August 21, 2020
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2010-N-0128 for "Reauthorization of the Prescription Drug User Fee Act; Public Meeting; Request for Comments"

Dear Sir or Madam:

Thank you for the opportunity to submit comments on behalf of the National Organization for Rare Disorders, or NORD, regarding the Food and Drug Administration (FDA) Public Meeting, *Reauthorization of the Prescription Drug User Fee Act*. Founded in 1983, NORD represents over 320 different rare disease patient organizations and the rare disease community at large. It is estimated that 1 in 10 Americans are afflicted with a rare disease, meaning NORD represents over 30 million Americans that are struggling with a rare disease nationally. We are committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services. It is in support of, and on the behalf of, our organizations and our broader rare disease constituency that we write to you today.

NORD appreciated FDA's invitation to present at the July 23 Prescription Drug User Fee Act (PDUFA) public meeting. NORD's participation in that meeting, and in the PDUFA reauthorization process, is a testament to the commitment of FDA and Industry to the idea that patients deserve to be partners throughout the drug development process. This could not be more important than in rare disease drug development.

Before addressing the advances NORD believes are necessary in PDUFA VII, it is important to recognize the great success that is the user fee model itself. FDA's user fee programs have been tremendously effective, permitting FDA to maintain its gold standard while also conducting efficient reviews of the products patients need. As we embark on another process of reauthorizing these critical user fee programs, it is an important time to recognize the ongoing work by the FDA to implement PDUFA VI. The FDA has fulfilled many commitments for rare diseases, including holding planned meetings and workshops, issuing guidances on rare diseases and patient-focused drug development (PFDD), advancing reviewer training to aid in rare disease drug review, meeting with global regulators, and establishing important web resources. We appreciate the hard work the FDA has done and continues to do.

NORD's comments will focus on four areas that NORD hopes will be incorporated into the PDUFA VII agreement:

1) Center for Biologics Evaluation and Research (CBER) Resource Needs

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2) Enhancement of the Rare Disease Cures Accelerator (RDCA) Program
3) Strengthen PFDD Efforts
4) Advancements in Drug Development: Learnings from a Pandemic

I. Increase in CBER Resources

There are over 7,000 rare, monogenetic diseases that currently do not have a treatment. With the advances in science, these conditions are prime candidates for gene and cell therapies. The Center for Biologics Evaluation and Research (CBER), will be the epicenter of review and approval for a wave of innovative cell and gene therapies in the coming years. There were over 900 active investigational new drug applications (IND) in house at CBER as of the end of last year.[1] Over 200 INDs were submitted in 2018 and then again in 2019, a doubling of submissions just since 2017 when approximately 100 INDs were submitted.[2] Projections based on this number of INDs predict that over the next 10 years, we will see 40-60 launches of new gene therapies, with 15-30 of these in the next five years.[3]

This oncoming increase threatens to overwhelm current resources at CBER. Currently, the Center for Drug Evaluation and Research (CDER) has about 5 times as many staff as CBER (5612 vs. 1179).[4] To continue the progress that CBER has made in important, but for resource-intensive, programs like INTERACT and RMAT, additional staff and appropriations will be critical.

Under the PDUFA VI and Biosimilars User Fee Act (BsUFA) II hiring goals, CDER was allotted 171 new positions, while CBER was allotted only 32 over the 5-year cycle.[5] As of June, CBER had fulfilled 71% of their FY20 hiring goal to bring on additional staff; over the past five years, while CBER has seen a 90% growth in original IND submissions and a 357% increase in meetings, the product reviewer staff has grown by only 15% (for a total of 79 people as of 2019).[6] We hope that CBER will be able to continue to hire and retain staff through the remainder of the PDUFA VI cycle and provide estimates on how many additional staff are needed for PDUFA VII.

But CBER's needs go beyond new FTEs. Given the anticipated exponential increase in regulatory submissions, and the complexity of the data likely to be associated with these scientifically complex biological products, including novel data sources and large and varied

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[1] Pink Sheet, Scientific Wave Pushes CBER Into Brighter Light, March 26 2020 https://pink.pharmaintelligence.informa.com/PS141927/Scientific-Wave-Pushes-CBER-Into-Brighter-Light
[2] Ibid
[3] MIT NEWDIGS, Projections from the existing pipeline of cell and gene therapies: Launches and patient numbers, October 29, 2018 https://newdigs.mit.edu/sites/default/files/FoCUS%20Research%20Brief%202018F210v027.pdf
[4] Food and Drug Administration, FDA Fiscal Year 2021 Justification of Estimates for Appropriations Committees, https://www.fda.gov/media/135078/download
[5] Food and Drug Administration, PDUFA Reauthorization Performance Goals And Procedures Fiscal Years 2018 Through 2022, https://www.fda.gov/media/99140/download
[6] Food and Drug Administration, Reauthorization Act of 2017 (FDARA) Hiring Data, https://www.fda.gov/industry/prescription-drug-user-fee-amendments/food-and-drug-administration-reauthorization-act-2017-fdara-hiring-data

data sets, modernization of the Center's information technology infrastructure will be critical to ensure that CBER is well-positioned to address these challenges.

We should recognize, though, that any proposed user fee increases cannot occur until the reauthorization of these programs in law, which Congress is not poised to do until September 2022. CBER needs additional resources now. The workload is enormous and, if additional resources are not provided, we are concerned that a backlog will develop. NORD will be acting, alongside other partners like the Alliance for a Stronger FDA, to pursue Congressional appropriations for CBER's critical work in the interim 27 months.

As science continues to rapidly evolve and gene therapies are primed for the not so distant future, we are already starting to see the next phase of genomic medicine, individualized therapies. This advancement has many names, "bespoke," "n of 1," but they all mean the same thing, that genomic medicine is advancing to the point where therapies that target genetic mutations are being customized to an individual's genome to treat or correct a disease or condition. This field is burgeoning and will require extensive time and effort from CBER, and FDA broadly, to understand these therapies, their safety profiles, and differing characteristics. This technology will demand flexibility and will require stark paradigm shifts from the traditional drug development model. It is essential to ensure CBER is prepared and adequately resourced for the task.

A robust CBER that has the ability to review cell and gene therapies efficiently and effectively, monitor the life of these therapies that, by their nature, will require long term observation, and evaluate innovative statistical models for small populations, like those in rare disease trials, will be absolutely essential to ensuring that patients will be able to receive these innovative therapies in a timely manner.

II. Enhancing Innovation to Support the Development of New and Better Treatments for Rare Diseases Through the Rare Disease Cures Accelerator

PDUFA VII presents a prime opportunity to build upon recent innovation and investment in the development of a groundbreaking rare disease initiative, the Rare Disease Cures Accelerator (RDCA).[7] NORD applauds FDA for spearheading this important project which will establish a collaborative scientific approach to the accelerated development of therapies across rare diseases. The Rare Disease Cures Accelerator, as FDA has described it, is comprised of three interconnected goals and components:

1. Rare disease characterization;
2. Development of standard core sets of clinical outcome assessments and endpoints relevant to rare conditions; and
3. Support conducting clinical trials in rare disease populations.

<u>Component 1: Rare Disease Cures Accelerator – Data and Analytics Platform</u>

[7] Food & Drug Administration, Rare Disease Cures Accelerator, https://www.fda.gov/drugs/regulatory-science-research-and-education/rare-disease-cures-accelerator.

NORD is proud to be a partner in the first component of the RDCA and work is already underway. Led by the Critical Path Institute and NORD, the Rare Disease Cures Accelerator-Data and Analytics Platform, or RDCA-DAP, is an FDA-funded cooperative agreement that will create a resource through which researchers and drug developers can access data about rare diseases and how they progress, leading to new insights about those diseases. It will also provide a way to develop new tools and processes to improve clinical trial design and empower the rare disease community. Ultimately, RDCA-DAP will contribute to more efficient and effective clinical trials and more rapid (and cost effective) development of new drugs.

RDCA-DAP promotes the sharing of existing patient-level data (including natural history studies, patient registries, and clinical trials) and encourages the standardization of new data collection. By integrating such data in a regulatory-grade format suitable for analytics, RDCA-DAP is positioned to generate solutions to drug development bottlenecks. As such, the utility of the patient-level data is maximized, and data may be used to develop tools that will be accessible to the community in order to optimize and accelerate drug development across rare diseases.

NORD's participation in the RDCA-DAP project has reinforced what we have known for years: patient groups have significant insights to share about the natural history of their particular disease, including symptoms, disease progression, and the effect of available treatments. To effectively tap into this valuable source of information, it is important to invest resources in the incorporation of community-driven approaches to research.

Component 2: Clinical Outcome Assessments

Toward the advancement of component two of the Rare Disease Cures Accelerator, NORD and C-Path are also collaborating on a second FDA-funded cooperative agreement that supports the development of standard core sets of clinical outcome assessments (COA) that measure impacts most important to patients. The Rare Disease Clinical Outcome Assessment Consortium is aimed at accelerating the development of new therapies by creating and curating a public resource of information on available COAs that have been identified as potentially fit-for-purpose as endpoint measures in treatment trials across multiple rare diseases. The curated, public resource will inform endpoint selection in rare disease clinical trials and help to identify where additional measure development may be necessary. This resource will support researchers in the generation of new, high quality, high utility data and may help to refine the development and design of clinical trials for rare disease drug development.

In addition to this work with C-Path, NORD is partnering with the Northwestern Clinical Outcome Assessment Team (NUCOAT) on an initiative to develop COAs on physical function for use across a set of common and rare diseases. Developing a COA that is fit-for-purpose for its intended use in drug development can be a lengthy and costly process and User Fees could have a high impact in this regard.

Component 3: Clinical Trial Network

The third component of the RDCA, the subject of FDA's recent Request for Information[8], is aimed at creating a global rare disease clinical trials network to support improvements in the design, conduct, and completion of clinical trials in rare disease populations.

NORD's collaboration on the first two goals of the Rare Diseases Cures Accelerator underscores that it is imperative for patient perspectives and preferences are incorporated in meaningful ways throughout rare disease drug development. NORD believes that the coordination of the three components of the RDCA initiative has the potential to bring critical innovations to the rare disease drug development space and common disease drug development alike. Additional and sustained funding from PDUFA VII would contribute to the long-term success of the program and its goal of bringing treatments to patients faster.

III. Strengthening Patient Focused Drug Development

NORD is greatly appreciative of the efforts by the FDA to incorporate the patient experience in drug development and regulatory decision-making. In compliance with agreements made in PDUFA VI, FDA has held workshops, released guidance, and established a website with resources relating to patient experience data.

NORD has been honored to work closely with FDA on two externally-led patient focused drug development meetings, including one on Polycystic Kidney Disease last September and an upcoming meeting on Krabbe Disease. Also, in conjunction with the Patient Affairs Staff at FDA, NORD has jointly conducted 9 listening sessions with review divisions across CBER and CDER on a variety of disease states.

NORD worked to bring the patient community together for these meetings and, as we have learned, both the patients and the FDA benefit. We have heard time and time again from patients how appreciative they are that FDA is willing and able to hear directly from them.

The progress made thus far is a significant step forward to address the PDUFA VI requirement that FDA indicate whether the sponsor submitted and FDA relied upon patient-focused drug development data in the review process, but more needs to be done. If we agree there is great value in patients taking the time and making the effort to convey their concerns and experiences to FDA and to sponsors, there should be a robust feedback loop to the patient community about what impact that input had on FDA's decisions. NORD stands ready to be a partner in this endeavor to determine how best to articulate these impacts to the patient community so that patients understand the value of their participation and seek to continue to be a part of this process.

Additionally, in PDUFA VII, NORD urges that additional PDUFA resources be directed to ensuring PFDD plans are discussed with FDA review divisions early in the drug review and

[8] Food and Drug Administration, Rare Disease Clinical Trial Networks; Request for Information and Comments, https://beta.regulations.gov/docket/FDA-2020-N-0837

approval process. Early engagement is the mantra of the FDA and our aim is to facilitate that early and often communication to allow for ample consideration of the patient experience.

IV. Advancements in Drug Development: Learnings from a Pandemic

Rare disease patients have been impacted by the COVID-19 public health emergency in unique and challenging ways. However, a bright side for so many in the rare disease community, is that telemedicine has taken hold in an unprecedented manner. The promise of telemedicine is something rare disease patients have wanted since the dawn of telecommunication. There are usually many challenges related to in-person participation in a rare disease product trial and even visiting a practitioner. In the case of many rare diseases, there few providers who are experts in the disease and, if that person is across the country, rare disease patients and/or family caregivers have no choice but to take time off work and travel to see that provider. The same is true for participation in clinical trials. For many rare disease patients, it has always been a struggle to participate in clinical trials that are distant from their homes and this can have negative consequences on clinical trial adherence.

FDA has responded to this changed world by issuing strong and clear guidance to industry on the conduct of clinical trials during the pandemic. The pandemic has revealed new ways to achieve the goal of ensuring that clinical trials continue, while simultaneously allowing patients to participate in a safe, and when necessary, remote, way. NORD is delighted to be partnering with FDA on an upcoming webinar during which FDA will continue its efforts to communicate directly to the rare disease patient community about all of this work in an effort to allay the many concerns we have heard. The pandemic has revealed new ways to achieve the goal of ensuring clinical trial work that meets FDA's gold standards continues, while simultaneously allowing patients to participate in a safe way. PDUFA VII resources should be directed toward ensuring these learnings are memorialized and carried forward in guidance or regulations that can facilitate broader adoption of these decentralized clinical trial models, and other innovative trial designs, to allow those types of flexibility that were proven successful during the COVID-19 pandemic.

Critical to the goal of creating an ecosystem where clinical trials can be effectively decentralized is increased acceptance of real-world evidence, which can be produced by digital technologies, such as wearable devices and remote monitors. NORD believes that the generation and use of real-world evidence by regulators to make decisions is essential to the future of drug approvals. There are numerous learnings from the COVID-19 pandemic that focus on techniques to effectively collect and curate real-world data and its use in any regulatory decision making that occurred. Use of real-world evidence has the potential to speed approval of therapies for rare diseases by providing a promise of long-term data collection that can aid in greater regulatory flexibility, especially when considering products such as gene therapies.

There are many emerging technologies that have the potential to revolutionize remote data collection. However, for effective uptake of these tools, FDA needs to assess and validate them. NORD believes that the consideration of these technologies and assessment of their impact on regulatory decision making should be a top priority for the Agency, both in and out of the context of COVID-19. For patients with rare or debilitating diseases the more data a patient can

provide from their own home and reduce the amount of travel to clinical trial site, the better. Therefore, it is essential for the FDA to consider and validate these tools as rapidly as possible.

Finally, another potential area for focus by FDA and Industry that the COVID-19 pandemic laid bare is the need for modern manufacturing techniques. COVID-19 has highlighted both quality issues, as well as supply chain vulnerabilities when it comes to drug manufacturing. NORD believes that a full examination of the agency's lessons learned from COVID-19 can yield important benefits for all stakeholders. Outside of the context of COVID-19, the gene therapies regulated by CBER will have complicated manufacturing techniques that will require thorough examination by FDA in order to ensure a robust product. NORD believes that PDUFA VII should include commitments by the agency to advance its thinking around innovative manufacturing for gene therapies and pandemic preparedness.

NORD appreciates the opportunity to provide these comments. NORD stands ready to remain a constructive partner to the FDA and to our industry partners throughout the PDUFA reauthorization process. For questions regarding NORD or the above comments, please contact me at rsher@rarediseases.org, or 202-588-5700.

Sincerely,

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NORD