



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**Re: Docket No. FDA-2017-D-6617-0001: Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease; Draft Guidance for Industry; Availability**

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to provide comments on the Agency's "Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease; Draft Guidance for Industry."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.

A rare disease is defined by the Orphan Drug Act as any disease or condition that affects 200,000 individuals or fewer in the United States. While there are certainly many rare diseases that affect close to 200,000 individuals, the vast majority of the estimated 7,000 known rare diseases affect much smaller patient populations. Most of these diseases are genetic and can often affect only a handful of individuals in the entire world. Many diseases with the same or similar manifestations and phenotype result from a constellation of genotypic mutations.

This is precisely why targeted therapies are so critical to the rare disease patient population as therapies that target the genetic underpinnings of the disease hold the most promise for substantial life improvements.

This is also why efforts from FDA, such as the creation of this Draft Guidance, are crucial in advancing innovative drug development for rare disease patients with genetic diseases. Additional guidance from FDA on how industry can best conduct uniquely innovative and flexible clinical trial models is particularly valuable.

Genetic subtypes of an already rare disease result in even smaller patient populations that may be amenable to targeted therapies. Such small populations have an even smaller likelihood of drug development due to their incredibly low prevalence.

Before offering a handful of areas to improve within this Draft Guidance, there are several incredibly important facets of this proposal that we wish to highlight.

First, we applaud FDA for its willingness to, “accept grouping patients [within clinical trials] with different molecular alterations if it is reasonable to expect that the grouped patients will have similar pharmacological responses based on a strong scientific rationale.” With the pharmaceutical industry’s propensity for narrow inclusion criteria for clinical trials, FDA’s encouragement for, “grouping patients with different molecular alterations” is critical to ensuring all patients who may benefit from the therapy are able to participate. FDA clearly supports this goal, stating, “[i]deally clinical trial assays should be designed to detect all possible molecular alterations that comprise the group that is expected to respond.”

We also thank FDA for its consideration of various evidence to support clinical trial grouping. We urge FDA to continue to encourage industry to explore all options of evidence generation, particularly since some methods may be impractical, or at the very least particularly difficult, within certain patient populations.

FDA’s acceptance of, “evidence from other drugs in the same pharmacological class” is also incredibly valuable in order to reduce inefficiencies and the regeneration of already-existing evidence.

Second, we strongly support FDA’s suggestions for extrapolation across genetic subtypes. Including each genetic subtype that may benefit from the therapy within the clinical trial can be prohibitive. Thus, using other forms of evidence for effectiveness, in order to include all potential patients who may benefit within the label, is important. This will facilitate better prescribing and access to the therapy once on the market.

Third, we support FDA’s suggestion for, “an FDA— cleared or — approved assay” for the diagnosis of the molecular subtype to be available at time of approval, with a potential exception in the case of serious or life-threatening conditions. Accurate diagnoses, particularly when treating genetic subtypes with targeted therapies, is critical. Industry developing these therapies should also ensure accurate diagnosis, as FDA requests.

Finally, FDA’s consideration of an incremental expansion of the population eligible for a drug is important in expanding a drug’s availability to additional subpopulations. However, we would prefer FDA to encourage this expansion, not simply acknowledge its possibility.

There are several additional areas in which FDA can improve this draft guidance prior to finalization. For example, the guidance could use additional clarity on how best to extrapolate data from studies conducted prior to the current development pathway. Given the time difference, and potential for varying data collection methods, further instruction from FDA on how historical data sets can be used as evidence would be helpful.

Two of the more significant omissions from this draft guidance are instructions for extrapolating data across diseases with similar molecular underpinnings and for using data from a different sponsor to support approval of a targeted therapy.

The Advancing Targeted Therapies for Rare Diseases Act, which NORD assisted in authoring and was enacted as part of the 21<sup>st</sup> Century Cures Act, was specifically written in order to facilitate data extrapolation not only between molecular subtypes of the same phenotypic disease, but also between molecularly-related, but phenotypically different, diseases.

The statutory text reads, “[t]he purpose of this section...is to facilitate the development, review, and approval of genetically targeted drugs and variant protein targeted drugs to address an unmet medical need in one or more patient subgroups, including subgroups of patients with different mutations of a gene.”<sup>1</sup> The statutory text does not preclude FDA from including guidance on how to extrapolate among genetic subtypes of phenotypically different diseases with highly similar molecular underpinnings. We request FDA to revise this draft guidance to include such instructions.

Finally, FDA does little to clarify how companies can go about using data from other sponsors or really any entity that is not the originating sponsor itself. Additional clarity from FDA on how to navigate these situations would be helpful.

We thank FDA for the opportunity to comment and we look forward to working with FDA in facilitating and encouraging the development of targeted therapies. 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

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<sup>1</sup> 21<sup>st</sup> Century Cures Act, 21 U.S. Code § 360ff-1 (2016)