April 2, 2019

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Re: Docket No. FDA-2015-D-2818: Rare Diseases: Common Issues in Drug Development, Guidance For Industry; Draft Guidance

Dear Sir or Madam:

On behalf of the 30 million Americans with one of the approximately 7,000 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(NORD) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency's Draft Guidance entitled "Rare Diseases: Common Issues in Drug Development" (Draft Guidance).

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.

Overall NORD remains supportive of FDA's revised guidance and the Agency's continued dedication to supporting drug development for the rare disease community. NORD particularly appreciates the additions and clarifications made to the Natural History Studies section. These changes further emphasize the importance of natural history studies to the rare disease drug development process. As further discussed below, NORD's IAMRARE Registry Program could play a critical role in ensuring that natural history data is appropriately and expediently collected.

In addition, we are appreciative of FDA's further modernization of rare disease clinical trials. FDA's expanded flexibility in the use of non-placebo controls, coupled with its encouragement of the use of broader and more representative inclusion/exclusion criteria, will further focus rare disease clinical trials on the needs of the rare disease patient. Finally, we appreciate FDA's consideration of data obtained through expanded access programs (EAPs) as these data can potentially expand access to on-label therapies for particularly intractable conditions.

Below are our comments on each of these proposals, including specifically on how FDA can incorporate registries, such as NORD's, in these efforts, as well as further considerations for FDA as it modernizes rare disease clinical trial design

II. Background.

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NORD notes that the Agency has revised its introductory discussion of drug development under the Orphan Drug Act. In discussing the challenges that confront investigators and sponsors pursuing treatments for rare diseases and disorders, the 2015 draft guidance "acknowledge[d] that certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases."[1] In contrast, this Draft Guidance puts greater emphasis on placing these challenges on a continuum. By stressing that FDA "regulations provide flexibility in applying regulatory standards because of the many types and intended uses of drugs" and that FDA "exercise[s] its scientific judgment" in determining the kind and quantity of data a sponsor is required to provide for individual drug development programs," the Draft Guidance provides important advice to investigators and sponsors intending to treat small patient populations without imposing boundaries on the utility or applicability of such advice for other drug development programs for more common diseases. NORD concurs with FDA that this shift is warranted because it reflects how historic, successful experience with small patient populations and innovative trial designs for orphan drugs has greatly promoted regulatory flexibility for new drugs and biological products generally.

However, in the same section, FDA has omitted the following statement from the 2015 draft guidance, which remains true and compelling.

> "Many rare disorders are serious conditions with no approved treatments, leaving substantial unmet medical needs for patients. FDA recognizes that rare diseases are highly diverse and is committed to helping sponsors create successful drug development programs that address the particular challenges posed by each disease."[2]

The Agency's commitment to meaningful and substantial collaboration has been unwavering since the Orphan Drug Act's enactment. It is estimated that there are over 7,000 rare diseases, which are defined in the U.S. as a disease affecting 200,000 or fewer people. Today, over 90 percent of rare diseases still have no treatment (approximately 500 approved orphan products treat nearly 600 rare diseases).[3] The barriers and significant obstacles that hinder the pursuit of rare disease therapies to meet the substantial unmet medical needs of patients with rare disorders requires the continued partnership of FDA, patients, investigators, and sponsors. We consequently believe the inclusion of this statement of vision and mission is important in this Draft Guidance.

III. Natural History Studies.

A. Considerations for Natural History Studies.

NORD strongly supports the Agency's emphasis upon the conduct of natural history studies as a critical component of orphan drug development, with an emphasis upon the early conduct of

[1] FDA, Rare Diseases: Common Issues in Drug Development, August 2015, p. 3.
[2] *Id.* at 2-3.
[3] IQVIA Institute for Human Data Science. Orphan Drugs in the United States: Exclusivity, Pricing and Treated Populations. 2018 Dec. https://www.iqvia.com/institute/reports/orphan-drugs-in-the-united-states-exclusivity-pricing-and-treated-populations

natural history studies to inform subsequent development decisions and the design of clinical trials that meaningfully reflect the patient experience. FDA notes that an assessment of extant natural history knowledge is prudent "to inform... drug development programs", and newly notes that "a natural history study initiated early may run in parallel" with preclinical work, forestalling some objections regarding feasibility. [4]

Additionally, NORD strongly supports FDA's call on sponsors and investigators to make "data from natural history studies publicly available to support and promote rare disease drug development."[5] As we commented on the 2015 draft guidance, we are concerned about the development of natural history studies that reflect redundant registry efforts and restricted data ownership. Absent the sharing of data that FDA encourages, crucial patient experience data will continue to be siloed in a fashion that inhibits scientific advancement and progress towards new treatments. We urge FDA to take concrete steps to facilitate such data sharing and ask the Agency to continue support of a patient-centric approach to drug development that precludes the conduct of multiple natural history studies by multiple sponsors for the same population of patients.

B. Implementation of the Draft Guidance Must Leverage Rare Disease Registries and Reflect Patient Perspectives.

NORD strongly endorses FDA's expansive discussion of retrospective, prospective, cross-sectional, and longitudinal natural history studies as critical components of orphan drug development and as a basis for the Agency's regulatory decision-making and premarket reviews. Historically, FDA has worked diligently to anchor their work around the patient, meaningfully incorporating patient perspectives into the drug approval process. Consistent with the Draft Guidance, the Agency should encourage sponsors and investigators to utilize and leverage existing sources of real world evidence (RWE) for rare disease patient populations, such as the IAMRARE™ Registry Program, which supports the collection of longitudinal patient-reported, patient-experience natural history data and provides a pathway for patient perspectives to continue to be central to the design and execution of advancements for orphan drug development.

In order to facilitate the development of treatments for rare diseases and support the generation of RWE, NORD created the IAMRARE™ Registry Program, a Natural Histories Patient Registry Platform, with extensive input from FDA, the National Institutes of Health (NIH), patients, organizations, and experts in the field. NORD's platform is an easy to use system that allows patients and organizations to inform and shape medical research and translational science for rare diseases by launching high-quality, customized registries to collect the data needed to define the natural progression of their disease – ultimately advancing product development.

NORD partners with patient organizations on the development of disease-specific longitudinal, natural history studies. NORD provides a common data collection infrastructure across conditions that gathers both common cross-disease survey data in addition to disease-specific

[4] *Id.*
[5] Draft Guidance at 5.

survey data. The platform has the ability to capture longitudinal data on a set schedule while also allowing for *ad hoc* real-time data capture through surveys designated to accept updates.

In addition, the IAMRARE™ platform collects related electronic medical record information via an upload feature, where participants can share lab results, genetic testing, images, and clinical medical record data. NORD also provides best practice guidance and templates for emails, social media, and legal agreements (consent, data sharing) for patient organizations to engage with their patient populations. Rare diseases present unique challenges for researchers and companies working towards treatments and cures and NORD provides a collection of services to support collaborative research partnerships to advance scientific discovery for rare conditions.

C. Encouraging Use of Rare Disease Registries to Facilitate Orphan Drug Development.

NORD believes that the Draft Guidance underscores the importance of registries like IAMRARE™ to the feasibility, design, and initiation of natural history studies. Patient registries can mitigate structural concerns with RWE data gathered through observational study designs and the ability to reach causal inferences from such data.

Registries such as IAMRARE can capture data from an entire rare disease community, across many diseases and conditions, providing robust and reliable sources of baseline data, indices of existing evidence for the natural history of a given rare disease or condition, and the ability to look across conditions for commonalities. The data collected has the ability to inform and transform patient care, unite patient groups, and provide an understanding of how specific diseases are expressed over time. Longitudinal patient-reported, patient-experience data can also contribute to a more robust knowledge-base for the evaluation of individual and global economic burden of disease and inform therapeutic development for the rare disease community.

As an example of how patient registries can serve as a platform for collecting natural history data across platform trials, and potentially even serving as a historical control, we refer to the 2016 cooperative agreement between the Agency and NORD (U24 FD005664) to develop natural history studies with twenty rare disease patient groups through NORD's Natural History Study Registry Platform. The agreement enabled the collection of disease-specific longitudinal, natural history information from individuals diagnosed with selected rare diseases. Examples of core data elements that are measured within and across each registry at NORD include patient-reported, patient experience outcomes related to diagnosis and treatment, quality of life, management of care, clinical testing samples, and clinical reporting.

Additionally, the IAMRARE™ registry program can enable the "pragmatic and hybrid clinical trials, including decentralized trials that are conducted at the point of care – and that incorporate real world evidence (RWE)" that Commissioner Gottlieb cited as recently as January 28 as means to increase efficient clinical investigations, reduce administrative burdens, and most importantly, "allow patients to receive treatments from community providers without compromising the quality of the trial or the integrity of the data that's being collected."

IV. Disease Pathophysiology, Clinical Manifestations, and Identification and Use of Biomarkers.

Consistent with the Draft Guidance, NORD applauds FDA's continuing efforts to facilitate biomarker development for serious and life-threatening diseases and conditions, including rare diseases. The Agency's implementation of the 21st Century Cures Act, through such initiatives as the CDER Biomarker Qualification Program (BQP), provides sponsors and investigators with clear pathways to secure advice and feedback on concepts, methodologies, and study designs.

NORD also supports FDA's flexibility and willingness to encourage identification and validation of new biomarkers for study proof-of-concept and orphan drug development, including potential use in "adaptive and enrichment designs for greater efficiency."[6] We believe the Draft Guidance provides meaningful advice that can assist sponsors and investigators as they consult with the Agency early in the development process.

V. Nonclinical Studies.

NORD applauds FDA's more robust statement that "[r]egulations state that it is appropriate for FDA to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness, for drugs to treat serious and life-threatening diseases... includ[ing] determining the nonclinical data necessary to support clinical development programs."[7]

We have long encouraged the Agency to remain open to non-animal testing methods that have the potential to develop equally and potentially more accurate safety and toxicology data.[8] While we acknowledge that "[t]oxicology testing in an animal model of disease may contribute to the nonclinical support for clinical trials but usually will not substitute for toxicology testing in healthy animals",[9] we believe FDA should, consistent with patient safety, pursue policies to broaden sponsors' testing options by establishing clearly that both animal testing and non-animal testing that is shown to be predictive of human response may be accepted as preclinical test methods.

VI. Efficacy Endpoints.

NORD strongly supports FDA's emphasis on patient participation in endpoint identification and selection, including but not limited to patient-reported outcomes (PRO). The Agency rightly notes that endpoint selection must "involve understanding... [t]he aspects of the disease that are meaningful to the patient and that could be assessed to evaluate the drug's effectiveness."[10] To that end, FDA must do everything in its power to encourage the biopharmaceutical industry to include patient perspectives at the initial stage of endpoint identification so the drugs being

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[6] Draft Guidance at 7.
[7] *Id.* at 9.
[8] See, e.g., NORD Citizen Petition to FDA on Use of Modern Test Methods for Pre-Clinical Research, July 31, 2015.
[9] Draft Guidance at 10.
[10] *Id.* at 11.

developed to treat rare diseases are the therapies that patients with the diseases and their loved ones actually want.

The Draft Guidance conveys this policy clearly to sponsors and investigators. 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 FDA plays a crucial role 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.

VII. Evidence of Effectiveness and Safety.

NORD appreciates and applauds the historic, progressive philosophy that FDA has taken to accepting a range of trial designs, alternative study protocols, reliance on RWE and PROs, post-market commitments, and historic data to support the approval of safe and effective orphan drugs. There is extensive literature[11] and testimony confirming the Agency's flexibility in interpreting its statutory responsibility to require substantial evidence that a new drug will have its claimed effect[12] on the basis of adequate and well-controlled clinical studies.

We note FDA's recognition that historical controls can be appropriate, albeit in “limited and special circumstances” for clinical trials to support effectiveness, and applaud the Draft Guidance's new acknowledgement that "[n]atural history studies should be part of earliest drug development."[13] However, initiation of prospective natural history studies should not delay 537 interventional testing otherwise ready to commence for a serious disease with unmet medical 538 need."

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. Many rare disease patients are children, and many patients are facing rapidly progressing degenerative diseases in which the experimental therapy could be the last hope. Furthermore, given the lack of alternatives for the vast majority of rare disease patients, a placebo could entail no treatment whatsoever rather than a marginally acceptable standard-of-care. These are all reasons for why alternative controls, including historical controls, are particularly necessary within rare disease clinical trials.

We also thank FDA for acknowledging the importance of ensuring “that inclusion and exclusion criteria do not unnecessarily constrain patient eligibility for not only patient accrual but for an adequate representation of the safety in the intended treatment population.” Too often we see companies including only a very small subset of a disease population within clinical trials. This

[11] See, e.g., F. 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).
[12] Section 505(d) of the FD&C Act (21 U.S.C. 355(d)) and section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)).
[13] Draft Guidance at 14.

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. With FDA's encouragement, we hope sponsors will expand their inclusion criteria to closely represent the likely population seeking access to the therapy upon marketing approval.

Additionally, we commend FDA's recognition of EAPs as potential data collection tools for sponsors. Traditionally, EAPs have been employed by sponsors to either provide their investigational therapy to patients between the conclusion of the final clinical trial and the marketing approval, or if a substantial number of patients are requesting access to the investigational therapy for clinical purposes. Only recently have attitudes shifted to acknowledge that sponsors can also collect data from EAPs to supplement the clinical trial. We are grateful for FDA's evolution in thinking as well, evidenced by FDA stating,

> "Systematic collection of expanded access safety data might identify important premarketing signals that might otherwise not be observed until the drug is used in the more diverse practice setting. Expanded access programs can also randomize participants to more than one dose or duration of therapy. Plans for these cohort should be discussed early in the development process with the review divisions."[14]

With this encouragement, sponsors can now view EAPs not only as a vehicle for philanthropically offering their investigational product to patients in medical need (often for no charge), but also as a means to collecting additional data. We hope this will further encourage sponsors to pursue EAPs as routine parts of their drug development program.

IX. Additional Considerations.

A. Participation of Patients, Caregivers, and Advocates.

NORD is once again grateful for FDA's continued emphasis on the importance of including rare disease patients, caregivers, and advocates within the drug development and review processes. The value of patient experiences and perspectives cannot be overstated, and FDA's acknowledgement of the many ways in patients and their caregivers and advocates can contribute is conclusive. In addition, we are thankful for FDA's encouragement to sponsors for integration of patients into to the earliest stages of drug development. We hope these encouragements continue in direct FDA-to-sponsor interactions.

B. Ensuring Alignment Across FDA Guidances.

While NORD is grateful for, and supportive of, everything within the Draft Guidance, we request that FDA ensures all other relevant draft guidances put forward by the Agency conform with the recommendations included within this Draft Guidance. For example, FDA continues to publish many disease-specific draft guidances for various rare diseases, and we encourage FDA to continue to do so. However, we also request that FDA ensures each of these disease-specific guidances align with the various provisions of the Draft Guidance put forth here. This includes

[14] Draft Guidance at 17.

the importance of natural history data registries, allowance of flexible clinical trial designs, broadened inclusion criteria, and EAPs.

Additionally, there are other draft guidances put forward by FDA in the previous few years that are quite pertinent to the information contained in this Draft Guidance, but not mentioned. For example, we would encourage FDA to include a section on using targeted data for related diseases or disease subsets as discussed in the Agency's "Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease" finalized in October 2018.

By better synergizing rare disease guidances with this guidance, and further including additional rare disease drug development issues discussed in other published FDA material, we believe this Draft Guidance can be strengthened even further.

X. Conclusion.

We thank the Agency for the opportunity to comment, and look forward to working with FDA on further revolutionizing the development of safe, effective, and innovative therapies for rare disease patients. For questions regarding NORD or the above comments, please contact me at rsher@rarediseases.org, or 202-588-5700 ext. 112.

Thank you in advance for your consideration of these comments.

Sincerely,

Rachel Sher
Vice President of Regulatory and Government Affairs