



December 10, 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**Re: Docket No. FDA-2018-D-2258: Human Gene Therapy for Rare Diseases; Draft Guidance for Industry**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Administration (FDA) for the opportunity to provide comments on the Agency's "Human Gene Therapy for Rare Diseases; Draft Guidance for Industry."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 fully committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

NORD thanks FDA for its continued efforts to facilitate the expedited development and approval of innovative treatments and cures for rare diseases. Gene therapies in particular hold incredible promise to potentially cure genetic disorders. With these exciting possibilities already arriving and with many more on the near horizon, it is incredibly important that FDA provide regulatory clarity and certainty to sponsors developing gene therapies for rare diseases.

The following comments offer NORD's perspective and advice on a variety of gene therapy development issues that FDA explores as part of this Draft Guidance. Overall we are very pleased with the guidance provided by FDA but have several targeted suggestions for improvements to be included in the final guidance.

**Developing Gene Therapies for Particularly Small Patient Populations:**

NORD thanks FDA for recognizing the many challenges associated with developing products for particularly small rare diseases. We are also pleased that FDA acknowledges that the unique challenges of developing gene therapies make the development process for these small populations all the more complex.

Consequently, it is all the more important for FDA to provide specific recommendations and guidance on how to overcome these issues. We are pleased that FDA has done exactly that by

recommending specific manufacturing practices for sponsors to pursue, including establishing assays for characterizing product-related variants, establishing potency tests early on, and other manufacturing approaches.

With this said, we request that FDA provide additional guidance on ways to avoid conducting additional clinical studies if product comparability is not well established. We understand the necessity of demonstrating product comparability, but we ask that FDA and sponsors do everything possible to avoid additional clinical studies as they would further delay patient access to gene therapies.

### **Importance of Natural History Studies**

NORD once again thanks FDA for its recognition of the importance of collecting natural history data through natural history data registries. 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<sup>(TM)</sup> 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.

In order to facilitate the collection of these important data, we reiterate a request from our September 11, 2018, comments to FDA on your “Draft Guidance for Industry Patient-Focused Drug Development Collecting Comprehensive and Representative Input.” Guidance from 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 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 FDA in addition to the needs and experiences of the community.

### **Selection of Study Populations:**

While we understand that the selection of inclusion/exclusion criteria for trials only becomes more complex as gene therapy and targeting the genetic underpinnings of disease are considered, we still implore FDA and sponsors to consider as broad of inclusion criteria as practicably possible.

Gene therapies hold an immense amount of promise for disease populations with little to no alternative therapies. If patients are excluded from the trial but still could benefit from the therapy, they will almost certainly seek the therapy through expanded access. This only further complicates decision making for the company and the sponsor.

We applaud FDA for encouraging sponsors to consider individuals with severe or advanced disease and for not automatically disqualifying them as has happened many times in the past. We

hope sponsors carefully consider this advice and choose to include all types of patients who could benefit from participating in the clinical trial.

### **Patient Experience Data and Patient Preference Information**

We strongly support FDA's encouragement for collecting patient experience data (PED) and patient preference information (PPI) during product development. These data may mitigate some of the complexities of developing gene therapies by better elucidating the risks and benefits the patient population is willing to incur.

For example, FDA cites the ethical concerns associated with developing gene therapies for pediatric populations. With PED or PPI in hand, sponsors and FDA will have a much better idea of the risks and benefits children and their loved ones are willing to undertake. FDA also encourages sponsors to choose endpoints that are meaningful to patients, another endeavor that would greatly benefit from the use of PED or PPI.

We encourage FDA to urge sponsors to use patient experience data in as many circumstances as possible. For example, rather than simply encouraging companies to collect PED throughout their development processes, we also request that FDA amend this guidance to reflect where PED could be helpful to FDA and sponsors in the many decisions discussed.

### **Clinical Trial Design**

We are particularly supportive of FDA's stated flexibility with various clinical trial structures. By doing so, FDA recognizes the inherent difficulty in ascertaining the safety and effectiveness of orphan therapies and appropriately offers various alternatives for sponsors to consider. For example, FDA has shown an openness to single-arm trials that use historical controls as well as using natural history data as the basis for historical controls.

FDA's flexibility will be critical in ensuring that gene therapies are able to come to market for patients with serious and unmet rare diseases.

### **Patient Education**

We encourage FDA to add additional language to the guidance pertaining to educating patients and their families on gene therapy prior to product release. Ideally these efforts would be conducted in partnership with patient organizations, such as NORD.

While the rare disease community is quite excited by the possibilities offered by gene therapy, there can still be plenty of misunderstandings and misconceptions. For example, patients will need to better understand that not all gene therapies are curative, and the risks of taking a gene therapy may include exclusion from future gene therapy opportunities.

We ask that FDA include within this guidance advice to sponsors on launching patient education campaigns to ensure the target population following approval is well educated and well prepared for taking a gene therapy. NORD is already pursuing similar efforts by putting forward

educational materials on gene therapy, including this video:  
<https://www.youtube.com/watch?v=5ChXI6cSQs0>.

We thank FDA for the opportunity to comment, and we look forward to working with FDA to ensure gene therapies for rare diseases are successfully developed and reach our patients. 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, sweeping horizontal line extending to the right.

Paul Melmeyer  
Director of Federal Policy