Biotechnology Innovation Organization

February 5, 2018

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

Re: Docket No. FDA-2017-N-6476: Pediatric Rare Diseases-A Collaborative Approach for Drug Development Using Gaucher Disease as a Model; Draft Guidance for Industry; Availability

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) appreciates the opportunity to provide comments to the Food and Drug Administration's (FDA or Agency) Draft Guidance for Industry "Pediatric Rare Diseases-A Collaborative Approach for Drug Development Using Gaucher Disease as a Model" (Draft Guidance).

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's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO appreciates the FDA's intended goal of the Draft Guidance, which is to reduce the total number of children needed for enrollment in clinical studies. We also applaud the Agency's willingness to accept innovative trial designs to limit the number of patients in the control arm and improve trial efficiency. However, BIO has several concerns regarding the Draft Guidance, particularly in reference to the FDA's suggestion for the use of multi-arm, multi-company clinical studies, which have inherent limitations and challenges. BIO has identified the following concerns with respect to this Draft Guidance which are addressed in more detail below:

1. The Draft Guidance lacks detail regarding applicability across a broad range of rare diseases.

2. The Draft Guidance outlines the use of multi-arm, multi-company clinical studies, but does not provide procedural information regarding how challenges of this approach will be addressed.

3. The Draft Guidance fails to address other possible methodologies that would help reduce the total number of children required for enrollment in clinical trials.

In addition to the concerns mentioned above, BIO has also provided additional comments and line edits beginning on page six of this letter.

1201 Maryland Avenue SW
Suite 900
Washington DC 20024

202.962.9200 P
202.488.6306 F
bio.org

1. The Draft Guidance lacks detail regarding applicability across a broad range of rare diseases

BIO is concerned that the Draft Guidance is positioned as an approach for supporting rare disease drug development; however, the Guidance lacks detail and clarity regarding how the approach may be utilized more broadly in drug development for other rare diseases beyond Gaucher disease. Additionally, it is unclear which concepts in the Draft Guidance are specific to Gaucher disease, and which concepts would apply more generally to pediatric rare diseases. The Guidance also does not indicate disease states (beyond Gaucher disease) where the outlined approaches may, or may not, be feasible. The Guidance also leaves out important details that would be needed to implement the outlined approaches. For example additional information regarding the identification of endpoints, study design, operational information regarding cross-center registries, and extrapolation is needed. Beginning on page six in this comment letter we have also outlined several other additional areas in need of clarification in order for broad use of the Guidance. Given the lack of detail, BIO requests that the FDA re-position the Draft Guidance as a disease-specific guidance, or at a minimum, provide greater clarity and detail regarding how the specific approaches outlined in the Guidance may be used more broadly for a wider range rare diseases.

2. The Draft Guidance outlines the use of multi-arm, multi-company clinical studies, but does not provide procedural information regarding how challenges of this approach will be addressed

BIO has several concerns regarding the recommendations for the use of multi-arm, multi-company trials for rare diseases. As noted in the Draft Guidance (lines 252-255), there are inherent challenges associated with conducting multi-arm, multi-company clinical trials. BIO does not believe that the FDA has provided adequate information to address many of the regulatory challenges presented by the use of multi-arm, multi-company trials. Specifically, BIO requests greater detail regarding the FDA's procedural approach for ensuring that such a multi-arm, multi-company trial receives adequate divisional review. The Guidance document also fails to address important questions such as:

a. How a multi-arm, multi-company study might meet requirements for the Best Pharmaceutical for Children Act (BPCA) or the Pediatric Research Equity Act (PREA);
b. How multiple companies and the FDA will agree on pediatric study plans when a written requests has been issued;
c. How companies that are conducting a multi-arm, multi-company trial may qualify for rewards linked to a completed written request;
d. How multi-arm, multi-company trials might be coordinated when multiple investigational new drugs or investigational products do not reach milestones at the same time;
e. Whether the FDA will identify a third-party convener to facilitate the multi-arm, multi-company trial process to address anti-trust considerations that

may prohibit competitive companies in early/late phase development from some necessary activities related to the implementation of such an approach; and

f. How to address the scenario when a novel agent emerges years into a study. If this compound is also tested, then at the time of filing, Regulatory Agencies may ask if comparison to the control arm which started enrollment years previously is appropriate, especially since in some indications, overall survival improves over time, due to measures such as improved supportive care of medical issues related to cancer.

In addition to the issues mentioned above, BIO is also concerned about issues such as the protection of proprietary information and the governance of multi-arm, multi-company clinical trials. We ask the FDA to provide more clarity on how these challenges may be addressed. We also ask the FDA to consider that the challenges and potential negative consequences of the approaches outlined in the Draft Guidance may result in the perception of lack of incentives for pediatric rare disease drug development and ultimately a lack of interest in developing products for pediatric rare diseases.

3. The Draft Guidance fails to address other possible methodologies that would help reduce the total number of children required for enrollment in clinical trials

BIO believes that there are numerous approaches and methodologies, beyond the conduct of multi-arm, multi-company clinical trials, which can and should be considered to facilitate efficient product development in rare diseases. These approaches and methodologies include the use of modeling and simulation; innovative clinical trial designs; biomarkers and surrogate endpoints; and historical controls; as well as support for patient organizations to maintain data for universal control arms. While the goal of the Draft Guidance is to help reduce the total number of children needed for enrollment in clinical trials, the FDA fails to describe or support these approaches in the Draft Guidance. BIO also requests that the FDA reference other initiatives that are developing master protocols in support of collaborative development such the Lung-MAP and I-SPY and those mentioned in New England Journal of Medicine article by Janet Woodcock[1] or those discussed at the September 2016 Pediatric Master Protocols workshop,[2] or the TransCelerate template.[3]

Additional Comments:

- The Guidance states in several locations (lines 30-32, 96-99, 244-245, 259-262 and table 1) that the recommendations regarding drug development for Gaucher disease applies only to systemic, non-neurological manifestations of Gaucher

[1] Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both, New England Journal of Medicine,
[2] Pediatric Master Protocols, FDA University of Maryland CERSI Co-sponsored Workshop,
[3] Common Protocol Template, TransCelerate BIOPHARMA Inc.

disease. We ask the FDA to clarify whether the recommendations in this Guidance that can apply to other pediatric rare diseases, would only be applicable in non-neurological pediatric rare diseases and non-neurological manifestations of pediatric rare diseases only, or instead would they apply to other pediatric rare diseases with neurological manifestations.

- We ask that the FDA provide clarity on whether concepts discussed in section III, Nonclinical and Clinical Considerations, apply only to drug development programs that utilize the proposed new multi-company trial, or in general to drug development for pediatric rare diseases.

- Enzyme replacement therapies (ERTs) are the current standard of care for pediatric Gaucher disease for the non-neurological (i.e., somatic) manifestations of the disease in patients with Type I and Type III phenotype. While we encourage development of new and innovative products, BIO is concerned about the overall negative tone toward ERTs conveyed in the Guidance. Since the Guidance intends for the industry to apply the recommendations to other pediatric rare diseases, where ERTs may not be the standard of care (SOC), we recommend replacing references to ERT with SOC more generally. We also recommend using the term SOC rather than specifying ERT, as the SOC may evolve over time and the use of the term SOC will provide longevity to the guidance as well as broad applicability across different pediatric rare diseases.

- We appreciate the FDA's recommendation for cross-registry agreement, we agree with the concept of a uniform set of core data elements to be collected by all existing or future disease registries. To this end, we request that the FDA provide guidance regarding:
    - How the FDA envisions such cross-registry agreements to operationalize;
    - Who the FDA envisions should manage such agreements, and develop and maintain the uniform set of core data elements. It is important to note that typically registries are driven by patient groups or academic centers;
    - How such data will be used and who it will be shared with; and
    - How the FDA envisions this approach to apply to other pediatric rare diseases.

- The Guidance makes note of age-specific endpoints but disease-specific endpoints are not specified. We ask the FDA to acknowledge and consider the challenge of developing and validating endpoints with a small population size, as is the case for rare diseases. We ask the FDA to provide specific guidance on identification of endpoints, with examples of what has been successful and what the sponsors should avoid, and specifically when it is possible and acceptable for the patient group to contribute to identification of endpoints and outcome measures. We also ask the FDA to provide guidance on possible scenarios when the endpoint and study design are robust and rigorous, but there is discordance between the selected endpoints and/or study design, and the patient preference.

- Finally, BIO recommends that the FDA Rare Disease staff be sufficiently staffed to serve as subject matter experts to help educate Review Division staff on how to effectively operationalize these collaborative approaches.

BIO appreciates this opportunity to submit comments regarding FDA's Draft Guidance: "Pediatric Rare Diseases-A Collaborative Approach for Drug Development Using Gaucher Disease as a Model". Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

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

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 37	This section states "Sponsors are advised to consult the appropriate regulatory agency(ies) prior to initiation of such trials." As implied by the text, clinical trials in pediatric rare diseases (particularly oncology populations) typically require conducting the study in multiple countries to enroll sufficient numbers of patients to satisfy FDA requirements. Use of existing processes for reaching agreement on a study design when two regulatory agencies are involved can take years.	We ask the FDA to establish and provide guidance on a timely mechanism for consulting multiple regulatory agencies simultaneously and reconciling differing recommendations on study designs prior to initiating the trial in these pediatric rare disease settings.
II. BACKGROUND		
Disease Characteristics and Response to Treatment		
Unmet Needs in Pediatric Gaucher Disease		
III. Nonclinical and Clinical Considerations		
Nonclinical Models of Gaucher Disease		
Endpoint Assessment in Gaucher Disease		
Lines 136-137	The Guidance makes note of age-specific endpoints but disease-specific endpoints are not specified.	BIO asks that FDA acknowledge the challenge of developing and validating endpoints with a small population size (rare diseases).
Lines 137-138	Many pediatric rare diseases lack natural history data.	BIO asks FDA to provide specific guidance on identification of endpoints, with examples of what has been successful in the past and what sponsors should avoid, and specifically when it is possible and acceptable for the patient group to contribute to identification of endpoints and outcome measures.

SECTION	ISSUE	PROPOSED CHANGE
Lines 144-147		We ask FDA to provide guidance on possible scenario when the endpoint and study design are robust and rigorous, but there is discordance between the selected endpoints and/or study design, and the patient preference— e.g., patient preference is for other endpoints.
Line 149	The Draft Guidance states: "If for any reason studies cannot be blinded, biases should be addressed." However, there is no additional detail, recommendations, or examples that Sponsors should take into account in addressing biases.	BIO recommends that FDA expand the guidance to provide specific examples of biases that would arise as well as acceptable approaches to address them that would be acceptable to the Agency.
Long-term Clinical Aspects		
Lines 188-195	We appreciate the concept of a uniform set of core data elements to be collected by all existing or future disease registries; however, we feel that the FDA needs to provide additional detail regarding the operationalization of such an approach.	BIO believes that further guidance on following would be helpful: i. How does FDA envision such across-registry agreements to operationalize? It is possible that the first registry that is set-up may set the tone/standards for future registries that join in as part of a cross-registry agreements. If the first registry is restrictive, future registries will stay restrictive as well, or are bound by the limits set by the first registry. ii. It is important to clarify who FDA envisions managing such agreements, and should develop and maintain the uniform set of core data elements. iii. How will such data be used and who will it be shared with?

SECTION	ISSUE	PROPOSED CHANGE
		iv. How does FDA envision this to apply to other pediatric rare diseases?
The Use of Extrapolation of Efficacy for Pediatric Gaucher Disease		
		If this is Guidance is to serve as a model for pediatric rare disease drug development, we ask the FDA to clarify how the section on extrapolation of efficacy for Gaucher disease can be generalized to extrapolation of efficacy for all pediatric rare diseases, and how the guidance will be reconciled with current and ongoing regulatory efforts on extrapolation (e.g., ICH E11, FDA guidance)
Lines 216	Line 216 reads, "…growth rate, onset of puberty and progression of pubertal development) are not amenable to extrapolation. These characteristics should be specifically addressed in pediatric studies." These types of demands can only be made if applicable to the population of interest. For example, clinical trials in relapsed pediatric oncology patients will have such a high rate of mortality due to progressive disease that it will be fortunate if one or two patients attain long term survival. The cost of keeping a trial open indefinitely versus the knowledge gained from one or two patients is a burden to companies.	We ask the FDA to consider alternatives that might be considered, including late effects study in which all patients who are on clinical trials are enrolled into an ongoing study that continues to monitor side effects indefinitely.
IV. The Proposed Multi-Arm, Multi-Company Trial for Pediatric Gaucher Disease		
Table 1	In the section on 'Study design features' it is unclear when arms of the study might start.	We ask the FDA to provide clarity on whether all arms would start at the same time.

SECTION	ISSUE	PROPOSED CHANGE
Table 1	In the section on 'major objectives: to evaluate noninferiority or superiority of new drug products to an improved ERT treatment' it is unclear requirements the FDA might have for sample sizes.	We ask the FDA to provide information on sample size requirements.
Table 1	In the section on 'study population and subset definition', in some countries the pediatric upper limit is above 18, but this not true for all countries.	To be more globally applicable, we ask the FDA to use more general terms.
Table 1	In the section 'Number of Study Participants by Pediatric subset (e.g., age, sex, severity, or stage) is unclear.	The calculated sample size should be sufficient to detect noninferiority in the proposed primary endpoint with at least 80% power and a type I error rate of 0.025 for each investigational drug product in the trial. Superiority trials are acceptable. The noninferiority margin should be carefully chosen and prespecified. This is particularly crucial because the assay sensitivity of the trial cannot be assessed ~~in the usual way~~ as in placebo controlled studies due to lack of a placebo control group. Consulting regulatory bodies for scientific advice about this issue before study start is therefore highly recommended.
Table 1	In the section 'Main Inclusion Criteria,' it is not clear what the FDA's thoughts are regarding stratification.	We ask the FDA to clarify whether there would be any stratification by pediatric age range (e.g., 0-23 months; 2-11 years; 12-18 years). BIO also requests that the Guidance be edited to define the required grade of disease severity" for enrolled patients as part of the inclusion criteria. Namely, if change *versus* baseline will be a main measure for the most relevant endpoints (e.g., hemoglobin or platelet count), only patients should be included who show some grade of disease severity, otherwise no treatment effect versus baseline can be shown (e.g., a patient with normal hemoglobin at

SECTION	ISSUE	PROPOSED CHANGE
		baseline will show no increase in hemoglobin as result of the therapeutic intervention).
Table 1	In the section 'External independent Data Safety Monitoring Board,' it is unclear who might conduct the study, monitor the study, or have access to the generated data.	We ask the FDA to clarify who would conduct the study, monitor the study, and have access to the data.
Table 1	In the "Dosage, treatment regimen, route of administration" and the Control(s) section it is unclear if the dose adaptation is current standard of care is in this section.	BIO recommends that the table specifically include reference to dose adaptation as current standard of care in this section.
Table 1	In the section on endpoint(s) with time(s) of assessment there are additional biomarkers that could be included.	BIO recommends that the suggested list in determining relevant endpoints be edited to include biomarkers such as lyso-Gb1, CCL18, or Chitotriosidase.
V. General References and Guidelines		