



December 17, 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-3268-0001: Rare Diseases: Early Drug Development and the Role of Pre-Investigational New Drug Application Meetings; Draft Guidance for Industry;**

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) for the opportunity to provide comments on the Agency's "Rare Diseases: Early Drug Development and the Role of Pre-Investigational New Drug Application Meetings; Draft Guidance for Industry."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.

Ever since the passage of the Orphan Drug Act of 1983, NORD's foundational public policy mission has been to ensure that therapies for rare diseases are developed by private industry, and FDA thoroughly yet expeditiously reviews them. An integral step in this process is the interaction between sponsors and FDA in the early drug development or pre-clinical stages.

Consequently, the information put forward in this draft guidance will be incredibly important in guiding these interactions, and, more broadly, in ensuring safe, effective, and patient-focused therapies for rare diseases are developed. We are grateful for FDA putting forward this draft guidance as we hope the additional clarity within will streamline the development and approval processes, and will help therapies reach our patients quicker.

Overall we are pleased with the draft guidance, and support many of FDA's assertions within, particularly regarding the inclusion of patient perspectives and patient reported outcomes in orphan drug development. There are also a handful of places in which improvements can be made, particularly around natural history studies and inclusion/exclusion criteria. The following sections outline our thoughts and considerations.

## **Clinical Considerations:**

### *FDA's Continued Flexible Approach:*

We thank FDA for reiterating its flexible approach to reviewing orphan therapies. As FDA well recognizes, the inherent problems of testing a therapy in small patient populations require FDA to flexibly review orphan therapies, all while ensuring the therapy meets the same standard as all other therapies: safe and effective.

Furthermore, FDA also recognizes that “patients and physicians (in the rare disease community) are generally willing to accept greater risks and side effects from treatment of life-threatening and severely debilitating diseases than they would for other diseases.” This critical recognition should always guide FDA as it is considering the benefit/risk calculation for new therapies.

### *FDA Should Encourage Sponsors to Collect Longitudinal Natural History Data:*

FDA accurately recognizes that one of the many challenges sponsors face when developing therapies for rare diseases is the “lack of understanding of the natural history of the disorder.” FDA later continues by requesting that sponsors prepare to discuss “the knowledge gaps in the disease’s natural history.”

While we appreciate the recognition of the issue of the frequent dearth of natural history data, we are disappointed that FDA does not suggest that anything is to be done about it. Within this draft guidance, FDA has the perfect opportunity to encourage sponsors to present a plan for filling the gaps in natural history data by partnering with patient organizations to collect this very data.

FDA has reiterated many times the importance for sponsors to collect natural history data, particularly on rare diseases, most recently in its “Patient-Focused Drug Development Guidance Methods To Identify What Is Important to Patients and Select Develop or Modify Fit for Purpose Clinical Outcome Assessments Public Workshop” discussion documents.

FDA should once again reiterate this importance, and as part of this guidance, request, or at least advise, sponsors to support the collection of natural history data in rare diseases ideally with a patient organization partner.

As FDA well knows, NORD is developing IAMRARE™ natural history data registries that aim for precisely this goal. NORD partners with patient organizations to run rare disease registries, and we are fully prepared to assist FDA in collecting this data through our IAMRARE™ 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.

We encourage FDA to not miss this opportunity to encourage sponsors to invest in the collection of these incredibly important longitudinal natural history data.

*FDA Should Encourage Broad Inclusion/Exclusion Criteria:*

As part of the clinical considerations that sponsors should prepare, FDA requests that sponsors prepare their rationale for the inclusion/exclusion criteria within their upcoming trial. FDA also states that sponsors should prepare to discuss that, “If the trial population is a subgroup of the population with the rare disease, plans for evaluating the drug in other subgroups to determine whether trial results can be generalized to the broader disease population.”

Once again, we request that FDA more emphatically encourages sponsors to prepare plans for as broad inclusion/exclusion criteria within their trial as feasibly possible. NORD has long encouraged sponsors and FDA to structure trial inclusion/exclusion criteria to best target all rare disease patient populations that could benefit from the therapy.

This guidance offers FDA an opportunity to encourage sponsors to craft inclusion/exclusion criteria to match the patient populations who will seek the therapy once on the market. We encourage FDA to take this opportunity.

*FDA’s Encouragement for the Inclusion of Patient Perspectives*

NORD is grateful for FDA’s request for sponsors to prepare to discuss the “Inclusion of patient perspectives in the drug development process.” This guidance from FDA will hopefully lead to sponsors more routinely and robustly including patient perspectives early on within the drug development process, often when they are most influential.

As FDA well knows, patient perspectives on everything from clinical trial design and endpoint selection to dosing schedules and clinical trial locations can be critical to ensuring that tomorrow’s new therapies are patient-friendly and patient-focused. This can only happen if sponsors are considering patient perspectives from the outset.

Sponsors should also invest in patient experience data (PED) collection in parallel with the clinical trials as discussed within FDA’s recent discussion document entitled, “Select, Develop, or Modify Fit-for-Purpose Clinical Outcomes Assessments”. An additional guidance coming forward (the third of four total guidances on patient-focused drug development) will further educate sponsors.

These instructions from FDA, plus FDA’s encouragement within this draft guidance, will hopefully result in orphan drug sponsors developing, collecting, and utilizing patient perspectives throughout their development processes.

*FDA’s Encouragement for the Inclusion of Patient Reported Outcomes*

We are similarly supportive of FDA’s encouragement for sponsors to come prepared to discuss novel endpoints, including patient-reported outcomes (PROs). PROs could allow for the therapies being developed for rare disease patients to be truly patient-focused by measuring their safety and effectiveness based upon patient-centered metrics.

Once again, by FDA encouraging sponsors to discuss this option as part of their pre-IND meetings, FDA is further pushing the proliferation of patient-focused therapies.

**Pediatric Studies:**

We support FDA’s encouragement to sponsors to “submit pediatric study plans for all drugs intended for pediatric indications” regardless of whether or not the Pediatric Research Equity Act (PREA) requires the sponsor to complete such plans. We also remain supportive of the orphan exemption from PREA where it still remains (non-oncology) as we believe there is not enough evidence justifying a removal of the exemption, and therefore the benefits of doing so do not outweigh the costs.

We are aware that many organizations, including some offices within FDA, support removing the orphan exemption from PREA entirely. However, we are concerned that doing so, particularly without assurances of an adequate waiver and deferral process, could push prospective sponsors away from rare diseases. Without proper evidence from FDA or other entities that the benefits of the resulting additional pediatric studies would outweigh the risks of possibly disincentivizing development in the first place, we will not support such a change.

We thank FDA for the opportunity to comment and we look forward to working with FDA to further improve the early stages of orphan drug development. For questions regarding NORD or the above comments, please contact me at [pmelmeyer@rarediseases.org](mailto:pmelmeyer@rarediseases.org), or 202-545-3828.

Thank you in advance for your consideration.

Sincerely,

A handwritten signature in black ink, appearing to read 'Paul Melmeyer', with a long horizontal flourish extending to the right.

Paul Melmeyer  
Director of Federal Policy