December 17, 2018

Dockets Management
Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2018-D-3268: FDA Draft Guidance, Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on the Draft Guidance for industry entitled Rare Diseases and Early Drug Development and the Role of Pre-IND Meetings.

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 applauds the FDA's initiative to continue to advance drug development and review for therapies to treat rare diseases by releasing the Draft Guidance on Rare Diseases: Early Drug Development and the Role of the Pre-IND Meetings. It is estimated that there are 7,000 identified rare diseases, and only 5% of those rare diseases have an approved therapy[1], underscoring the need for new therapies. The Draft Guidance provides important information to drug developers regarding Pre-IND meetings to support better the consistency, transparency, efficiency of drug development, and the review of rare disease therapies. BIO has included comments below as line edits for the FDA's review as the Draft Guidance is finalized.

BIO appreciates the Agency's consideration of our comments regarding FDA's Draft Guidance, Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings. 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

[1] National Institutes of Health, FAQs About Rare Diseases

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SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
II. BACKGROUND		
III. REGULATORY AND SCIENTIFIC CONSIDERATIONS		
Pharmaceutical Quality Considerations		
Nonclinical Considerations		
Lines 169-171	In this section the FDA details what Sponsors may discuss with the FDA at pre-IND meetings, however the FDA does not indicate that Sponsors may discuss combination toxicology studies to support clinical trials/development.	BIO requests that the FDA consider the following edit: "In a pre-IND meeting, Sponsors can discuss with FDA the additional nonclinical studies that may be necessary to support clinical trials (e.g., chronic toxicity, **combination drug toxicity testing**, developmental and reproductive toxicity (DART), carcinogenicity studies) and the timing of those studies, as applicable."
Clinical Pharmacology Considerations		
Lines 186-187	In this section, the FDA indicates that clinical pharmacology studies may serve as supportive evidence of effectiveness, however dose- or exposure-response studies could be substantial evidence rather than just supportive evidence.	BIO requests that the FDA consider the following edit: "Therefore, careful planning of the clinical pharmacology aspects of the drug development plan for a rare disease is important, because information from such studies and analyses can inform trial design and serve as ~~**supportive**~~ **substantial** evidence of effectiveness provided they meet the **requirements for adequate and well-controlled studies in 21 CFR 314.126."**
Lines 216-218	This section indicates that detailed synopses of all proposed studies including planned pharmacokinetic/pharmacodynamic sampling and	BIO requests that the FDA consider the following edits:

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	biomarker assessments that will inform dosing should be included to address specific clinical pharmacology questions, however there is no reference to exposure-response studies that contribute to substantial evidence and effectiveness.	"Detailed synopses of all proposed studies including planned pharmacokinetic/pharmacodynamic sampling and biomarker assessments that will inform dosing**, as well as exposure-response studies representing well-controlled clinical studies, that contribute to substantial evidence of effectiveness (where clinical endpoints or accepted surrogates are studied).**"
Clinical Considerations		
Lines 231	This section outlines challenges that Sponsors may face when it comes to rare disease drug development and indicates that lack of natural history data may be one of those challenges, however in some cases natural history of the disease is understood.	Bio requests that the FDA consider the following edit: "Sponsors developing drugs for rare diseases face many challenges. These may include the small number of disease-affected individuals, **potential** lack of understanding of the natural history of the disorder, lack of precedent for drug development (e.g., established clinical endpoints, validated biomarkers), phenotypic heterogeneity, and the need to conduct trials in pediatric populations, among others."
Lines 243-245, 281	The guidance currently states, "...it is appropriate for FDA to exercise the broadest possible scientific judgment in applying the evidentiary standard in the rare disease setting. To that end, FDA will consider: (1) benefits and risks of the drug; (2) seriousness of the disease; and (3) if there is an unmet medical need." BIO recommends that the guidance explicitly include the role of patient experience in the regulatory decision making process per the 21st Century Cures	BIO requests that the FDA consider the following edits: "To that end, FDA will consider: (1) benefits and risks of the drug; (2) seriousness of the disease; ~~**and**~~ (3) if there is an unmet medical need; **(4) and patient experience data in regulatory decision making.**" BIO acknowledges that the plan to develop guidance documents to support patient focused drug development are underway but also recognizes that patient experience data

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	Act, Title III Section 3002. Per the "Plan for Issuance of Patient-Focused Drug Development Guidance" (May 2017), "patients are in a unique position to contribute to an understanding of benefit-risk considerations...." and FDA Commissioner Gottlieb's statement to enhance the patient perspective and experience in drug development and review (March 2018).	has been used to support regulatory decision making today and has been presented in FDA approved product labeling. BIO also acknowledges that the guidance states, "Inclusion of patient perspectives in the drug development plan" (line 281) but recommends specific inclusion of "patient experience" in lines 243-245 as it pertains to evidentiary standard, particularly in the rare disease setting.
Lines 259-261	This section outlines items that the Sponsor may wish to discuss with the FDA at Pre-IND meetings, however, adaptive/seamless designs, RWE, and natural history data can all enhance efficiency in studying rare diseases and should be included as possible discussion items at Pre-IND meetings.	BIO requests that the FDA consider the following edits: "Description and rationale for the following: proposed clinical trial design(s) **including innovative clinical trial designs, such as adaptive/seamless or the use of Real World Data/Evidence (RWD/RWE),** efficacy endpoints, biomarkers trial population, patient selection criteria, choice of control group **(if using natural history data as a historical comparator, provide appropriate detail),** methods used to minimize bias overview of statistical analysis plan (including the sample size and power calculation when possible), and statistical analysis methods."
Lines 264-266	For this bullet it may be important for the FDA to reference the Agency's thinking that was included in the FDA *Guidance for Industry Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease October 2018.*	BIO requests that the FDA include an analogous bullet for targeted therapies in Low-Frequency Molecular Subsets of a Disease.
Line 287	This section indicates that considerations related to novel endpoints including the development of clinical	BIO requests the FDA to consider the following edits:

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	outcomes assessments (e.g., patient reported, observer reported, clinician reported, performance outcome measures) may also be items that a Sponsor may speak to the FDA about at Pre-IND meetings, however several additional items were not included in this bullet, including wearable devices and activity monitors which can contribute to novel endpoints, including the development of clinical outcomes assessments.	"Considerations related to novel endpoints including the development of clinical outcomes assessments (e.g., patient reported, observer reported, clinician reported, performance outcome measures, **wearable devices/activity monitors and other patient experience data**)."
IV. ADDITIONAL CONSIDERATIONS		
Expedited Programs for Serious Conditions		
Companion Diagnostics		
Orphan Drug Product Incentives		
Pediatric Studies		
Lines 347-348	This section indicates that prospect of direct benefit for pediatric studies can come from adult data, or in some instances, nonclinical animal disease models can also provide proof of concept that the investigational drug may have a beneficial effect in affected children, however, natural history data can also provide information regarding the direct benefit, (e.g., substantial improvement in outcome is observed with treatment in a disease that does not naturally remit).	BIO request that the FDA consider the following edit: "Prospect of direct benefit can come from adult data, **natural history data,** or in some instances, nonclinical animal disease models can also provide proof of concept that the investigational drug may have a beneficial effect in affected children."
Data Standards for Electronic Submission		
IV. REFERENCES		
Line 375		BIO requests that the FDA add the FDA several additions to the reference list, including:

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		• *Guidance for Industry Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease October 2018* • *Guidance for Industry Principles of Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product July 2016* • *Guidance for Industry Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics September 2018* • *Guidance for Industry Adaptive Designs for Clinical Trials of Drugs and Biologics September 2018* to the reference list.