April 1, 2019

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

Re: Docket No. FDA–2015-D-2818: FDA Draft Guidance, Rare Diseases: Common Issues in Drug Development.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the Draft Guidance on Rare Diseases: Common Issues in Drug Development. 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 diseases, and to prevent diseases in the first place.

BIO commends the FDA for its efforts to update the 2015 Draft Guidance on Rare Diseases: Common Issues in Drug Development. The updated Draft Guidance serves as an important communication tool between the FDA and Sponsors on issues pertaining to rare disease drug development. Such guidance ensures that Sponsors have appropriate information for developing new therapies for rare disease patients, especially given that many rare diseases still do not have an FDA approved treatment. In the following pages of this letter, BIO has included general comments as well as line edits that we believe will make the Draft Guidance more useful for rare disease drug developers.

Request for Additional Detail Pertaining to Drug Development Tools and Innovative Approaches and Trial Designs:
While BIO appreciates the FDA's work to update this Draft Guidance, we note that the Draft Guidance lacks detail pertaining to the use of new drug development tools that have been prioritized by the Agency in recent years, including, real-world evidence, innovative clinical trial designs, and development and use of biomarkers, among others. Additionally, there are several elements of drug development described within the Draft Guidance for which the Agency does not seem to provide specificity regarding rare diseases.

For example, the sections of the Draft Guidance focused on historical controls appears contrary to the FDA's overall sentiment outlined in the FDA's Framework on Real-World Evidence[1] where the Agency appears to be open to exploring the use of historical controls. Generally, the draft guidance implies that the FDA has taken the following positions:

- That prospective studies are more useful than retrospective;
- That prospective longitudinal studies are most useful; and

[1] Framework for FDA's Real-World Evidence Program.

- That retrospective studies typically cannot be used as an external control group.

More specifically, the Draft Guidance indicates that the FDA may not be open to use of retrospective historical controls, indicating that historic comparison only be conducted in "limited and special circumstances" and stating that "[t]hese limitations often preclude the use of such studies as an external control group for drug trials." Often, concurrent controls, especially for rare diseases, are infeasible. To this end, BIO requests that the FDA's final guidance discuss the utility of retrospective natural history studies, when appropriate, while limiting the discussion of the broad use of prospective natural history studies. The recommendation for prospective natural history studies when there is useful and usable retrospective natural history data available may lead to duplicative and redundant studies, impairing cost-effectiveness of drug development. BIO also requests that the FDA include in the Draft Guidance discussion on designs based on within-patient comparisons of pre- versus post-treatment outcomes.

Similarly, we request that the Agency provide additional information regarding how biomarkers can be leveraged as efficacy endpoints in the context of the rare disease therapies, including specifics on the acceptance of biomarkers as surrogate endpoints for accelerated approval. To further enhance the meaningful science-based use of biomarkers and surrogate endpoints, BIO recommends early FDA advice to Sponsors considering their use in clinical studies. To this extent, we appreciate the existence of one avenue for early advice from FDA on surrogate endpoints via a Type C meeting that was established under PDUFA VI and requires preliminary human clinical data. However, to facilitate an impactful early discussion with FDA, BIO recommends that the early discussion not be based necessarily on preliminary human clinical data, but on the potential for use of a surrogate endpoint based on prior experience and/or preclinical evidence and before human clinical data is collected. Collection of human clinical data, albeit preliminary, can still be a significant burden. This is especially important for rare diseases, where preclinical studies and very early human clinical studies that are not designed for efficacy assessment may form the basis of use of a surrogate endpoint. BIO recommends that the need for preliminary human clinical data for these meetings is eliminated or made optional for Sponsors developing rare disease products in order to maximize the usefulness of these meetings.

BIO applauds the Agency for continuing to support patient-focused drug development approaches in the context of rare diseases, particularly use of signs and symptoms which are most important to patients for development of sensitive endpoints and explicitly referencing "Patient-Focused Drug Development: Collecting Comprehensive and Representative Input"[2] and "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims"[3] guidances. Given the series of planned draft guidances under the Prescription Drug Use Fee Act (PDUFA) VI, we encourage the Agency to consider referencing those efforts as well.

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[2] FDA Draft Guidance on Patient-Focused Drug Development: Collecting Comprehensive and Reprehensive Input.
[3] FDA Guidance on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.

Request for Clarification and Additional Recommendations Related to Expanded Access:
BIO recognizes the value and regulatory flexibility by FDA's addition of "Auxiliary Safety Cohorts", particularly as this section relates to use of expanded access data. However, discussion during the November 2018 "Leveraging Real-World Treatment Experience from Expanded Access Protocols"[4] public meeting and resulting report, indicates that expanded access data could be used for other regulatory purposes, including[5]:

- Support of safety and efficacy, including previously unapproved products
- Label expansion for rare disease products

While the general consensus was that formal regulation was premature and unnecessary, this Draft Guidance presents an opportunity for FDA to provide recommendations, or recognize the potential uses of expanded access data to support efficacy. BIO, therefore, recommends that FDA expand this Draft Guidance to discuss ways in which data from expanded access programs can be used to support product efficacy.

Request for Additional Detail on Phenotype and Genotype of Rare Disease Patients:
In multiple sections, the Draft Guidance suggests that Sponsors should consider the "phenotype" of a given disease as an endpoint for the full range of the patient population under study. However, there can be disadvantages to only utilizing "phenotypes" of diseases to define endpoints. Additionally, the Draft Guidance does not include discussion regarding the "genotype" of patients, which may also be helpful in identifying clinical variance in certain rare diseases and sub-populations. Moreover, if genotype-phenotype correlations are identified, that information may help establish better endpoints for the clinical studies. Given that gene therapies are being developed to address rare diseases, it would be beneficial for the Draft Guidance to discuss the interplay between genotypes and phenotypes.

Request for Global Guidelines for Severely Debilitating or Life-Threatening Diseases:
BIO believes that this guidance forms a starting point for more general global guideline on development of therapeutics for severely debilitating or life-threatening diseases. Because there are diseases/indications that are severely-debilitating or life-threatening that do not qualify as rare diseases and a lack of international regulatory guidance to enable global development of severely debilitating or life-threatening disease therapeutics, we strongly encourage FDA to work with other Regulatory Authorities to develop a standardized global guideline for severely-debilitating or life-threatening diseases that applies across therapeutic areas and regardless of size of patient population.

Additional Comments:
We also urge the FDA to consider a more holistic approach in the guidance based on the totality of evidence emphasizing risk-based principles to evaluate the impact of manufacturing changes in rare disease setting.

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[4] Reagan-Udall Foundation Meeting on Leveraging Real-World Treatment Experience from Expanded Access Protocols
[5] Reagan-Udall Foundation Public Meeting Report on Leveraging Real-World Treatment Experience from Expanded Access Protocols

Finally, disease natural history is essential to drug development programs but are often poorly understood in the context of rare diseases. For this reason, BIO developed several comments pertaining to natural history studies for rare diseases in the context of this Draft Guidance. Given that the FDA released the Draft Guidance entitled *Rare Diseases: Natural History Studies for Drug Development*[6] at the end of March 2019, BIO has included specific comments pertaining natural history studies in the appendix of this letter. We are also looking forward to the opportunity to providing the FDA with additional comments to the Draft Guidance on *Rare Diseases: Natural History Studies for Drug Development*[6]*.*

In addition to the comments above, we have also included several line edits that can be found on the following pages. BIO appreciates this opportunity to submit comments regarding FDA's Draft Guidance, Rare Diseases: Common Issues in Drug Development. 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

[6] FDA Draft Guidance on Rare Diseases: Natural History Studies for Drug Development

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 19-23	In this section, the FDA indicates that "Although the statutory requirements for marketing approval for drugs to treat rare and common diseases are the same and issues discussed in this guidance are encountered in other drug development programs, these issues are frequently more difficult to address in the context of a rare disease for which there is often limited medical and scientific knowledge, natural history data, and drug development experience."	BIO requests the follow edits: "Although the statutory requirements for marketing approval for drugs to treat rare and common diseases are the same and **some** issues discussed in this guidance are encountered in other drug development programs, ~~**these**~~ **evidentiary** issues are frequently more difficult to address in the context of a rare disease for which there is often limited medical and scientific knowledge, natural history data, and drug development experience**, as well as a greater unmet need.**"
II. BACKGROUND		
Lines 75-78	The Draft Guidance states that "This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively."	BIO acknowledges the statement limiting the scope of this Draft Guidance as well as references provided, but also recognizes that there are many unique challenges and opportunities for statistical innovation in rare disease development which are not sufficiently covered by the referenced guidances. BIO, therefore, requests that the FDA expand this draft guidance to include additional comment and discussion of issues from a statistical perspective, including borrowing historical control or external data, use of Real-World Data and Evidence and statistical evidence needed for confirmatory trials.
III. NATURAL HISTORY		
A. Considerations for Natural History Studies		

SECTION	ISSUE	PROPOSED CHANGE
Lines 109-233	Section III, on "Natural History Studies" does not include sufficient information with regard to data collection and quality.	BIO requests that that the FDA expand the Natural History Studies section by adding a paragraph or subsection that addresses data considerations, including: • Data collection • Data verification/adjudication • Audit trail • Data standards
Lines 125-128	The bullet point indicates "Define the disease population, including a description of the full range of disease manifestations and identification of important disease subtypes. This may allow selection of patients more likely to progress and develop the endpoints assessed in the context of a clinical trial (prognostic enrichment)." Disease manifestation may result from primary or secondary effects, with the latter perhaps contributing to stage and severity and, therefore, may impact patient selection.	BIO recommends the following edits: "Define the disease population, including a description of the full range of disease manifestations **(e.g. primary or secondary)** and identification of important disease subtypes **that may affect disease stage and severity**. This may allow selection of patients more likely to progress and develop the endpoints assessed in the context of a clinical trial (prognostic enrichment)."
Line 133	In this section the FDA indicates "Select clinical endpoints and develop sensitive and specific outcome measures." We suggest that this sentence be edited as follows to reinforce that clinical endpoints should not just be measurable but also relevant and meaningful to patients and their caregivers.	BIO requests the follow edit: "Select clinical endpoints and develop sensitive**,** ~~**and**~~ specific, **and meaningful** outcome measures **that are relevant to patients and caregivers**."
Lines 140 - 141	This section indicates that "In special circumstances, such as when it may be impractical or unethical, a	BIO requests that the FDA consider the following edit:

SECTION	ISSUE	PROPOSED CHANGE
	well-designed and conducted natural history study can provide an external control group for interventional trials." However, data gathered through observational study designs (e.g., the natural history of the disease), could be appropriate to generate real-world evidence for the purpose of supporting effectiveness determinations, consistent with the *Framework for FDA's Real-World Evidence Program, December 2018.*	In special circumstances, such as when it may be impractical or unethical, a well-designed and conducted natural history study can provide an external control group for interventional trials. **Additionally, real world evidence, (e.g., natural history from an independent historical control group) could also be used as an external control group for interventional trials.**
Lines 161-163	The Draft Guidance states that "A Sponsor can modify the type and extent of data collection in a natural history study based on accumulated knowledge as the study proceeds."	BIO recommends the guidance discuss considerations for and approaches to how a Sponsor can modify a natural history study based on accumulated data as the study proceeds.
Lines 165 - 168	In this section, the FDA indicates that Sponsors should "Include patients across a wide spectrum of disease severity and phenotypes, rather than focus on a particular subtype. Broad inclusion criteria can allow identification and better characterization of disease phenotypes for which therapy development may be more feasible or needed." However, for this text, 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 text to address targeted therapies in Low-Frequency Molecular Subsets of a Disease.
B. Types of Natural History Studies		
Lines 208-214	The Draft Guidance states, "However, retrospective studies are limited in that they can only obtain data elements available in existing records. Retrospective	By virtue that for many rare diseases the only available natural history data may be in medical records, any study would necessarily constitute a retrospective, cross-sectional

SECTION	ISSUE	PROPOSED CHANGE
	studies are also limited by many factors including but not limited to inconsistent measurement procedures, irregular time intervals, and unclear use of terms that may limit the completeness and generalizability of the information. These limitations often preclude the use of such studies as an external control group for drug trials if it is not possible to match characteristics of patients in the drug trial with the historical controls."	or longitudinal study. While limitations for use of these data are apparent and accepted, BIO recommends that FDA expand the Draft Guidance to include a discussion and examples illustrating situations in which data from retrospective studies would be appropriate for use as an external control. Furthermore, this text may be interpreted to be limited to patient matching only. Since patient matching is not the only method by which we are able to control for differences at baseline, this should be reflected in the text, particularly when matching is not feasible. BIO recommends that the Draft Guidance be clarified and offers the following proposed edit for lines 212-214: "These limitations often preclude the use of such studies as an external control group for drug trials if it is not possible to match **or otherwise adjust for differences in the** characteristics of patients in the drug trial with the historical controls."
IV. DISEASE PATHOPHYSIOLOGY, CLINICAL MANIFESTATTIONS, AND IDENTIFICATION AND USE OF BIOMARKERS		
Lines 251-252, Footnote 13	The bullet point in lines 251-252 refers to footnote 13, states "See the guidances for industry Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products and Adaptive Design Clinical Trials for Drugs and Biologics (December 2012). When final, these guidances will represent the FDA's current thinking on these topics."	The 2010 Draft Guidance entitled "*Adaptive Design Clinical Trials for Drugs and Biologics*" has been updated in September 2018, as correctly noted in footnote 28. BIO recommends the FDA amend footnote 13 accordingly.

SECTION	ISSUE	PROPOSED CHANGE
Lines 282-283	In this section, the FDA discusses the use of a surrogate endpoint that requires demonstration of "analytical validity" of the biomarker test. However, there is a lack of explanation on the "clinical validity" in this section.	BIO requests that the FDA provide additional details regarding "clinical validity" or reference other relevant FDA guidance. The addition of discussion on "clinical utility" would help the Sponsor better design a test that can provide more useful information about diagnosis, treatment, management, or prevention of a disease (i.e. enzyme replacement therapy, gene therapy), if applicable.
Line 285	The text in the Draft Guidance reads: "The analytic validity should be confirmed *before* starting the clinical trial."	BIO has full appreciation for this recommendation and the underlying rationale. However, there may be instances in which this may cause delays for drug development (e.g. programs that have qualified for one or more of FDA's expedited programs). In interest of regulatory flexibility, we recommend the following edit for FDA's consideration: "The analytic validity should be confirmed *before* starting the clinical trial, **but FDA may allow concurrent confirmation in some circumstances.**
Lines 298-300	The text in the Draft Guidance indicates: "The guidance for industry and FDA staff Qualification Process for Drug Development Tools (January 2014) includes important information about the features of biomarkers used as endpoints."	The 2018 Draft Guidance entitled "*Biomarker Qualification: Evidentiary Framework*" provides additional relevant information. BIO requests that FDA includes this reference to this Draft Guidance as well: "The guidance for industry and FDA staff Qualification Process for Drug Development Tools (January 2014) **and Draft Guidance for industry and FDA Staff Biomarker Qualification: Evidentiary Framework (December 2018)** ~~**includes**~~ **include** important information about the features of biomarkers used as endpoints."
V. NONCLICNIAL STUDIES		

SECTION	ISSUE	PROPOSED CHANGE
Lines 336-346	In this section, the FDA provides flexibility that is acceptable for rare disease therapies as it related to non-clinical studies. However, the text does not appear to be consistent with ICH S9. For example, the FDA mentions that they will consider toxicology studies in a single species, or of less than chronic duration to support clinical data; however, in the next paragraph (lines 344-346) the FDA indicates that data need to be submitted before dosing of any patient exceeds the duration of the available nonclinical data. For large molecules, a single relevant species is already in the ICH S6(R1) guidance. Additionally, ICH S9 covers delay or deferral of submission of certain nonclinical studies and has a reduced chronic duration timeline.	BIO recommends that the FDA apply the flexibility articulated in ICH S9 to rare and serious, though not necessarily life-threatening, diseases to non-clinical studies for rare diseases.
Lines 337-343	The FDA Draft Guidance reads: "The ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010) and *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (July 1997) outline chronic toxicology studies to support clinical indications of chronic, lifetime use. A chronic toxicity study calls for a 6-month duration of dosing in a rodent and a 9-month duration of dosing in a nonrodent species."	The stated recommendation from the referenced S6(R1) guidance is referring to low molecular weight molecules. BIO recommends FDA clarify these statements and suggests the following edit for text in lines 341-343: "A chronic toxicity study **for low molecular weight chemical entities** calls for a 6-month duration of dosing in a rodent and a 9-month duration of dosing in a nonrodent species. **For many biologics, a study of 6-month duration, often in a single species, is considered sufficient."**
Lines 368-370	The Draft Guidance states, "When clinical trials are to be conducted in pediatric patients, POC data is required to establish a prospect of direct benefit to the pediatric population. Robust animal model results	BIO believes that the guidance would benefit greatly if it were expanded to address generating POC data using juvenile animal studies. We recommend that the Agency include a discussion of whether and how studies in juvenile animals can be used to support the POC data requirement

SECTION	ISSUE	PROPOSED CHANGE
	may support the possibility of clinical benefit and the potential for a favorable benefit-risk assessment."	and outline and discuss which factors would guide a requirement for juvenile toxicity studies to support pediatric clinical development for rare diseases
VI. EFFICACY ENDPOINTS		
Lines 369-378	We ask the Agency to detail specific conditions wherein a Sponsor will be allowed more flexibility to substitute animal studies with non-animal testing methods in order to more adequately predict a favorable benefit-risk balance. We also ask the Agency to provide clarity on the additional non-clinical data requirements or aspects that may be in scope for increased flexibility.	
Lines 390-392	The first bullet point under the endpoint selection considerations, states that "The range and course of clinical manifestations associated with the disease. Sponsors can often obtain this knowledge, along with possible differences among patient subtypes, from a natural history study of the disease (see section III., Natural History Studies)."	Natural History Studies could be conducted by different Sponsors and/or Institutions (e.g. academia, patient organizations), not necessarily just the Sponsor developing interventional studies. For publicly available studies not conducted by the Sponsor, FDA should outline and clarify criteria/standards they intend to apply, in order to make a determination whether or not data from these studies are acceptable for use in regulatory decision-making.
Lines 397-398	In this section, FDA indicates that "The aspects of the disease that are meaningful to the patient and that could be assessed to evaluate the drug's effectiveness," however there is no reference to caregivers.	BIO recommends the following edit: "The aspects of the disease that are meaningful to the patient **and caregivers** and that could be assessed to evaluate the drug's effectiveness."
Lines 411 - 414	In this section, the FDA indicates that Phase 2 studies may serve to guide selection of dosing and frequency of administration. However, dose- or exposure-	BIO requests that the FDA consider the following edit:

SECTION	ISSUE	PROPOSED CHANGE
	response studies could be substantial evidence rather than just supportive evidence. Additionally, the recommendations in the guidance regarding dose selection are overall applicable to drug development; but are not specific to rare disease drug development programs with limited patient populations. Regulatory flexibility in study design with regard to dose selection needed for rare disease drug development should be discussed.	Sponsors should conduct early- and mid-phase (e.g., phase 2) clinical investigations to guide selection of dose strength and frequency and can rely on pharmacodynamic or intermediate clinical effects, which may be seen earlier than more definitive endpoints. **Considering challenges in rare disease drug development, other approaches may augment the dose finding studies. For example, data from animal models of disease for target dose/exposure, as well other approaches such as intra-patient dose escalation, can be considered. Exposure-response studies also can contribute to substantial evidence of effectiveness (where clinical endpoints or accepted surrogates are studied) provided they meet the requirements for adequate and well-controlled studies in 21 CFR 314.126.** Late-phase clinical investigations are generally designed to provide clear determinations of efficacy and further evaluation of safety.
Line 420	In this section the FDA indicates "However, adaptive seamless trial designs may allow early evidence to be used later in a study, especially helpful when there are limited numbers of patients to study," however, the Adaptive Design guidance allows for endpoint adaptation and it is not mentioned in this section.	In addition to the adaptive seamless trial design, Bayesian designs are particularly applicable to rare disease drug development, with borrowing from early phase trials. BIO recommends that the FDA edit the guidance to reflect use of all appropriate innovative clinical trial designs, rather than seemingly limiting to use of the adaptive seamless trial design only. Additionally, given the flexibility required for rare disease drug development, we recommend FDA allow for endpoint adaptation in developing drugs for rare diseases.

SECTION	ISSUE	PROPOSED CHANGE
		We also recommend that the Agency clearly reference the guidance "*Adaptive Designs for Clinical Trials of Drugs and Biologics*"
Lines 431-434		We request the Agency clarify that digital monitoring sensors can also be used to collect these outcome assessments, as noted in FDA's 2018 Discussion Document: "Methods to Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments". We also request the that Agency to modify the language in the Draft Guidance that states that performance outcome assessments "may complement" reports from patients and caregivers regarding function and to clearly acknowledge the potential of such assessments to be counted on their own merit.
Line 438 - 443	In this section, the FDA indicates that a broader range of disease severity may be warranted for rare disease trials, but validity, sensitivity, reliability, or interpretability of an endpoint may be different for patients with different ranges of disease severity or rapidly progressive forms of the same disease.	BIO requests that the FDA provide additional guidance or examples of ways in which Sponsors might design an endpoint or interpret results in a trial that includes patients with a range of disease severity or more rapidly progressive forms of the same disease. Additionally, we suggest clarifying that concepts that are relevant and meaningful will likely differ depending on the disease stage and severity.
Lines 457 - 460	In this section, the FDA suggests Sponsors should consider using or modifying existing clinical outcome assessments (COAs), due to the time and uncertainty involved in developing novel measures.	BIO agrees with FDA that use or modification of existing clinical outcome assessment (COA) measures (e.g. for the general population) and application to rare disease drug development is more efficient. However, we note that the regulatory acceptability is variable, even in situations in which there are no COAs for a particular rare disease.

SECTION	ISSUE	PROPOSED CHANGE
		BIO requests that FDA provide additional guidance to include a discussion of the criteria to consider when considering a modification and validation of an existing COA or examples of acceptable flexible approaches to developing or modifying COAs in rare disease (e.g., using the same patients in both qualitative and quantitative validation of a measure or using qualitative data to define meaningful change when a development of a novel measure is required for a small population) or referencing other FDA guidance.
VII. EVIDENCE OF EFFECTIVENESS AND SAFETY		
A. Effectiveness		
Lines 488-489	Under the "Effectiveness" heading, the first bullet point of the list of design features of an adequate and well-controlled trial, indicates "A clear statement of the trial objectives, a statement and rationale regarding planned sample size, and a summary of the methods of analysis being used"	For clarity and completeness, BIO recommends the following addition: "A clear statement of the trial objectives, **estimands (where appropriate),** a statement and rationale regarding planned sample size, and a summary of the methods of analysis being used".
Line 492	This section indicates that "A design that permits a valid comparison with a control that may be concurrent (e.g., placebo, standard of care, active treatment, dose comparison) or, in limited and special circumstances, historical," however the language does not support the work ongoing at the Agency to support the use of innovative clinical trial designs.	BIO requests that the FDA consider the following edit: "…or, in ~~**limited and special**~~ **certain** circumstances, historical"

SECTION	ISSUE	PROPOSED CHANGE
Lines 498-499	Under the "Effectiveness" heading, the fourth bullet point of the list of design features of an adequate and well-controlled trial, indicates: "Methods that minimize bias in assigning patients to trial groups and ensure comparability between or among trial groups (e.g., randomization)"	Comparability is only asymptotically ensured by randomization, and sample sizes are often small for rare disease trials. In addition, when external/historical population is used as the control group, those treatment assignment decisions are not made by the trial Sponsor. In that case, one can only plan the analysis to minimize bias rather than ensuring the whole trial groups are comparable. Therefore, BIO recommends the following edit: "Methods that minimize bias in assigning patients to trial groups and ensure **maximizing** comparability between or among trial groups **in the analyses** (e.g., randomization)"
Line 509	Generally, the standard for FDA to establish effectiveness is based on two adequate, randomized controlled trials (RCT) showing statistical significance in the analysis of primary endpoints, with each trial providing a p-value < 0.05. However, the Draft Guidance indicates that "FDA has relied on only a single adequate and well-controlled efficacy study to support approval — generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds" (FDA Guidance for Industry Providing Clinical Evidence of	To recognize precedent in rare disease drug approvals, FDA's modernization of drug approval initiatives, the emerging use of real-world evidence, and the FDA stated flexibility in the demonstration of substantial evidence[7], BIO recommends the following new text/subsection be added to VII. Evidence of Effectiveness and Safety: (line 509) ***Data and Analysis Considerations*** ***"Data from one adequate and well-controlled clinical investigation and confirmatory evidence to constitute substantial evidence may be sufficient."***

[7] Regulatory Flexibility and Lessons Learned: Drugs for Rare Diseases

SECTION	ISSUE	PROPOSED CHANGE
	Effectiveness for Human Drugs and Biological Products). When testing a new treatment regimen in a rare patient population, the totality of evidence from one RCT may be sufficient for approval. This would include, but not limited to, strongly trending results in favor of the experimental treatment in all pre-specified endpoints, including sensitivity, supplemental and sub-group analyses, in addition to a positive benefit/risk ratio. While specifics of such criteria are difficult to standardize and can be an issue of the application review process, the nature of studying potential treatment benefits in a rare population allows flexibility in standards to establish effectiveness.	
B. Use of Historical Controls and Early Randomization		
1. Historical (external) controls		
Lines 510-563	Section VII, B: "Use of Historical Controls and Early Randomization"	BIO suggests that FDA expand the Draft Guidance in the next version to include discussion and comment on the role of propensity score matching in settings lacking randomization and general discussion on methods that help minimize bias (e.g., matching, and principles for regulatory agreement without biasing the analysis).
Lines 513-515	The Draft Guidance states that "Concurrent control designs and randomization minimize unknown variables that could affect the outcome independent of the intervention."	For clarity, BIO recommends FDA reword this statement, since confounding by the variables are minimized, not the variables themselves.
Lines 537-539	This section indicates that "initiation of prospective natural history studies should not delay interventional	BIO recommends the following edit:

SECTION	ISSUE	PROPOSED CHANGE
	testing otherwise ready to commence for a serious disease with unmet medical need" however historical/external controls should be able to be collected at any time.	"However, the initiation of prospective natural history studies **can commence at any time and** should not delay…" BIO also requests that the FDA provide recommendations regarding the need and length of a "lead in" observational period in cases where interventional testing should not be delayed.
2. Early randomization when feasible		
Lines 555-558	This section indicates that "These designs retain the advantages of placebo-controlled trials and include features that minimize placebo exposure and enhance access to experimental therapies (e.g., dose-response, delayed start, randomized withdrawal, crossover, adaptive designs with interim analysis)."	BIO recommends that the Agency expand the Draft Guidance to include a discussion about use of the adaptive randomization design in these settings, as this design minimizes the number of patients exposed to less effective treatment arms.
C. Safety		
Lines 590-592	This section indicates that "Many rare diseases are genetic in origin and characterized by more than one phenotypic subtype (e.g., infantile, juvenile, adult). Prevalence estimates should include all phenotypic subtypes of a disorder anticipated to respond to the investigational drug. Sponsors also should determine prevalence estimates for all countries in which trial sites are being considered. Sponsors should provide the individual sources of current published prevalence estimates, rather than calculated averages, because published prevalence estimates can vary widely depending on study details (e.g., case definition), country or region, and advances in diagnostics and treatment over time." BIO believes that the above statements are a departure from current practice and	BIO recommended the following edit: "Prevalence estimates should include all phenotypic subtypes of a disorder which includes adults and children **in which the drug is being investigated.** Sponsors should provide the individual sources of current published prevalence estimates, rather than calculated averages, because published prevalence estimates can vary widely depending on study details (e.g., case definition), country or region, and advances in diagnostics and treatment over time. **Should there be an identified reason that estimates vary across countries in which trial sites are being considered (e.g. higher mortality rates), Sponsors**

SECTION	ISSUE	PROPOSED CHANGE
	finding prevalence estimates across countries may be overly burdensome, especially if there isn't reason to believe a substantial difference. BIO believes prevalence estimates should include all subtypes of a disease in which the drug is being investigated, not all potential treatable disease.	**should evaluate the potential differences in prevalence estimates**".
Lines 595-598		Sponsors should be encouraged to collaborate with patient groups and academics to publish data from registries. However, lack of publication should not preclude consideration of said data by the Agency.
Line 608-610	This section indicates "Robust natural history data can also help distinguish drug-related adverse effects from underlying disease manifestations." For clarity, BIO requests the following edits.	BIO requests the following edit: "Robust natural history data can also help distinguish drug-related adverse effects from underlying disease manifestations **via establishing background rates**."
VIII. PHARMACEUTICAL QUALITY CONSIDERATIONS		
Lines 678	In this section the FDA indicates that they will provide some flexibility as it relates to manufacturing for rare diseases therapies; however, flexibility on information expected at the time of submission is also needed in terms of setting the initial shelf-life and on setting initial commercial specifications for testing.	BIO recommends the following edit: "FDA may exercise some flexibility on the type and extent of manufacturing information that is expected at the time of submission and approval for certain components (e.g., stability **data** updates, **use of supporting stability data to set initial shelf-life,** validation strategies, inspection planning, manufacturing scale-up**, initial commercial specifications for testing**)."
Lines 697-712	This paragraph describes the various manufacturing changes and their potential impact. However, we request that the FDA add a statement that the planned changes (both during development and post-	BIO requests the following edits: "**Planned pre- and post-approval manufacturing and testing changes should be discussed with FDA during**

SECTION	ISSUE	PROPOSED CHANGE
	approval) should be discussed with FDA, such that the supporting data needed can be agreed on.	**development and at submission.** Examples of some of the many ways a change in drug characteristics may adversely affect drug development include the following:
IX. ADDITIONAL CONSIDERATIONS		
A. Participation of Patients, Caregivers, and Advocates		
B. Expedited Programs		
C. Pediatric Considerations		
Lines 749 - 750	In this section the FDA indicates that "In general, Sponsors should include pediatric patients with rare diseases in premarketing clinical studies to develop data on the full range of people with the disease." In situations where the feasibility of studies in a rare disease is restricted, extrapolation principles could be applied. Where the clinical response is expected to be similar to the adult population, a PK-PD relationship, modeling data, or data from an exposure-response study can be used to support use of a drug in a pediatric population, also based on a good understanding of the pathophysiology of the disease. Supported by the following FDA and EMA guidances: • Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998 • Guidance for Industry Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications, April 2003 • Reflection paper on the use of extrapolation in the development of medicines for paediatrics, October 2018	BIO requests that the FDA consider the following edit: In general, Sponsors should include pediatric patients with rare diseases in premarketing clinical studies to develop data on the full range of people with the disease. **It should be noted that, where the clinical response is expected to be similar to the adult population, a PK-PD relationship or modeling data or data from an exposure-response study could be used to support use of a drug in a pediatric population**.
Lines 752-754	The FDA *Guidance for Industry Considerations for the Inclusion of Adolescent Patients in Adult Oncology*	BIO requests that the FDA consider the following edit:

SECTION	ISSUE	PROPOSED CHANGE
	Clinical Trials, June 2018 recommends the inclusion of adolescent (ages 12 to 17) in relevant adult oncology studies and reference to this may be helpful in this section.	FDA strongly encourages Sponsors to study the drug in all relevant pediatric populations, birth to younger than 17 years of age, so that the drug can be properly and completely labeled for pediatric use. **In cancer, FDA also recommends the inclusion of adolescents in disease- and target-appropriate adult oncology trials.**[8]
Lines 758-760	In order to minimize exposure of pediatric patients to obtain relevant data, extrapolation should also be considered.	BIO requests the following edits: "…single statistical analysis. **In addition, if the rare disease is similar in adults and children with anticipated similar dose response, extrapolation should be considered to leverage data from the source population.**"
Lines 760-762	This section does not include reference to appropriate safeguards for adults with severe cognitive impairments and an inability to consent.	We ask the Agency to acknowledge that additional safeguards may also be appropriate for adults with severe cognitive impairment and inability to consent.
X. INTERACTIONS WITH FDA		
Lines 782-785	This section indicates that Sponsors should engage with the Agency regarding their rare disease drug development program but does not provide detail regarding with whom at the FDA Sponsors should discuss various elements of their drug development program.	We ask the Agency to provide details with whom at the FDA Sponsors may discuss various elements of their drug development program during "informal" interactions.
REFERENCES		

[8] FDA Guidance on Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials.

SECTION	ISSUE	PROPOSED CHANGE
Lines 800 - 801		BIO requests that the FDA add several additions to the reference list, including: • Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications, April 2003 • Guidance for Industry: *Adaptive Design Clinical Trials for Drugs and Biologics* • Guidance for Industry: Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease October 2018 • Guidance for Industry and FDA staff Biomarker Qualification: Evidentiary Framework, December 2018 • Framework for FDA's Real-World Evidence Program, December 2018 BIO also requests that the FDA reference the new guidance on Rare Diseases: Natural History Studies for Drug Development.

Appendix I.

Request for Additional Detail Pertaining to Natural History Studies:
BIO recognizes that the FDA recently released the Draft Guidance entitled *Rare Diseases: Natural History Studies for Drug Development*[9] at the end of March 2019; however, we have included in this appendix specific comments pertaining natural history studies and we are also looking forward to the opportunity to providing the FDA with additional comments to the Draft Guidance on *Rare Diseases: Natural History Studies for Drug Development*[6].

While we recognize that the referenced ICH guidance "E10 Choice of Control Group and Related Issues in Clinical Trials"[10] provides considerations and recommendations about which circumstances would warrant selection of a natural history study as an external control, we also note that the guidance does not specifically address this issue in the context of a rare disease, in which the target patient population is frequently very small and often necessitates regulatory flexibility. Therefore, this Draft Guidance would greatly benefit from greater specificity and content expansion regarding the rationale and criteria for regulatory acceptability/unacceptability of the different types of natural history studies (retrospective or prospective and cross-sectional or longitudinal) as an external control in pivotal clinical trials; this should include, but is not limited to:

1. Clarifying the implied relative value of different types of natural history studies in the context of clinical trial design (e.g. in table format)
2. Describing circumstances and/or provide examples which would match the natural history study data type (i.e. prospective/retrospective/cross-sectional/longitudinal) with an acceptable or unacceptable regulatory use, including as an external control in support of demonstrating efficacy (e.g. in a table format)
3. Either in the "Natural History Studies" or "Effectiveness" section examples which would illustrate "special circumstances" as well as situations which would be considered "impractical or unethical" and would allow use of natural history studies

BIO also appreciates that the Agency made several updates to the section of the Draft Guidance covering natural history studies which is later referenced in the "Use of Historical Controls and Early Randomization" in the context of clinical trial design to support approvals. However, we request that the FDA provide additional guidance for Sponsors as they collect natural history data for rare diseases. Rare diseases are often diagnosed based on clinical signs and symptoms, and multiple distinct diseases often exhibit similar, overlapping symptoms leading to heterogeneous entries in natural history databases. Recently, however with advances in diagnostic technologies and a greater understanding of disease biology, patients with certain rare diseases can be diagnosed earlier and with greater accuracy. In cases where new diagnostic techniques allow for more accurate identification of patients with a specific rare disease, we suggest that information in existing databases be utilized by matching prior entries with emerging test results to confirm diagnosis of patients thereby enhancing natural history data sets. In cases where researchers identify sub-cohorts (e.g., spinal muscular atrophy (SMA) sub-types), we suggest that the dataset may be split based on pre-specified criteria which in-turn will allow application of disease modeling and data interrogation methods to develop sophisticated and appropriate comparator arm data. This, in turn, will allow for a more meaningful comparison of natural history data such

[9] FDA Draft Guidance on Rare Diseases: Natural History Studies for Drug Development
[10] International Conference on Harmonization, Choice of Control Group and Related Issues in Clinical Trials.

that signs and symptoms, disease progression, and endpoints are more evenly matched between the historical data (comprising data from all subsets of the disease) and the treatment data set (composed of data from a specific subtype). We propose this approach as a viable option to leverage existing rare disease natural history data while acknowledging the complex nature of diseases that present on a spectrum and while ensuring that distinct subpopulations/cohorts have treatment options developed to address their specific needs. We also request the Agency specify in the Draft Guidance circumstances in which emerging data allows for delineation of sub-populations of disease. We also ask the FDA to specifically indicate in the Draft Guidance that Sponsors may use approaches outlined in the FDA's guidance for industry entitled "Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease."[11]

Given that natural history studies can be difficult to conduct due to limited patient populations[12], BIO also believes that existing natural history data has value and relevance for Sponsors after an new treatment is approved for the disease or condition in question, in part because such an approach would increase the options for these still underserved and often desperate on rare disease patients. In the interest of more quickly creating treatment options in response to patient needs, we suggest that Sponsors should have the flexibility of comparing their rare disease development programs to either the natural disease history of the given rare disease prior to a new treatment becoming available, or to a new treatment , after a new treatment has been approved for the following reasons:

- While a new treatment might provide patients with a significant benefit, it will take time to develop sufficient evidence to fully understand the benefit-risk profile in a real-world setting. Furthermore, if a new treatment is approved for a specific condition, it may only be effective for a specific stage of the disease process and more therapeutic options may be needed, due to the varied course of the disease in patient populations.

- FDA has recognized that a new treatment on the market does not automatically become the Standard of Care (SoC) and there is usually a lag between a new treatment being approved, its uptake in the clinic, acceptance by the medical community, and inclusion in practice guidelines as SoC. If the new treatment introduced is accepted and endorsed as SoC by the medical community, it may still be impractical to perform active comparator studies. In such cases, Sponsors should be able to use the natural history database with the (newly accepted) SoC as a synthetic control arm to perform non-inferiority or superiority studies. Sponsors could use the natural history data pre- and post-introduction of the new treatment and treat that introduction as an inflexion point in the registry.
    - If the new treatment introduced has not yet been accepted as the SoC by the medical community, especially in the situation where the treatment is not disease

[11] FDA Guidance for Industry "Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease": *"In some situations, it may be desirable to include patients who have molecular alterations that are less likely to be responsive (e.g., unmet medical need) or for which the likelihood of response is not known based on the available evidence. In this setting, the Sponsor has the option of either splitting study alpha assessment of the primary efficacy endpoint between a subgroup of patients with specific molecular alterations of interest and a broader enrolled population or using an adaptive design with interim assessments of efficacy. Alternatively, the Sponsor may limit the assessment of the primary efficacy endpoint to the subgroup of patients with the specific molecular alteration(s) of interest while enrolling additional subgroups to generate preliminary clinical data."*

[12] Especially relevant in the pediatric population where the incidence of the disease may be quite low and the general course of the disease may be very progressive.

modifying, other Sponsors should be able to leverage the existing natural history database as a comparator arm.

Additional detail regarding the statistical approaches that allow for leveraging data from natural history studies would also be helpful for the FDA to include in the Draft Guidance.

Finally, the collection of natural history data in the context of rare diseases can be difficult. To alleviate challenges encountered when designing prospective natural history studies, we suggest that the FDA encourage pre-competitive collaboration between industry, academia, and patient advocacy groups, where possible, there should be collaboration to generate natural history data in a way that brings the greatest value to patients, rather than defaulting to multiple independent observational studies. Additionally, we encourage the Agency support non-proprietary rare disease registries, with appropriate data access for all stakeholders. Given that many stakeholders including patient organizations are now developing their own natural history studies, it would also be helpful for the FDA to provide guidance regarding which standardized collection methodologies, quality standards, and medical terminologies should be used in order to best prospectively acceptable natural history data that can be used as best practices.


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