September 25, 2018

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA 2018-D-2456: FDA Draft Guidance Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition that Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance on Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition that Results from Dingle Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO appreciates the Agency's efforts to support and advance drug development for individuals with rare diseases, including through the issuance of this Draft Guidance to clarify considerations for the development and types and amount of evidence and data to support effectiveness of slowly progressive rare diseases characterized by substrate deposition resulting from single enzyme defects.

In the Draft Guidance, the Agency uses the term "low-prevalence rare disease" and defines it as a condition affecting approximately 5,000 persons or less (page 1, footnote 3). BIO believes that the criteria outlined namely Slowly Progressive, Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects is sufficient to characterize and appropriately describe the diseases to which the Draft Guidance applies. Accordingly, the terminology "low prevalence rare disease" should be eliminated from the guidance when finalized.

BIO notes that terminology that subdivides "rare disease" (e.g., ultra-rare) has been used in literature and by Commissioner Gottlieb (Taking New Steps to Meet the Challenges of Rare Diseases — FDA Marks the 11th Rare Disease Day on February 26th, 2018) nevertheless, currently there are no statutory or regulatory definitions for such terminology. Additionally, while the footnote defining "a disease of low prevalence" as a condition affecting approximately 5,000 persons or less in the United States is caveated by the phrase "for the purposes of this guidance", it nonetheless could be subsequently interpreted as precedent setting and the qualitative descriptor "low" may imply that there are rare diseases in the "medium" or "high" prevalence range. Additionally, the same footnote in the Draft Guidance

1201 Maryland Avenue SW
Suite 900
Washington DC 20024
202.962.9200 P
202.488.6306 F
bio.org

goes on to reference 21 U.S.C.360bb which is a statutorily defined limit for products that are eligible for orphan designation. Using the statute in conjunction with a new definition (i.e. disease of low prevalence) is also confusing and potentially misleading.

Taken together, proliferation of multiple terms that are ill-defined from a statutory and regulatory perspective could potentially have unintended consequences and should be curtailed until such time as consensus around these terms is achieved. BIO encourages the Agency to continue to employ the established definition and terminology of a rare disease (i.e., affecting less than 200,000 persons in the United States) and remove reference to "low prevalence" in the Draft Guidance.

BIO appreciates this opportunity to submit comments regarding FDA's Draft Guidance, Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition that Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
Danielle Friend, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 19-22, 28-30, 32-33, and Footnote 3	In the title of the Draft Guidance and lines 19-22, 28-30, and 32-33, FDA's Draft Guidance utilizes the term "low-prevalence" rare disease, defined as (footnote 3, page 1): "*For the purposes of this guidance, a disease of low prevalence is defined as a condition affecting approximately 5,000 persons or less in the United States. To be eligible for orphan drug designation, product must be one for a disease or condition that: "(A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug" (21 U.S.C. 360bb).*" "Low prevalence" is not defined in statute or in any prior regulatory document. Defining and establishing a smaller subset (e.g. < 5000) within the current rare disease definition of 200,000 or less in the US may contribute to regulatory and policy uncertainty resulting in potential rare disease product development delays beyond those within the scope of this Draft Guidance.	BIO recommends that the Agency remove "low-prevalence" from the Draft Guidance a well as a definition of "low-prevalence" as outlined below: 1. Slowly Progressive, ~~**Low-Prevalence**~~ Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects "~~**For the purposes of this guidance, a disease of low prevalence is defined as a condition affecting approximately 5,000 persons or less in the United States.**~~ To be eligible for orphan drug designation, product must be one for a disease or condition that: "(A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug" (21 U.S.C. 360bb)."
II. DRUG DEVELOPMENT CONSIDERATIONS		

SECTION	ISSUE	PROPOSED CHANGE
III. TYPE AND QUANTITY OF EVIDENCE NECESSARY TO SUPPORT EFFECTIVENESS FOR REPLACEMENT OR CORRECTIVETHERAPIES		
C. Animal Toxicology/Pharmacology and Animal Models of Disease Activity – Key Considerations		
D. First-in-Human Dosing and Dose Selection – Key Considerations		
E. Providing Evidence of Substrate Reduction		
A. Other Considerations		
REFERENCES		