by changes in insurance status or other significant events in the patient's life (e.g., relocation, transition from pediatric to adult care).

NORD is confident that with appropriate Agency partnership, we can help FDA achieve meaningful improvements in the development and approval of new orphan drugs and rare disease diagnostics to help address the tremendous unmet medical needs that exist in our community. NORD again thanks FDA for the opportunity to provide comments on this important initiative and we look forward to continuing the dialogue around the Rare Disease Innovation Hub 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 Heidi Ross, Vice President, Policy and Regulatory Affairs, at HRoss@rarediseases.org or Hayley Mason, Policy Analyst, at hmason@rarediseases.org.

Sincerely,

Pamela Gavin

Pamela Gavin
Chief Executive Officer
National Organization for Rare Disorders

cc: Michelle Tarver, PhD., M.D., Director, Center for Devices and Radiological Health