October 16, 2015

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2015-D-2818-0001: Rare Diseases: Common Issues in Drug Development; Draft Guidance for Industry

Dear Sir or Madam:

On behalf of the 30 million Americans with one of the nearly 7,000 known rare diseases, NORD would like to thank the Food and Drug Administration (FDA) for the opportunity to provide comments on the Agency's Draft Guidance titled, "Rare Diseases: Common Issues in Drug Development; Draft Guidance for Industry".

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

First and foremost, NORD would like to thank the FDA for its continued commitment to the rare disease patient population. This draft guidance is one of many attempts by the FDA to accelerate the pace of orphan drug development, and nowhere is the public health need for more and better rare disease treatments better understood than at the FDA.

Overall, NORD supports this guidance, and thanks the FDA for its creation. This guidance provides a clear, albeit general, description of the FDA's recommendations for overcoming potential pitfalls in orphan drug development, and it is NORD's hope that this guidance, when finalized, will provide additional clarity and predictability to the biopharmaceutical industry.

We do request that the FDA continue its efforts to work with individual rare disease patient populations in the development of guidances on specific rare diseases or rare disease areas. Most recently, the FDA collaborated with the Duchenne Muscular Dystrophy community on the creation of a draft guidance titled, "Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment; Draft Guidance for Industry".

We believe the process that the FDA and the Duchenne Community embarked on together can serve as a model for other rare and common disease communities in ensuring the patient voice is included within the FDA review processes. We encourage the FDA to move forward in codifying the process the FDA and Duchenne Community have undertaken in order for patient organizations and the rare disease communities they represent to proactively engage with the FDA in the development of similar Draft Guidances for other rare, neglected, and often misunderstood diseases. We hope this

model will be reproduced and will become a common practice in FDA engagement with rare disease patient organizations. Finally, we hope that the creation of this general guidance on rare disease drug development would in no way replace draft guidances for individual diseases.

The following are our comments on specific sections of the Draft Guidance.

Section II: Background

NORD concurs with the FDA assertion that "rare diseases are highly diverse" and we thank the FDA for its continued willingness to work with sponsors in crafting "successful drug development programs that address the particular challenges posed by each diseases".

Section III: Natural History Studies

We thank the FDA for its emphasis on the importance of natural history studies. We support and echo the sentiments raised by the FDA, particularly the recommendation starting on line 130 advocating that:

> "Natural history studies include patients across as wide a spectrum of disease severity and phenotypes as possible, rather than focusing too early on a particular subset. This broad inclusion can allow identification and better characterization of disease phenotypes for which therapy development may be more feasible or needed".

NORD is concerned about the development of natural history studies that are developed for a specific treatment. We urge the support of a patient centric approach that looks at the disease across potential therapies, thus avoiding a situation where there is more than one natural history study for the same population of patients. This requires patients to be in more than one study, which can be quite burdensome.

Section V: Nonclinical Studies:

NORD thanks the FDA for acknowledging the need for potential "additional flexibility in evaluating development programs for drugs to treat serious and life-threatening disorders". We agree that additional flexibility is warranted in the acceptance of nonclinical data. Rare diseases are incredibly under-researched, and traditional animal models are likely difficult to come by.

For this reason, we encourage the FDA to remain open to non-animal testing methods that have the potential to develop equally and potentially more accurate safety and toxicology data. Patient safety must never be compromised, and the FDA should always remain vigilant in ensuring products are safe to use through the collection of toxicology data, but we request the FDA to flexibly accept where that data may come from.

For more information on this position, please see the citizen petition we signed in July 2015 requesting that the FDA show this flexibility.

Section VI: Efficacy Endpoints:

The FDA's prescribed considerations for endpoint selection, while comprehensive, are lacking in one key way: an emphasis on patient participation in endpoint identification.

The FDA recognizes that, "an understanding of which aspects of the disease are meaningful to the patient and might also be affected by the drug's activity" is a step in the right direction. But as one sentence in over two pages of recommendations within this section, the FDA is burying the importance of the patient's input in endpoint identification.

NORD recognizes the importance of indefatigable empirical and statistically valid analysis in defining an assessment tool, and the FDA's assertions on the importance of validity, reliability, feasibility, and other statistically sound principles are entirely appropriate.

However, the FDA needs to also encourage the biopharmaceutical industry to include patient perspectives at the initial stage of endpoint identification so the drugs being developed to treat rare diseases are the therapies that patients with the diseases and their loved ones actually want. The FDA needs to ensure the regulatory process encourages companies to strive to develop the orphan drugs that rare disease patients so desperately need, rather than encouraging companies to pursue the lowest hanging fruit due to easier statistical compliance.

The endpoints that companies choose for their products must be chosen in concert with patients, and the FDA has an incredibly important role to play in encouraging companies to do so. Without this input, we will continue to observe companies developing therapies for the same symptom of a rare disease while the remaining symptoms go untreated.

Section VII: Evidence of Effectiveness and Safety:

We thank the FDA for its consistent recognition of the need for flexibility in accepting alternative clinical trial designs for small disease populations. NORD's 2011 analysis, and Mr. Sasinowski's subsequent update, found that the FDA employs regulatory flexibility in two-thirds of orphan product reviews.[1] [2] Flexibility in clinical trial design is particularly important, as placebo-controlled trials are becoming less and less appropriate (and often even unethical) in rare disease drug development.

There is a growing body of evidence supporting the use of non-placebo controlled trials, and we encourage the FDA to continue to display regulatory flexibility by accepting these clinical trial designs. We thank the FDA for the recognition that historical controls can be appropriate, albeit in "limited and special circumstances".

We also request that the FDA encourage sponsors to develop more appropriate inclusion/exclusion criteria. The FDA argues that trial design features need to include "methods of patient selection that are well-defined and result in the selection of an appropriate population for study". Too often we see companies including only a very small subset of a disease population within clinical trials. This is because sponsors often prioritize statistical integrity, thus excluding patients who may be deemed too young, too old, too healthy, too sick, or myriad other disqualifications.

[1] Frank Sasinowski, Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Cataloging FDA's Flexibility in Regulating Therapies for Persons with Rare Disorders, 46 Drug Information Journal 238 (Mar. 2012)

[2] Frank Sasinowski, Erika Panico, and James Valentine, Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Update, July 2010 to June 2014, Therapeutic Innovation & Regulatory Science, (April. 2015)

The results of these stringent qualification standards are far reaching. Patients who could clearly benefit from the therapy cannot access it, and must hope to access the therapy through voluntary expanded access programs within a non-transparent and difficult to navigate system. Once approved, the drug is likely to have a much narrower indication, leading many rare disease patients who would greatly benefit from the drug to attempt to obtain it off-label. Many patients fail, as coverage and reimbursement for off-label therapies in both private and public insurance is limited.

Here again the FDA has an important role to play. While the FDA cannot set exclusion/inclusion criteria, it can encourage sponsors to include all patient subgroups that may benefit from the drug within their trial. Expanded access problems will be alleviated, and greater insurance coverage will follow.

The FDA should again encourage that the patient voice be included throughout this process. As the draft guidance is currently constructed, there is little mention of patient input in developing the outlined parameters for each study.

We thank FDA for the opportunity to comment, and we look forward to working with FDA to strengthen orphan drug development in the United States. For questions regarding NORD or the above comments, please contact Paul Melmeyer, Associate Director of Public Policy, at pmelmeyer@rarediseases.org or (202) 588-5700, ext. 104.

Thank you in advance for your consideration.

Sincerely,

Peter L. Saltonstall
President and CEO