Statement for the Record
National Organization for Rare Disorders

"The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight"
Subcommittee on Health
Committee on Energy and Commerce
March 17, 2022

Chairwoman Eshoo, Ranking Member Guthrie and Members of the Health Subcommittee, the National Organization for Rare Disorders (NORD) appreciates the opportunity to provide this statement for the record for the hearing "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight."

Founded in 1983, NORD represents over 300 different rare disease patient organizations and the 25-30 million Americans living with a rare disease. We are committed to identifying, treating, and curing rare disorders through programs of education, policy, research, and patient services.

NORD appreciates the efforts of Congress, the FDA and negotiating parties in advancing a strong Prescription Drug User Fee Act (PDUFA) VII Commitment Letter and the efforts to reauthorize PDUFA before its current authorization expires September 30, 2022. Despite the significant progress made possible by the passage of the Orphan Drug Act of 1983 and previous PDUFA agreements, rare diseases remain an area with significant unmet need. Over 90% of the estimated 7,000 known rare diseases still do not have an FDA-approved treatment indicated for their specific rare disease.[1] Therefore, we support the approaches outlined in the PDUFA VII Commitment Letter to facilitate drug development, as well as timely review by FDA to ensure more treatment options are available to address the needs of rare disease patients. It is critically important that Congress reauthorize PDUFA, and the other user fee programs before their current authorization expires.

Beyond the PDUFA VII Commitment Letter, NORD has identified several policy priorities for consideration as part of the PDUFA reauthorization that would help ensure a regulatory environment capable of addressing the tremendous unmet needs of the rare disease community.

Support Strengthening the Accelerated Approval Pathway

The accelerated approval pathway has proven to be a vital tool in bringing safe and effective treatments to patients with rare disorders. Many facets of rare diseases make them particularly difficult to study in clinical trials targeting direct clinical benefit. For example, the number of patients with a rare condition can be small and heterogeneous, with highly diverse clinical manifestations and a long timeframe for disease progression. Furthermore, there is often a lack of prior clinical studies and a limited number of clinical investigators and treatment centers

[1] Jennifer Huron, *New Study Investigates the Number of Available Orphan Products, Generics and Biosimilars,* Nat'l Org. for Rare Disorders (Mar. 25, 2021), https://rarediseases.org/new-study-investigates-the-number-of-available-orphan-products-generics-and-biosimilars/.

knowledgeable about a given rare disorder. This makes accelerated approval, and the ability to use surrogate endpoints in the approval process, a particularly important tool for the development of treatments for rare diseases.[2]

However, the pathway faces mounting criticism from a variety of stakeholders who have raised concerns about the accelerated approval pathway. Critics of the accelerated approval pathway claim that these treatments have yet to demonstrate clinical benefit and should therefore be treated differently because they have been studied using surrogate endpoints and are not yet "clinically proven." Some critics have characterized accelerated approval drugs as "experimental." These criticisms of the accelerated approval pathway misunderstand the law and regulations that govern it.[3] Accelerated approval—both as it is set forth in law and in regulations—does not alter FDA's gold standard of substantial evidence of safety and effectiveness.[4] To the contrary, accelerated approval is granted based on FDA's finding that a drug is safe and effective for its intended use— the same approval standard used for traditional approval.[5]

Furthermore, Congress and the FDA have considered – and rejected – the notion that accelerated approval is a different or lesser standard than traditional approval. In fact, while codifying the accelerated approval pathway in 2012,[6] Congress acknowledged the vital role the accelerated approval pathway serves for patients with rare diseases and expressed their hope that it would bring life-saving drugs to the market expeditiously.[7] Congress also affirmed FDA's conclusion that accelerated approval did not create a different standard for drug approval, stating in a "Sense of Congress" Congressional understanding that accelerated approval "may result in fewer, smaller, or shorter clinical trials... without compromising or altering the high standards of the FDA for the approval of drugs."[8]

Still, NORD believes the accelerated approval pathway could benefit from certain reforms, that if implemented, would both help to alleviate payer concerns and support continued robust patient access to these FDA approved treatments. In a June 2021 white paper, FDA's Accelerated Approval Pathway: A Rare Disease Perspective, NORD outlined several recommendations to improve the pathway.[9] Such recommendations include:

Post-market Confirmatory Study Transparency
Post-market confirmatory studies are already a condition of accelerated approval but requiring more robust and frequent reports on manufacturers progress on their confirmatory studies would give all stakeholders more confidence that these confirmatory studies are being done with due

---

[2] U.S. Food & Drug Admin., CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint (Jan. 14, 2021), https://www.fda.gov/ media/88907/download
[3] 57 Fed. Reg. at 58944
[4] 57 Fed. Reg. at 58944.
[5] *Id.*
[66] Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112–144, §§ 803, 901(b), 902(a), 126 Stat. 993, 1079, 1083–87 (2012)
[7] See H.R. Rep. 112-495, *35–36 (2012)
[8] See 158 Cong. Rec. H3825-01, H3848 (2012).
[9] Temkin E, Trinh, J. FDA's Accelerated Approval Pathway: A Rare Disease Perspective. October 2021. https://rarediseases.org/wp-content/uploads/2021/06/NRD-2182-Policy-Report_Accelerated-Approval_FNL.pdf

diligence. Reports should compare actual progress on the milestones that the manufacturer agreed to at the time of accelerated approval and explain where progress is falling short of the agreement. The FDA should also be required to make the information contained within these reports easily accessible to the public by putting them on the FDA's website.

Use of Real-World Evidence for Conversion to Traditional Approval
The FDA already utilizes real world evidence (RWE) in the post-market setting to evaluate safety and we believe that the utilization of RWE in the post-market to evaluate efficacy is often appropriate and should be considered. Consideration of RWE as part of the evaluation of whether the drug has an effect on the intended clinical benefit would permit FDA to convert accelerated approval drugs to traditional approval, when scientifically appropriate, at an earlier point in time.

Expedited Withdrawal of an Accelerated Approval Product
It can be difficult to design, enroll, and complete post-marketing confirmatory studies for rare disease drugs and there are frequently legitimate reasons for delays in converting a product from accelerated approval to traditional approval. However, delayed confirmatory studies also give fodder to critics of accelerated approval who claim they are a result of an inability by FDA to properly address or enforce action against accelerated approval products that have not proven clinical benefit. Clarifying the circumstances under which the expedited withdrawal of an accelerated approval product would be appropriate is important for building confidence in the pathway. However, it also critical that some flexibility be retained by the FDA in the event sponsors are pursuing conversion to traditional approval with due diligence but are falling behind on established milestones and targets.

Increased Funding and Resources for FDA
Many of these proposals would require additional, targeted resources at FDA. An increase in federal funding and resources through budgeting and appropriations could provide FDA with the resources necessary to implement some of the reforms contemplated and to exercise its existing and ideally expanded authorities when appropriate.

FDA approval is only the first step to a patient obtaining access to a treatment. True access is achieved when patients can get their treatments prescribed and affordably covered by their health program or insurer. NORD looks forward to working with Congress to ensure this pathway remains a viable way for patients to obtain access to FDA approved treatments for their rare condition at the earliest possible time.

Support Optimizing Patient Focused Drug Development

NORD appreciates that the Commitment Letter continues FDA's focus on incorporating the patient voice into the drug development and regulatory review processes. Through our work assisting Member Organizations planning several externally-led Patient-Focused Drug Development (EL-PFDD) meetings, and our own work directly coordinating several EL-PFDDs, NORD has seen firsthand the transformative impact for the patient communities in hosting PFDDs. Patients are the ultimate experts of their disease because they live with it every day.

NORD has had the opportunity to assist in planning and conducting several externally-led PFDD meetings, including one on Pyruvate Kinase Deficiency in September 2019 and on Krabbe Disease in October 2020. FDA has a special Memorandum of Understanding (MOU) with NORD and in collaboration with their Office of Patient Affairs, NORD has jointly conducted 12 Patient Listening Sessions with review divisions across CBER and CDER on a variety of disease states. Shortly after the COVID-19 pandemic began, NORD helped facilitate two special public FDA listening sessions with the rare disease community at large regarding COVID-19 and drug shortages, personal protective equipment, and participation in research and clinical trials. NORD has worked to bring the patient community together for these meetings, and, as we have learned, both the patients and FDA benefit.

The virtual and in-person meetings for rare disease communities to share directly with FDA continue to be critical and galvanizing, providing researchers, drug developers, and FDA with a robust understanding of unique patients' and caregivers' experiences with their disease and treatments. NORD welcomes provisions in the Commitment Letter to increase the utilization of PFDD, including the draft guidance on the use and submission of patient preference information for regulatory decision making. Currently, patient data is inconsistently collected and can have limited value in regulatory decision making. Changing this paradigm to ensure robust, fit-for purpose patient data is consistently collected will increase the value and utility of patient data within the FDA review process.

Opposition to H.R. 1730, the Speeding Therapy Access Today Act of 2021

Although supportive of the intent of the Speeding Therapy Access Today Act (H.R. 1730), NORD is concerned about the unintended consequences that might ensue. The establishment of an intercenter institute for rare diseases would create a burdensome requirement for the establishment of an additional, unnecessary bureaucratic structure within FDA. Rare diseases are heterogeneous and affect every system of the body, which renders them not easily centralized into a center of excellence. NORD believes the priority should instead be ensuring expert reviewers are embedded in all of the review divisions with rare disease responsibilities and that this work is appropriately resourced. Furthermore, the Agency just completed a reorganization of the Office of New Drugs in the Center for Drug Evaluation and Research (CDER). As part of the reorganization, there is more collaboration across the Agency to streamline review for rare disease products.

To the extent one of the goals of H.R. 1730 is to enhance collaboration across the Agency, there are many efforts currently underway. Examples of intercenter and interagency communication include:

- The Rare Disease Drug Development Council, a CDER led collaboration aimed at creating a forum for intercenter communication about rare disease drug development issues or learnings from difficult solutions that is joined by many across the Agency;
- The Rare Disease Council, an Office of Orphan Product Development (OOPD) led interagency council to discuss rare disease issues with different Centers and Offices at FDA;

- European Medicines Agency/Health Canada/FDA Rare Disease Cluster Call, an interregulator group from the US, European Union, and Canada, which discusses issues that lend themselves to international collaboration and harmonization;
- The Zebragram, a CDER led internal newsletter that provides relevant information on topics like novel trial design, patient engagement strategies, recent approvals, and other information related to rare disease work to the Agency;
- The Rare Disease Consult Service, a CDER led FDA-wide internal consulting service that provides guidance to review divisions regarding drug development issues common to rare diseases, including endpoints and trial designs; and
- Disease area workgroups, which are Agency-wide small groups that meet on specific diseases area issues that arise during development or review, many of which often have rare disease considerations that contribute to the complexity of the issue.

In an April 2021 meeting with the Alliance for a Stronger FDA, then-acting Commissioner Woodcock expressed similar concerns about this approach. She described the stress the Agency is under and stated, "[t]hese major or even minor structural reorganizations take a couple of years to get in place and then you have to socialize them and make sure everyone plays together well and learns to work within the new systems." She concluded by saying "the last thing I think we need to do right now – our people are tired and they …. have a wall of work in front of us that has to be gotten through – is to do a lot of very disruptive things."[10] Reorganizations are often resource intense, years-long efforts that require a substantial amount of logistical planning and preparation and requiring a further restructuring of the Agency at this point would detract from this good work already being done at the FDA with respect to rare diseases.

Support Expanding Clinical Trial Diversity

Ensuring that clinical trials appropriately represent the intended patient populations is priority for NORD. We applaud several members of the Energy and Commerce Committee for advancing ideas to expand clinical trial diversity. This is a critically important issue and can be a challenge with rare diseases as they usually have much smaller clinical trials due to the limited number of eligible patients.

Many different issues – including geographic, linguistic, cultural, and socio-economic factors – exist that tend to reduce diversity in clinical trials and lead to unfortunate inequities for patients. The NORD Rare Disease Centers of Excellence program consciously aims to address those factors, to make clinical trial enrollment easier and more equitable. The network features 31 sites in multiple states, which should present patients with opportunities to enroll in clinical trials closer to their homes and serve diverse populations in a variety of regional settings. Many of the centers already have experience and programs devoted to reaching out to medically underserved communities in their region, enabling us to reach patients with a variety of backgrounds, such as:

- Black communities, both urban and rural, who may have a strong mistrust of clinical research due to historical and sadly even more recent unethical medical research.

[10] https://pink.pharmaintelligence.informa.com/PS144153/Woodcock-COVID-Is-Not-The-Time-For-Structural-Changes-At-US-FDA

- New immigrants and undocumented immigrant communities who, in addition to language and medical coverage barriers, may fear exposing themselves or family members to a perceived risk of increased scrutiny by US Citizenship and Immigration Services.
- Rural communities who tend to have a lower socio-economic status, limited access to health care facilities and/or to health insurance.

To increase the chances of overcoming these challenges regardless of where in our country a patient is located, NORD intends to identify best practices for community outreach and for equitable clinical enrollment at the centers where such practices have already been developed. We will share those best practices across all the centers, to increase the ease and the diversity of enrollment in clinical trials across the network and throughout the country.

Conclusion

Chairwoman Eshoo and Ranking Member Guthrie, thank you for the opportunity to submit this statement for the record and for your efforts to ensure the FDA has the resources and oversight it needs to review and approve new and innovative therapies for rare disease patients. NORD looks forward to working with you and your staff to see PDUFA VII signed into law in a timely manner and effectively implemented to benefit the rare disease community. For more information, please contact Heidi Ross, Acting Vice-President of Policy and Regulatory Affairs at HRoss@rarediseases.org.