National Organization for Rare Disorders
Comments on FDA Safety and Landmark Advancements Act Discussion Draft
Senate Committee on Health, Education, Labor and Pensions
May 22, 2022

Chairwoman Murray, Ranking Member Burr and members of the Health, Education, Labor and Pensions Committee, the National Organization for Rare Disorders (NORD) appreciates the opportunity to provide comments on the FDA Safety and Landmark Advancements Act (FDASLA) discussion draft. Founded in 1983, NORD represents over 300 rare disease patient organizations and the 25-30 million Americans living with a rare disease. NORD is committed to identifying, treating, and curing rare disorders through programs of education, policy, research, and patient services.

NORD appreciates the work of Congress, the FDA, and negotiating parties to reauthorize the user fee programs before their current authorizations expire September 30, 2022. Despite substantial progress made possible by the passage of the Orphan Drug Act of 1983 and previous user fee agreements, rare diseases remain an area with significant unmet needs. Over 90% of the estimated 7,000 known rare diseases still do not have an FDA-approved treatment indicated for the specific rare disease.[1] Therefore, we support the approaches outlined in the PDUFA VII Commitment Letter and HELP Committee's discussion draft 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.

However, NORD urges the Committee to incorporate additional provisions into the next FDASLA draft to further support a regulatory environment capable of addressing the tremendous unmet needs of the rare disease community and help ensure patient access to FDA-approved treatments.

Include Provisions to Strengthen 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, a limited number of clinical investigators, and treatment centers 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]

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[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/.
[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

However, some stakeholders have raised concerns about the drugs approved under the accelerated approval pathway. Critics of the pathway claim that these treatments should be treated differently because they have been studied using surrogate endpoints and as such, these drugs are not yet "clinically proven" and are "experimental." These criticisms of the accelerated approval pathway misunderstand the law and regulations that govern it.[3] By definition under the law, accelerated approval drugs meet FDA's gold standard of substantial evidence of safety and effectiveness, just as drugs approved under any other pathway do.[4]

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 refinements, 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] Furthermore, in April 2022, NORD partnered with 90 patient organizations in a letter to HELP and Energy and Commerce Committee leadership, urging Congress to strengthen the pathway as part of PDUFA reauthorization.[10] The recommendations outlined in NORD's white paper and supported by these 90 patient organizations include:

Enhanced 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 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

[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
[10] https://rarediseases.org/wp-content/uploads/2022/04/Patient-Letter-to-Congress-on-Accelerated-Approval-4.4.2022.pdf

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.

Better 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.

Improved Processes for Expediting Withdrawal of an Accelerated Approval Product
It can be difficult to design, enroll, and complete post-market 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 take enforcement 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 is 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 patient 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 urges the Committee to add provisions in line with NORD's recommendations to FDASLA 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.

Clarify the Scope of Orphan Drug Exclusivity by Including S. 4581, the RARE Act

The Orphan Drug Act (ODA) provides a set of incentives to support research and development into drugs for rare diseases. One of the key incentives is a seven-year term of "exclusivity," or market protection from competition for the orphan drug once it is approved and marketed. The law established a two-part process for obtaining orphan drug exclusivity. First, at an early stage in the drug development, a company can request that FDA "designate" the drug as an orphan drug to prevent, diagnose or treat a rare disease or condition. Once a company receives this designation, the company can access other ODA incentives, including tax credits for the research and clinical testing on the drug. Second, after completing the necessary clinical studies and

obtaining FDA approval, the drug is then awarded exclusivity that protects the specific use of the drug that is approved.

However, with the recent decision in the case of *Catalyst Pharms., Inc. v. Becerra*, the 11th Circuit Court rejected FDA's decades-long interpretation of the ODA that the exclusivity protects the "use or indication" ultimately approved. The Court instead held that the rare disease that is *designated* at the outset of the drug development process dictates the scope of the orphan drug exclusivity. NORD believes this is an incorrect interpretation of the statute, and in the absence of a legislative fix, is concerned there would be fewer orphan drugs approved for fewer special patient populations. That is not the goal of the ODA, and it is not in the best interest of the rare disease community.

Therefore, NORD is supportive of legislation recently introduced by Senator Tammy Baldwin and Senator Bill Cassidy, the "Retaining Access and Restoring Exclusivity (RARE) Act" (S. 4185), which would clarify that orphan drug exclusivity protects the approved use or indication. This legislation is critical to ensuring proper incentives are in place to continue to foster robust rare disease drug development. NORD urges the Committee to include the RARE Act in the next FDASLA draft.

Support Expanding Clinical Trial Diversity

Ensuring that clinical trials appropriately represent the intended patient populations is priority for NORD. 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.
- 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 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.

Comments on Subtitle C—In Vitro Clinical Tests

People with rare diseases face many challenges, but one of the most difficult phases is at the outset, as it takes a rare disease patient an average of 5-7 years to an accurate diagnosis. This stage of the rare disease journey has become so common, it has a name: the "diagnostic odyssey" and refers to the lengthy time period during which patients undergo a multitude of medical visits, tests, and procedures to try to identify their condition. Unfortunately, for many rare disease patients, they frequently get multiple wrong diagnoses and ultimately experience significant delays in obtaining appropriate care and treatment, resulting in the progression of their undiagnosed disease and irreversible damage in the absence of effective treatment.

One of NORD's goals is to reduce the burden of the diagnostic odyssey and help patients get an accurate diagnosis at the earliest possible time. A critical tool in achieving this goal is patient access to innovative diagnostic tests. In recent years, advancements in genetic and other types of testing have provided many patients with diagnoses earlier, literally saving lives as a result. Still, it is critical rare disease patients who undergo testing to identify their disease must have confidence that the results of such tests are accurate. Inaccurate test results can lead not only to delays in treatment, but also to potentially irreversible results from unnecessary, risky surgeries.

Under current law, many of these tests are regulated by FDA as medical devices. However, FDA has, over the years, applied enforcement discretion to exempt certain tests from otherwise applicable requirements under the Federal Food, Drug and Cosmetic Act. As science has progressed, and more and different tests have been developed by laboratories, it has become clear that this regulatory approach needs improvement and refinement. It is critical that any legislative changes to FDA's authorities allow the innovation in all forms of diagnostic testing that has benefited countless rare disease patients to continue to flourish. It is equally critical that FDA have carefully tailored tools to regulate tests that, if inaccurate, pose substantial patient risk. For developers of diagnostic tests on the cutting edge of medicine, statutory clarity must be maximized, and regulatory burden minimized. NORD is concerned that the five days allowed for comments on the FDASLA discussion draft are not sufficient to fully understand the implications of this proposal on rare disease diagnostics and innovation, but stands ready to work with Congress to ensure that these goals are met as legislation moves forward.

Conclusion

Chairwoman Murray and Ranking Member Burr, thank you for the opportunity to submit these comments to the FDASLA discussion draft. NORD looks forward to working with you and your staff to see these critical FDA user fee acts reauthorized in a timely manner and effectively implemented to benefit the rare disease community. For more information, please contact Heidi Ross, Vice President of Policy and Regulatory Affairs at HRoss@rarediseases.org.