



September 25, 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-2456: Slowly Progressive Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies - Guidance for Industry**

Dear Sir or Madam:

On behalf of the 30 million Americans with one of the 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 "Slowly Progressive Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies - 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.

NORD thanks FDA for its continued efforts to streamline orphan drug development and approval. This draft guidance is another indication of FDA's commitment to ensuring therapies are developed for the rarest and most isolated rare diseases. However, there is one critical change to the draft guidance that we ask FDA to make before finalization.

On page one of this proposal, FDA states that "This document is intended to provide guidance to sponsors on the evidence necessary to demonstrate the effectiveness of new drugs<sup>2</sup> or new drug uses intended for slowly progressive, low-prevalence rare diseases<sup>3</sup> that are associated with substrate deposition and are caused by single enzyme defects."<sup>1</sup> In the third footnote, FDA defines a low-prevalence rare disease for the sake of the guidance as, "a condition affecting approximately 5,000 persons or less in the United States."<sup>2</sup> We ask FDA to remove this arbitrary definition for a low-prevalence disease and instead return to previous precedents for addressing particularly rare diseases.

We disagree with FDA's alternative definition of rarity within this section and have long argued that subtyping rare diseases, in this case into diseases with a prevalence under 5,000 and diseases with a prevalence between 5,000 and 200,000 (or "low-prevalence rare diseases" and "non-low-prevalence rare

---

<sup>1</sup> Food and Drug Administration, Department of Health and Human Services, *Slowly Progressive Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies - Guidance for Industry*. Pg. 1

<sup>2</sup> *Ibid*, Pg. 1

diseases”), would likely do 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 an alternative definition of rarity. Earlier this month we submitted comments on FDA’s draft guidance entitled “Patient-Focused Drug Development: Collecting Comprehensive and Representative Input” in which we opposed the use of “ultra-rare” within the document.<sup>3</sup>

Our reasoning for this opposition is twofold. First, other sponsors looking to develop a drug for a disease in this space with a prevalence of over 5,000 individuals could also benefit from this guidance. By excluding them, FDA could create uncertainty in their development pathway. These developers would have to assume that the advice within this document does not apply to their products, potentially making development more difficult. Consequently, this arbitrary segmentation could generate more harm for the rare disease community at large than it would benefit those diseases with a prevalence of under 5,000.

Second, we believe FDA should use a more nuanced approach that targets the precise issues that plague therapeutic development within low-prevalence diseases, that can also often arise in other rare disease development pathways, instead of solely focusing on prevalence. Low clinical trial recruitment and retainment, complications in collecting longitudinal natural history data, and many other challenges are exacerbated in particularly small rare diseases but are not exclusive to these conditions. Rather than citing prevalence alone as a reason for additional guidance, we urge FDA to cite the specific issues that are necessary to overcome.

In fact, FDA used precisely this tactic to help define low prevalence within the December 2017 draft guidance on “Targeted Therapies in Low-Frequency Molecular Subsets of a Disease.” In this proposal, FDA defines low frequency as “frequencies low enough that enrolling a sufficient number of patients to conduct a clinical trial limited to the specific molecular alteration of interest is not feasible or practical.”<sup>4</sup> This approach is much more appropriate and will ensure that FDA does not inappropriately subdivide the rare disease community.

We thank FDA for the opportunity to comment, and we look forward to working with FDA to ensure that orphan products for rare diseases are successfully developed. 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,



Paul Melmeyer  
Director of Federal Policy

---

<sup>3</sup> NORD Comments on FDA’s *Draft Guidance for Industry Patient-Focused Drug Development Collecting Comprehensive and Representative Input* found here: <https://rarediseases.org/wp-content/uploads/2018/09/NORD-2018-Comments-on-Patient-Focused-Drug-Development-Guidance-1-Collecting-Comprehensive-and-Representative-Input-Guidance.pdf>

<sup>4</sup> Food and Drug Administration, Department of Health and Human Services, *Targeted Therapies in Low-Frequency Molecular Subsets of a Disease – Guidance for Industry* Pg. 2