February 16, 2018

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

Re: Docket No. FDA-2017-N-5896-0001: Patient-Focused Drug Development: Guidance 1—Collecting Comprehensive and Representative Input; Public Workshop; Request for Comments

Dear Sir or Madam:

On behalf of the 30 million Americans with one of the nearly 7,000 known rare diseases, NORD thanks the Food and Drug Administration (FDA) for the opportunity to provide comments on the Agency's "Patient-Focused Drug Development: Guidance 1—Collecting Comprehensive and Representative Input; Public Workshop; Request for Comments."

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.

NORD has long supported patient involvement in the drug development and regulatory review process. Therapies that are developed and reviewed in consultation with patients are much more likely to reflect the needs and desires of the patient population, and are more likely to offer greater benefits with fewer risks. Only patients who live with the disease can offer these uniquely important perspectives.

Over the course of the last ten years, FDA, often under the instruction of Congress, and in consultation with patients and their representatives, has made great strides in ensuring the patient voice is integrated within the therapeutic development and review process. The Patient Focused Drug Development (PFDD) initiative created by the Food and Drug Administration Safety and Innovation Act (FDASIA) established a series of public meetings in which patients with specific diseases could offer their experiences and perspectives. We believe these meetings were highly successful, and we are already aware of positive outcomes that have resulted.

More recently, the 21st Century Cures Act and the Food and Drug Administration Reauthorization Act (FDARA) further advanced the incorporation of the patient voice in the therapeutic development process. The December 18th workshop, the accompanying discussion document, and the upcoming draft guidances on the collection of patient experience data (PED) all result from these two laws. We were pleased to help craft these legislative and regulatory

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proposals, and we are excited to participate within the ensuing FDA initiatives. The following comments reflect our analysis of the discussion document accompanying the December workshop, and our suggestions for the upcoming draft guidances.

Overall, we believe the discussion document includes various helpful suggestions for collecting patient experience data. While many sections are thorough, and foretells comprehensive upcoming draft guidances from FDA, there are still several areas in which FDA should expound upon its suggestions, especially within the context of rare diseases.

Patient Organizations Will Need Greater Direction:

In general, we believe FDA needs to provide extensive guidance to patient organizations on what data collection efforts they should undertake and when. The discussion document does a good job of outlining the various data collection options patient organizations have to choose from, but does little to advise them on what makes the most sense for their particular disease, population, or stage of therapeutic development.

Patient organizations will look to FDA on whether a quantitative study or qualitative study makes more sense, or whether or not a comprehensive probabilistic analysis, or a smaller non-probabilistic model is wise. With all of the available PED collection methods extensively explained within this discussion document, FDA will need to advise and direct patient organizations on which option brings the highest value to them and the patients they represent. With the limited resources patient organizations have, we want to avoid situations in which patient organizations are wasting their resources on certain PED generation and collection that is not advisable in their current situation.

In addition, since most rare disease patient organizations may only be starting their efforts to collect PED, it would be incredibly valuable to them for FDA to construct a roadmap of PED collection, or at the very least specify where these organizations should start these efforts.

Rare Disease Patient Organizations Are Small and Under-resourced:

FDA must also be mindful of the incredibly limited financial and staff resources that rare disease patient organizations have to offer to PED generation and collection. In a recent survey of our over 270 member patient organizations, we found that over 70 percent of them have fewer than five full-time employees. Most have incredibly limited budgets, and many still rely on bake sales, walkathons, social media campaigns, and just about anything else that will attract small donors.

However, to conduct much of the analysis explained by FDA in this discussion document, these patient organizations would require statisticians and other experts in study design. They would also require the assistance of subject matter experts, as is mentioned several times in the document. FDA should consider how broadly accessible these data collection methods actually are to the rare disease patient community, and how to ensure small patient populations are not particularly disadvantaged.

Additional Guidance is Needed on Sampling in Rare Diseases:

As is frequently recognized by FDA, rare diseases and their small populations bring unique challenges to crafting scientifically rigorous and empirical quantitative analyses. While true in clinical trial design, this challenge exists in the collection of representative PED as well.

FDA recognizes this by stating on page 21 of the discussion document,

> "Having an insufficient sample size may produce unreliable and/or imprecise results. FDA recommends that if the sample size is limited due to practical considerations (e.g., rare diseases), the research objectives should be adjusted accordingly and noted as a limitation in the study report."

FDA does not, however, give any additional details on how "research objectives should be adjusted accordingly." We hope FDA will expand upon this more thoroughly within the upcoming draft guidances.

We also request FDA to consider the issues with probabilistic random sampling within rare diseases, and the potential for skewed data resulting from a small sample of an already small population. Guidance from FDA on if, how, or when non-probabilistic sampling is advisable in order to achieve representativeness would be helpful.

Additional Considerations for FDA:

Finally, there are a handful of additional considerations we wish to bring to FDA. First, we hope FDA will consider putting forward training materials for parents and caregivers on how to soundly and reliably collect PED. Often within rare diseases it is the parent or caregiver who observes many of the symptoms that could be captured as PED. Ensuring they have the training necessary to capture this information is key.

Second, FDA states that, "simulation(s) [can] be used" in certain circumstances where robust data collection is particularly difficult. Greater guidance on these situations is needed.

Third, FDA also discusses ensuring the target population is well understood and estimated within PED collection. This can be difficult within rare diseases, however, due to widespread misdiagnoses. Oftentimes rare diseases do not have a particularly reliable diagnostic, and therefore much of the patient community is actually undiagnosed or misdiagnosed.

Finally, FDA also discourages against single-site data collection. This may be particularly difficult to avoid within rare diseases due to rare disease patient populations clustering around centers of excellence or experts on their specific disease. While they may originate from across the country, or world, they often must congregate in certain areas as there are only a small number of experts in their disease.

We thank FDA for the opportunity to comment and we look forward to working with FDA to ensure rare disease patients and patient advocacy organizations are able to fully participate

within this exciting initiative. For questions regarding NORD or the above comments, please contact me at pmelmeyer@rarediseases.org, or 202-545-3828.

Thank you in advance for your consideration.

Sincerely,

Paul Melmeyer
Director of Federal Policy