September 11, 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Re: Docket No. FDA-2018-D-1893-0002: Draft Guidance for Industry Patient-Focused Drug Development Collecting Comprehensive and Representative Input

Dear Sir or Madam:

On behalf of the 30 million Americans with one of the approximately 7,000 known rare diseases, NORD thanks the Food and Drug Administration (FDA) for the opportunity to provide comments on the Agency's "Draft Guidance for Industry Patient-Focused Drug Development Collecting Comprehensive and Representative Input."

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 in question 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 that 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. This draft guidance, last year's December 18th workshop, the accompanying discussion document, and the additional upcoming draft guidances and public workshops all emanate from these two laws.

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We were pleased to help craft these legislative and regulatory proposals, and we are excited to participate within this exciting FDA initiative. The following comments reflect our analysis of the first of four draft guidances put forward by FDA on the collection of patient input. The focus of this guidance is specifically on "collecting comprehensive and representative input."

This draft guidance is particularly salient for those in the rare disease community as collecting comprehensive and representative input from rare disease patient populations can be uniquely difficult and complex. What may be a comprehensive approach in a rare disease may not be so in more common diseases, and vice versa. Furthermore, the standard of representativeness may be quite different in rare diseases than within common diseases.

Consequently, we are pleased to provide comments to FDA on this draft guidance. Overall, we believe this guidance will be quite helpful to the rare community as it explores collecting patient experience data (PED). However, we believe FDA needs to do more to provide extensive guidance to patient organizations on what data collection efforts they should undertake and when, including the technical requirements for such data collection and fit-for-purpose measures that are of high-value to multiple stakeholder groups, particularly in the regulatory community. This draft guidance 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, as well as which data is usable across stakeholder groups to accelerate confident and expedited decision-making.

NORD, for example, partners with patient organizations to run rare disease registries on the IAMRARE(TM) Registry Platform. We provide general research guidance, project management and IRB services, technical support, and opportunities for organization-to-organization mentorship. NORD requires that each patient organization have a Scientific Advisory Board to advise on the development of survey questions, the longitudinal measurement schedule, and other disease-specific aspects of the research development.

Guidance from the FDA about sound research approaches and best practices for the rare disease community, in addition to guidance on a standard set of (rare disease) research questions and high-value data elements that the FDA could then use to inform decisions would be incredibly meaningful. Of course, this information can vary to some degree from disease to disease, or population to population, but any further guidance from FDA would be helpful. This guidance would allow rare disease patient organizations to develop a bi-directional pipeline for data sharing and capture in a way that reflects the priorities of the FDA in addition to the needs and experiences of the community.

With all the available patient experience data collection methods contained 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 scenarios in which patient organizations are wasting their resources on patient experience data generation and collection that is not advisable for their current situation, or of the highest-value to the research and development process.

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 best practices, including data standards and requirements, or, at the very least, specify where these organizations should start when commencing PED collection.

There are also certain specific improvements that could be made to this proposed guidance to further benefit the rare community. Those suggested improvements follow below.

Further Guidance on Choosing a Research Question:

Many rare disease patient communities may desire to pursue studies that collect patient experience data from their patient populations. However, given that the foundation of knowledge is limited for many rare conditions, the organization may not know where to start.

It would be especially beneficial to the rare disease community if FDA could further expound upon what research questions may be most useful or what questions may be best to start with. This will allow rare disease patient organizations to determine what answers to which questions FDA would find most useful. Of course, this can vary from disease to disease or population to population, but any further guidance from FDA would be helpful.

Additional Guidance is Needed on Sampling in Rare Diseases:

In this proposed guidance, FDA puts forward various sampling options from which patient communities can choose to collect patient experience data. However, FDA devotes very little space and time on which of these many sampling methods should be pursued, outside of simply listing some limitations and advising organizations to consult with a statistician.

First, it will be difficult for the vast majority of rare disease patient organizations to access a knowledgeable statistician to provide advice. In a recent survey of our over 280-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 to raise funds. It will be quite difficult for these organizations to hire statisticians or other experts to help conduct studies.

Second, the rarity of the diseases within our community present additional challenges when choosing a sampling method. For example, the extremely low prevalence of some rare diseases may make it nearly impossible to employ a probabilistic sampling method without a risk of strongly skewing the data. If a patient population only numbers 100 patients, and the 20 individuals selected as a sample from this patient population happen to be healthier than the average, the results will be skewed.

Organizations may also need to take additional statistical precautions to ensure scientific rigor when using some of these sampling methods within rare diseases, and yet FDA chooses not to discuss such situations. This additional rigor would also likely require additional time and resources, two things that rare disease patient communities can be particularly short on.

These very same considerations that are of concern when contemplating sample size, also apply to representativeness. We are grateful that FDA acknowledges that, when evaluating representativeness, rare diseases present certain sample size limitations and, therefore, "the research objectives should be adjusted accordingly and noted as a limitation in the study report" (lines 584-586). However, we are hopeful that FDA will opine further in the finalized guidance.

We are concerned that those in the rare community may pursue patient experience data collection studies with this in mind and include this acknowledged limitation, only to be told that the limitation is too substantial to ignore. Alternatively, without further direction from FDA, rare disease patient organizations may decline to pursue such studies altogether given the lack of clarity on what degree of limitation would be acceptable, and for what purpose.

Clarity around data collection use cases and associated data requirements would greatly inform research study design in the rare disease community. For example, if a community is seeking to document the natural progression of a disease for informative research purposes then the data requirements, beyond general best research practices are less rigorous than, say, if an organization is invested in collecting research-grade data that could be used as a substitute for a control arm in a study, a potential study design that is incredibly valuable in the rare disease community where populations are small and therapeutic options limited.

We strongly encourage FDA to include a discussion on how these sampling methods can be applied to rare diseases within the finalized guidance.

Registries as Sampling Frames

We are grateful for FDA's inclusion of registries as a good construct from which to create a sampling frame. This is one of the many reasons why NORD has invested in the development of the IAMRARE™ Registry Platform, a longitudinal, natural history study data collection tool for the rare disease community that allows for comprehensive data collection from rare populations.

We have seen numerous successes from the data collected on NORD's registry platform demonstrating the far-reaching impact and value of longitudinal cohort studies in the rare disease space – from the discovery of previously unexplored indications in different body systems that relate to the progression of a disease to significant reductions in time to diagnosis and treatment to academic researcher requests for data access to presentations at international conferences and multiple papers in peer review. We hope NORD's registries will continue to be used by rare communities to create sampling frames from which patient experience data can be collected.

We're eager to work closely with FDA in encouraging the development, implementation, and use of rare disease longitudinal, natural history data registries for expanded uses in research and decision-making, particularly in the context of collecting patient experience data.

Leveraging Existing Data:

We are pleased that FDA acknowledges that existing data sources can be used when collecting data, and that for some conditions collecting primary source data may be infeasible. The FDA

states that they encourage "collaboration among multiple stakeholders and the use of methods to combine and reuse existing data" (lines 709-710). NORD supports this approach and acknowledges that this statement underscores the importance of the FDA providing additional guidance around data requirements, common data elements, and data standards to facilitate the harmonization of different data streams. We do not agree, however, that this paradigm would only apply to "ultra-rare" diseases.

In fact, we generally believe that subtyping rare diseases into "ultra-rare" and "non-ultra-rare" would likely do much more harm to our community than good. We have opposed proposals that would change the incentive structures, regulatory review pathways, or coverage policies based upon varying levels of rarity. Our reasoning is twofold.

First, we believe that the rare diseases that may need additional help or attention (in this case the allowance of existing data sources) do not break down solely upon prevalence. Rather, alternative variables can be much more impactful. For example, heterogeneity, complexity, and scientific investment can all be just as or more impactful than particularly-low prevalence.

Second, we envision those in the "non-ultra-rare" community may be more severely harmed by such proposals than those in the "ultra-rare" would be helped. Within the context of this proposal, we can envision a scenario in which FDA or others reject the use of existing data sources from a rare disease community simply because they are not "ultra-rare", and instead require these communities to collect de novo primary-sourced data as common-disease communities would be expected to do.

We request that FDA removes this alternative definition of a rare disease and, instead, maintain the existing definition of a rare disease set by statute. If certain situations for collecting patient experience data arise that require existing data sources to be used because primary data would be too difficult to collect, we ask FDA to make these determinations not based upon an arbitrary new definition of rarity but by the specific circumstances the situation presents.

Choosing a Method for Collecting and Analyzing Patient Experience Data:

We again are concerned with FDA's lack of direction for patient organizations on choosing between quantitative, qualitative, and mixed-method designs. FDA suggests that "stakeholders choose the best analysis approach for their research objective" (line 863). But this, again, leaves quite a bit of room for interpretation of FDA's preferred direction. We recommend that FDA provides greater clarity on the best methods to use for any particular situation, providing clear use case scenarios with associated data requirements.

Potential for Single-Site Collection:

FDA advises that "[i]n order to have adequate generalization for multicenter clinical trials, patients should generally not be located from a single site" (lines 881-882). 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 converge in certain areas as there are only a small number of experts in their disease space.

Importance of Social Media:

We thank FDA for acknowledging the role social media can play in collecting patient experience data. This is particularly pertinent within the rare disease community. When not gathered around a specific site of care, many rare disease communities congregate on social media platforms as patients are otherwise too few and far between to gather or find each other any other way.

Thus, robust online communities have developed within the rare disease space that could serve a crucial role in collecting patient experience data. We thank FDA's openness to this data collection option, and we expect many patient communities to explore the use of social media to collect such data.

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