Biotechnology Industry Organization

July 13, 2015

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

**Re: Docket No. FDA-2015-D-1246: Draft Guidance on Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment**

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment."

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BIO appreciates the release of this Draft Guidance and, overall, believes it to be well thought-out and written. It provides clarity and insights on FDA's flexibility for Sponsors to optimize the design of efficient nonclinical programs to support the development of Enzyme Replacement Therapy products (ERTs).

We note that the Draft Guidance contains recommendations for Sponsors to consult with the responsible review division to obtain agreement on study design before study initiation in a number of sections of the document (lines 193-195, 208-209, 224-225, and 379-388). In order to minimize redundancy, BIO suggests moving this recommendation to line 116 at the end of the introductory part of section III.B. (Recommendations for General Nonclinical Program Design), and delete the repetitive recommendations presently in lines 193-195, 208-209, and 224-225.

We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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**SPECIFIC COMMENTS**

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| **I. INTRODUCTION** | | |
| **II. BACKGROUND** | | |
| **III. NONCLINICAL STUDY CONSIDERATIONS** | | |
| *A. NONCLINICAL PROGRAM OBJECTIVES* | | |
| **Lines 85-86:** | The Draft Guidance discusses demonstrating biological plausibility and identifying biologically active dose levels. | BIO believes that "biologically active dose levels' needs to be clarified. For example, is FDA looking at serum level or tissue level? If FDA is looking at tissue level, this may be a high standard and could be tissue-dependent as some tissues may be easier to treat. Relatedly, what dose level is considered efficacious and what is this based on? Additionally, we note that the biologically active dose level may not be transferrable between species, because animal disease models may not represent 100% of human diseases, and immunogenicity or hypersensitivity could prevent the testing of higher doses in animals. |
| **Lines 88-92:** | The Draft Guidance discusses safety assessments informing the dose escalation schedule. | BIO believes that this needs to be clarified. Is FDA looking for dose escalation intra-group or inter-group? We believe that for inter-group, "dosing frequency" will address this topic, if needed, based on in vitro and/or animal studies. For intra-group, it may be unnecessary, and may be infeasible to do so in animals depending on the type of studies. |
| **Line 93:** | In order to ensure consistency with other nonclinical guidance documents, we suggest adding a 3rd bullet under "Nonclinical Program Objectives." | We suggest adding the following bullet:<br><br>"This guidance aims to facilitate and accelerate the development of ERT pharmaceuticals and to protect patients from unnecessary adverse effects, while avoiding unnecessary use of animals, in accordance with the 3R |

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| | | principles (reduce/refine/replace), and other resources." |
| *B. RECOMMENDATIONS FOR GENERAL NONCLINICAL PROGRAM DESIGN* | | |
| **Lines 109-111:** | The Draft Guidance states, "The availability of existing relevant safety information with the proposed clinical delivery device or delivery procedure for the product, or with any related device or procedure." | This issue is not unique to ERT products and is not particularly useful in the context of designing nonclinical development programs for ERT products. As such, BIO believes this bullet should be deleted. |
| **Lines 119-120:** | The Draft Guidance states, "The investigational ERT product that will be administered to the patient population should be used in the pivotal nonclinical studies (*i.e.,* studies used to determine a safe dose in humans)." | BIO would like FDA to confirm whether the product used in pivotal nonclinical studies needs to be from the same batch or just needs to be the same sequence as the product that will be used in the patient population. |
| **Lines 121-123:** | The Draft Guidance states, "Each lot of an investigational ERT product used in the nonclinical studies should be characterized according to prospectively established criteria, consistent with the stage of product development." | Investigational product should be characterized initially and after significant manufacturing process changes, but it is not necessary to re-characterize every single lot. As such, we suggest the statement be edited to read:<br><br>"~~Each lot of an I~~ Investigational ERT product used in the nonclinical studies should be characterized according to prospectively established criteria, consistent with the stage of product development." |
| **Lines 125-126:** | The Draft Guidance states that "the safety of all ingredients should be supported for the intended clinical use." | BIO suggests moving this sentence up and adding as the 5th bullet point under B (Line 94), or adding to 2nd bullet point (Line 106) under B (Line 94). This statement is important, in particular to highlight the need to address the safety of "novel" excipient(s) utilized in the formulations due to novel routes of administrations (RoAs) and clarify the Agency's |

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| | | expectation. |
| **Lines 142-169:** | The Draft Guidance states that animal disease models deficient in the targeted enzyme are preferable to using healthy animals in toxicology in some cases. In the same section it is acknowledged that the use of animal models of disease in toxicity studies has limitations and challenges that are not supportive of using such models in toxicology studies. | The text in the section is unclear regarding expectations and circumstances in which animal models of disease should be considered. On one hand, the text indicates the preference of using animal disease models over the use of healthy animals in "some" toxicology studies. On the other hand, the text cites a publication by Morgan et al. (2013), which states that "targeted animal models are typically inappropriate to use in general toxicity studies… Instead, animal models should be utilized in a second or third tier approach to elucidate safety risks that were identified in the first trier of traditional nonclinical safety studies."<br><br>BIO asks FDA to clarify its recommendations regarding the use of healthy animals versus animal models of diseases for the purpose of safety evaluation. |
| **Lines 154-155:** | The Draft Guidances references a publication by Morgan et al. regarding technical challenges and considerations for the use of animal disease models in safety studies. | BIO believes that the reference to the technical challenges described in the Morgan publication needs to be balanced with mention of the potential benefits associated with use of an animal disease model. Important disease phenotypes also influence the safety profile of the drug. As such, we suggest editing the statement to read:<br><br>"A publication by Morgan et al. (2013) provides a detailed discussion of the technical challenges and considerations for the use of animal disease models in safety studies. Consideration of the strengths of animal disease models should also be evaluated with respect to the ERT's mechanism of action on disease phenotype, physiological |

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| | | function and potential for generation of large amount of systemic catabolite(s) upon repeat administration." |
| **Lines 201-275:** | The Draft Guidance states that "sponsors can consider study designs that use animal models of disease that incorporate important safety parameters that allow for assessment of the potential toxicity" and "to prospectively assess toxicology endpoints, including microscopic examinations of tissues" in nonclinical proof-of-concept (POC) studies.<br>Later on, the section indicates that toxicology studies to support FIH in a disease that rapidly progress to death should include 1-month studies in rodents and non-rodents.<br><br>While the concept of leveraging POC studies to assess safety of ERT products may be a valuable approach, the recommendation to use two relevant species (where defining relevant species may be a challenge) in toxicology studies seems to be excessive and very conservative to support FIH trials in diseases that rapidly progress to death. Particularly, when safety endpoints could be included in POC animal models, toxicology studies in one species should be sufficient for a biologic product that is an analog of human enzyme. | BIO asks FDA to revise the text to align recommendations with the current intent to reduce animal use when safety of a product can be characterized in limited nonclinical studies (*e.g.,* safety endpoints in pharmacology studies and toxicology studies in one species). |
| **Lines 203-206:** | The Draft Guidance states, "POC studies in relevant animal disease model(s) modified to prospectively assess toxicology endpoints, including microscopic examinations of tissues, should be considered as support for initiation of human clinical trials." | BIO suggests editing the statement to read:<br><br>"POC studies in relevant animal disease model(s) modified to prospectively assess toxicology endpoints, including microscopic examinations of tissues, should be considered as |

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| | | support for initiation of human clinical trials potentially in lieu of a standalone toxicology study." |
| **Lines 220:** | The Draft Guidance states, "An adequate number of animals per sex that are appropriately randomized to each group." | BIO believes that the constraints of conducting studies in animal disease models and the risk-benefit relationship in the particular indication being studied should be accounted for in the design of these studies. As such, BIO suggests editing the text to read:<br><br>"An ~~adequate~~ appropriate number of animals per sex that are ~~appropriately randomized~~ assigned to each group." |
| **Lines 244-247:** | The Draft Guidance discusses including a vehicle control group and a vehicle plus antihistamine control group. | The effects of diphenhydramine (DPH) are well known for certain study types. As such, BIO suggests adding the following language:<br><br>"When it is necessary to co-administer an antihistamine (*e.g.,* diphenhydramine) to control hypersensitivity reactions to the ERT, the study should include a vehicle control group, and a vehicle plus antihistamine control group should also be considered taking into account the species and study type." |
| **Lines 272-275:** | The Draft Guidance states, "If the entry criteria define a phenotype that can be expected to rapidly progress to death or substantive irreversible morbidity over the course of 1 year, then repeat-dose toxicology studies in a rodent and a non-rodent species of 1-month dosing duration may be sufficient to initiate clinical trials." | While we acknowledge a benefit-risk profile must fit the nonclinical program, the current criteria would apply only to the severe forms of a rare genetic disease. The diagnosis of a disease with a disease progression of only one year to mortality and/or irreversible morbidity is unlikely to be diagnosed or treated in a timely fashion due to the rarity of the disease. An exception is for a younger sibling diagnosed with a disease after their older sibling.<br><br>The definition of disease severity and progression would be |

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| | | better served using the ICH S9 language with appropriate evaluation of benefit-risk.<br><br>As such, we suggest revising the text to read:<br><br>"If the entry criteria define a phenotype that can be expected to rapidly progress to death or substantive rapid irreversible morbidity resulting in a severe loss of quality of life, ~~over the course of 1 year,~~ then repeat-dose toxicology studies in a relevant rodent and a non-rodent species of 1-month dosing duration may be sufficient to initiate clinical trials." |
| **Lines 272-287; 363-375:** | | BIO is encouraged to see the Agency is not requiring a 6-month study to enable FIH (and for marketing applications – see Lines 349-350), but rather provides flexibility for Sponsors to conduct 1-month or 3-month studies to support FIH depending on disease progress/phenotype. However, it is not clear whether the Agency would allow topline data, or interim-reports, or unaudited reports from these studies at the time of IND submissions. We suggest that FDA clarify in lines 272-287 of the Draft Guidance, per Line 363 and below, that complete reports of these 1-month or 3-month studies are expected to support the safety of clinical trials. |
| **Lines 272-275:** | The Draft Guidance states, "If the entry criteria define a phenotype that can be expected to rapidly progress to death or substantive irreversible morbidity over the course of 1 year, then repeat-dose toxicology studies in a rodent and a non-rodent species of 1-month dosing duration may be sufficient | BIO asks FDA about a case where an animal model of disease is the chosen species for toxicology; would there still be a need to do a second species, especially if adequate justification is provided that a healthy animal model is unlikely to provide additional safety information? BIO suggests that in such a case, a second species would not be |

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| | to initiate clinical trials." | necessary. |
| **Lines 283-287:** | The Draft Guidance discusses the toxicology studies needed to initiate first-in-human trials when there is a slower disease progression expected. | BIO suggests editing the text to read:<br><br>"If the clinical trial entry criteria define a phenotype that would be expected to have slower disease progression, then toxicology studies in ~~a rodent and a non-rodent~~ the appropriate species of at least 3 months' duration will be ~~needed~~ sufficient to initiate first-in-human trials and to support market approval~~; this is because, given the chronic nature of these rare diseases, and unmet medical need, chronic dosing would be expected to start with first-in-human exposures~~." |
| **Lines 301-306:** | The Draft Guidance discusses safety endpoints. | BIO believes that clarification that data can be obtained from safety pharmacology studies would be helpful. As such, we suggest editing the statement to read:<br><br>"Safety endpoints that capture potential toxicities. Standard parameters evaluated should include mortality (with cause of death determined, if possible), clinical observations, body weights, physical examinations, food consumption or appetite, water consumption (as applicable), clinical pathology (serum chemistry, hematology, coagulation, urinalysis), organ weights, gross pathology, and histopathology. An assessment of the pharmaceutical's effect on vital organ functions (including cardiovascular, respiratory, and central nervous systems) should be available before the initiation of clinical studies; such parameters could be included in general toxicology studies. Detailed clinical observations following dosing and |

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| | | appropriate electrocardiographic measurements in nonrodents are generally considered sufficient. Additional developmental endpoints may be appropriate when conducting juvenile animal studies." |
| **Lines 342-345:** | The Draft Guidance states, "For example, if manufacturing or formulation changes occur such that the comparability of the later-phase ERT product to the product used in early-phase clinical trial(s) is uncertain, additional in vitro and/or in vivo nonclinical studies may be needed to bridge the two products." | BIO suggests editing the statement to read:<br><br>"For example, if manufacturing or formulation changes occur such that the comparability of the later-phase ERT product such that the analytical comparability to the product used in early-phase clinical trial(s) is uncertain, additional in vitro and/or in vivo nonclinical studies may be needed to bridge the two products." |
| **Lines 355-357:** | The Draft Guidance states, "However, flexibility in timing or requirements for specific studies may be warranted in certain cases with adequate justification. Certain studies can be waived or delayed until after licensure or approval depending on the indicated patient population." | BIO believes that it would be helpful for FDA to provide some examples on what can be waived or delayed to post-approval. |