Biotechnology Innovation Organization

May 24, 2019

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

Re: Docket No. FDA–2017-D-0481: FDA Draft Guidance, Rare Diseases: Natural History Studies for Drug Development.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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the Draft Guidance on Rare Diseases: Natural History Studies for Drug Development.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 appreciates the Agency's work to develop a much-needed guidance on natural history studies for rare disease drug development. The Draft Guidance serves as an important communication tool between the FDA and Sponsors on issues pertaining to natural history studies for rare disease drug development.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following pages of this letter, BIO has included general comments as well as line edits that we believe will make the Draft Guidance more useful for various stakeholders.

Guidance on Natural History Studies is Helpful Information for Stakeholders beyond Drug Developers:
Although this guidance is titled "guidance for industry," a growing number of advocacy and patient organizations have either initiated or have the potential to initiate or facilitate the development of natural history studies. Thus, the guidance should highlight and recognize that it can apply to a wider range of stakeholders, including patient organizations. To this end, BIO requests that the final Guidance should read "Guidance for Industry and Other Stakeholders." The guidance should also encourage patient organizations to consider the guidance when developing their natural history studies so that the data is robust and can be considered by the FDA for regulatory decision-making.

Accept and Encourage use of Appropriate Retrospective Natural History Study Data and Alignment Across FDA Guidance Pertaining to Rare Disease Drug Development:
The recommendations regarding natural history studies included in the recent revision of the Draft Guidance entitled "Rare Diseases: Common Issues in Drug Development" should align with

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

the recommendations made in this Draft Guidance and reduce duplicative language. Overall, with regarding to natural history studies the Draft Guidance on Rare Diseases: Natural History Studies or Drug Development takes a slightly more pragmatic approach than recommended in the guidance on "Rare Diseases: Common Issues in Drug Development". To this end, As the Agency finalizes both documents, we request that the updated guidance documents are carefully reviewed to ensure that the recommendations regarding natural history studies align and take a more forward-leaning approach as outlined in the natural history guidance.

In the interest of meeting unmet medical need and getting drugs to patients efficiently, the guidance should generally acknowledge that limitations may exist in rare disease natural history data, but that the limitations should not hinder drug development. FDA's stance to recommend prospective natural history studies may discourage efforts to collect natural history data to support multiple drug development programs. BIO requests that FDA adopt a more pragmatic approach to recommending use of prospective versus retrospective natural history studies and data, based on totality of evidence available, as well as the quality, appropriateness, and applicability of the available natural history data. Additionally, gaps in retrospective data may often be addressed by other means, such as using real-world data/evidence (RWD/RWE) or other data, instead of conducting a duplicative complete prospective natural history study. To this end, BIO suggests that FDA build on and provide further detail on their recommendation in guidance that "Real-world data (i.e., data relating to patient health status and /or the delivery of health care that is routinely collected from a variety of sources) may be useful to collect data for natural studies." It would be helpful if FDA could expand on their recommendation in the guidance to address RWD collection and analysis with respect to natural history studies, in line with their proposed RWE framework. BIO also requests that the FDA encourage the use of existing (e.g. retrospective) natural history data, when such data is available and appropriate, to enhance efficiency of drug development and to avoid unnecessary duplication of studies. It is acknowledged that FDA encourages the use of combination of data sets from natural history studies and from randomized controlled studies, FDA might provide further guidance on regulatory expectations for this hybrid approach.

Leveraging Existing Natural History Data When a New Treatment is Approved:
Increasing interest in developing rare disease treatments presents industry with a unique challenge. In instances, wherein, a treatment is approved (product A) for a rare disease where no treatment existed before, there may still be a case for other drug developers to leverage existing, non-proprietary, natural history data that was collected prior to the approval of product A to aid development of other products still in the pipeline (products B, C, D, etc.). Such circumstances may include:

1. When the newly approved treatment (product A) is symptom-alleviating and not disease-modifying. In these cases, existing natural history data can still be leveraged to aid in development of drugs in the pipeline (products B, C, D, etc.).
2. When the new treatment (product A) introduced is "disease-modifying" and/or has limited uptake or is not considered the standard of care. Sponsors of products in the pipeline (products B, C, D, Etc.) should be able to leverage existing natural history data to supplement an ongoing or new study.

Provide more flexibility and clarify considerations for the Statistical Analysis Plan (SAP):
The level of rigor recommended in the first paragraph of section on the "Statistical Analysis Plan" is desirable by all stakeholders, including FDA and industry alike. However, in some cases,

achieving such rigor may be difficult. BIO recommends that changes to a SAP should be documented with rationale, but should not necessarily require a protocol amendment [428-429]. BIO also acknowledges that some principles outlined in this section are pertinent to using the natural history data as a comparator in a treatment trial and should be considered when planning such analyses. Accordingly, BIO suggests that FDA consider distinguishing recommendations for analyses of natural history data on their own, independent of any drug effectiveness studies, from analyses of natural history data when used for comparative analyses. Additionally, topics such as language and cultural differences (and their impact on assessment instruments), intra- and inter-rater reliability, and biomarkers should perhaps be primarily addressed in a separate section about trial endpoints, instead of within the section on SAP. In addition, the analytical plan is mentioned several times throughout the Draft Guidance. For clarity, BIO suggests that the guidance note in these sections that, generally, protocols contain only a summary of planned statistical methods, with the details being relegated to the study's SAP.

BIO appreciates this opportunity to submit comments regarding FDA Draft Guidance, Rare Diseases: Natural History Studies for 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

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
II. BACKGROUND		
Line 45	The number of rare diseases that have been identified has increased to exceed more than 7,000.	BIO requests the following edit: "There are **more than** ~~**approximately**~~ 7,000 recognized rare diseases."
Lines 46-47	This section does not indicate the approximate number of people in the United States that are impacted by rare diseases.	BIO requests the follow edit: "...but cumulatively rare diseases affect about 1 in 10 people in the United States**, or more than 30 million Americans**."
Lines 50-52		BIO requests the follow edit: "The natural history of a disease is ~~**traditionally**~~ defined as the course a disease takes in the absence of intervention in individuals with the disease, from the disease's onset until either the disease's resolution, the individual's death **or permanent disability**."
Lines 57-58	This section indicates that disease registries are a frequent platform to acquire natural history data.	BIO requests that for prospective natural history studies the FDA reference additional 'platforms' that can aid the natural history studies.

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Lines 63-65	This section of the Draft Guidance indicates that "It [the Draft Guidance] also touches briefly on the potential use of natural history data as an external control in a clinical trial, but not as the primary focus of this guidance." The use of natural history data as an external control is an important tool for drug development. Further, the guidance provides important recommendations for this approach. Accordingly, we suggest that this text make note of the concept accordingly.	BIO requests the following edit: "It also **addresses** ~~**touches briefly on**~~ the potential use of natural history data as an external control in a clinical trial, ~~**but not as the primary focus of this guidance**~~."
Lines 70-72	We appreciate the Agency acknowledges the usefulness of natural history studies in the post-marketing setting. However, using natural history data as comparator for post approval studies (for efficacy or safety purposes) is not mentioned as a potential use elsewhere in the Draft Guidance.	We recommend the Agency reference the usefulness of natural history studies in the post-market setting in the final version of this document.
III. USE OF NATURAL HISTORY STUDY		
Drug Development		
Identifying a patient population		
Lines 83-84	This section indicates that some rare diseases have substantial genotypic and/or phenotypic heterogeneity, and the natural history of each subtype may be poorly understood or inadequately characterized. However, an additional benefit of natural history studies can be the recognition that there are distinguishable phenotypes of the disorder. Many rare diseases have been so little studied that it is not known if such sub-categories exist.	BIO requests that the FDA indicate in this section additional potential benefit of natural history studies for rare diseases, including the identification of disease subsets.

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Identification or Development of Clinical Outcome Assessments		
Identification of development of biomarkers		
Design of externally controlled studies: Use of natural history study data		
Line 140, 155-181	In these sections the FDA references that an 'adequate' control group is used to compare to the investigational drug group. Lines 155-181 describe some considerations in assessing data for a potential external control.	BIO requests that the FDA provide clear guidance on criteria (i.e., not just considerations) that may be applied to determine if the natural history data can be deemed to provide an adequate control group for an intervention trial.
Lines 143-145	In this section, the FDA indicates that the regulations recognize historical controls as a possible control group (usually reserved for special circumstances); however, inability to control for certain biases could limit the ability of externally controlled trials to demonstrate substantial evidence of effectiveness." However, the use of historical controls should not be reserved for special circumstances. Instead, it should be encouraged for when appropriate natural history data is available to support drug development for rare diseases.	Keeping with the Agency's operative principle of making a benefit/risk assessment for approval of medical products, the guidance should also explicitly state that the extent of benefit from an intervention should be balanced with the rareness of the disease and the unmet medical need of patients. BIO also requests the following edit: "FDA ~~**regulations**~~ recognize**s and encourages use of** historical controls as a possible control group ~~**(usually reserved for special circumstances)**~~; however, inability to control for certain biases could limit the ability of externally controlled trials to demonstrate substantial evidence of effectiveness"
Lines 143 and 184	In Line 143, the FDA recognizes historical controls as a possible control group. Later in the section, the FDA describes two types of external controls, nonconcurrent external controls and concurrent external controls. As currently written, it is unclear	BIO also requests that the FDA clarifies that historical controls are a subset of external controls. BIO requests the following edit:

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	whether historical and nonconcurrent controls are the same.	"Nonconcurrent external controls **(i.e., historical controls)** consider the subject-level data from a different group (external) of subjects followed in the past for whom the individual subject-level data are available for the same outcomes and same covariates as in the current trial."
Lines 155-181	These lines discuss considerations for assessing natural history data as a potential external control. However, consistent data from several separate sources can also strengthen the assessment of the data.	BIO requests that the FDA indicate that consistent data from several independent sources may strengthen confidence in the data. Additionally, given the limited patient pool for rare diseases, we suggest adding "*to the extent possible*" to this section as follows: "The external control group needs to be very similar **(to the extent possible)** to the treated group in all respects, including disease severity, duration of illness, prior treatments, and any other aspects of the disease that could affect outcomes and the timing of outcomes."
Lines 164-177	This section includes several considerations for the use of external controls, however; study subject matching and weighting might also improve the relevance of natural history data to the interventional trial but is not mentioned in this section.	BIO requests that the FDA indicate that study subject matching and weighting can also improve the usefulness of natural history studies as external controls.
Lines 183-191	This section indicates that "There are two types of external controls that provide varying strengths of evidence. Nonconcurrent external controls consider the subject-level data from a different group (external) of subjects followed in the past for whom the individual subject-level data are available for the same outcomes and same covariates as in the	BIO requests the FDA to reference the ability to use a study design where subjects of a prospective external control study have the option to be enrolled in a clinical study and serve as their own baseline control if the course of the disease is expected to remain stable over the period of the natural history study.

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	current trial. For example, subject-level data may be obtained from the comparator group from a prior clinical trial (e.g., placebo group) or a natural history study. The stronger concurrent external control design considers subject-level data collected at the same time as the group being treated in the clinical trial. However, in contrast with a completed natural history study, a concurrent control arm may not provide timely advice for planning the clinical trials." Concurrent external control design assessed to be stronger than nonconcurrent external control. The possibility to use a design where subjects of a prospective external control study have the option to be enrolled in a clinical study and serve by this as their own baseline control should be included.	
Other Uses		
Line 212	A natural history study may provide demographic data, estimates of incidence of outcomes associated with a disease, disease characteristics, and aid disease tracking but will not provide prevalence estimates.	BIO requests the following edits: "A natural history study **in and of itself** may not provide ~~**demographic data and epidemiologic**~~ **an** estimate~~**s**~~ of ~~**the**~~ **disease** prevalence, **but** ~~**of the disease and disease characteristics and aid disease tracking**~~ **it could provide an estimate of disease incidence in that population (if disease is the outcome of interest). For a disease registry, the process of identifying patients with disease from a population-based sampling scheme could provide an estimate of disease prevalence.**"

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IV. TYPES OF NATURAL HISTORY STUDIES		
Lines 216	This section discusses various sources of data for natural history studies, particularly for retrospective studies, however; the section does not mention new types of data that are becoming increasingly explored, including electronic health records (distinct form of patient charts) and administrative claims databases.	BIO requests that the FDA also indicate that novel data types such as electronic health records (distinct form of patient charts) and administrative claims databases are also sources of natural history data.
Lines 228-230	In this section the FDA indicates that "Retrospective studies are often used as first steps in collecting natural history information. This information is reviewed from existing medical records, such as patient charts, which were compiled for patient care rather than for use in a natural history study."	We fully agree that patient charts are not designed explicitly to collect natural history data, however patient charts can be successfully mined to generate robust natural history data. We therefore request that the Agency emphasize the utility of patient-level charts to aid in natural history data development.
Lines 238-270	In this section the FDA describes limitations of retrospective natural history studies but does not address issues and potential solutions arising from use of medical tests/testing which change over time (e.g. improved or new tests).	BIO requests that the FDA expand the Draft Guidance to address issues and potential solutions arising from use of medical tests/testing which change over time (e.g. improved or new tests).
Retrospective and Prospective Natural History Studies		
Cross-Sectional Studies and Longitudinal Natural History Studies		
Cross-sectional studies		
Longitudinal studies		
V. STUDY PROTOCL, DATA ELEMENTS, AND RESEARCH PLANS		
Study Protocol		
Data Elements		
Lines 349-350		We point the Agency towards the European Medicines Agency (EMA) recent discussion paper entitled "Use of patient disease registries for regulatory purposes –

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		methodological and operational considerations" and suggest the Agency's final guidance be in alignment with the overall principles outlined in the EMA paper.
Lines 384	As many rare disease patients come to clinical attention during early childhood and given the Agency's prior Draft Guidance on Pediatric Rare Disease Drug Development, consideration for pediatric treatment patterns should be added.	BIO requests the following edit: "A description of any regional treatment guidelines, ~~**or**~~ algorithms, **or patterns, especially in relation to children or adolescents**..."
Line 387	The bullet point that reads "Analytical plan", but it is unclear what the FDA is referring to.	BIO requests that the FDA clarify whether this refers to and/or includes a statistical analysis plan (SAP).
Lines 410-411	The bullet point reads "An analytical plan including a plan for how protocol deviations and drop-outs will be considered in the analysis", however it is unclear what plan the FDA is referring to.	BIO recommends that FDA clarify whether "analysis" refers to "statistical analysis plan" and recommends consistent use of terminology throughout the guidance.
Protocol Elements		
Statistical Analysis Plan		
Lines 426-427	This section indicates that "Preplanned interim analyses at certain intervals or milestones may suggest design changes to the protocol," however; Preplanned interim analysis may not be possible for all cases.	BIO requests the following edit: "**When possible,** preplanned interim analyses at certain intervals or milestones may suggest design changes to the protocol."
Practical Considerations for Study Design		
Lines 445-447	This section indicates that "These data may come from and be reviewed by a planning committee comprised of diverse stakeholder representatives such as patients and advocates, treating physicians,	BIO suggests the following edit for clarification: "**When t**hese data **are not collected for a particular drug development program, they** may come from and be reviewed by a planning committee comprised of diverse

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	other health care providers, researchers, investigators, and drug developers." BIO appreciates the recommendation for a planning committee. However, it seems this recommendation may be intended for groups undertaking such studies outside of an individual drug development program (e.g. by patient advocacy groups, when the planning committee may include more than one or multiple drug developers in the planning committee).	stakeholder representatives such as patients and advocates, treating physicians, other health care providers, researchers, investigators, and drug developers."
Early planning and implementation		
When to start a natural history study		
Lines 457-459	This section indicates that 'natural history studies need not delay drug development or delay approval of a needed treatment if drug development is already under way.'	BIO requests that the FDA provide recommendations as to how to limit any delay on a potential interventional therapy with a natural history study.
Lines 493	This section indicates that "Specialty medical centers may have expertise and testing equipment for making medical diagnoses and performing clinical and laboratory measurements". BIO suggest that the paragraph is clarified to highlight the various sources of patients.	BIO requests the following edit: "Natural history study data may be collected by various means and in a variety of locations**, including specialty medical centers as well as satellite centers with access to central testing etc**."
Finding patients and maintaining their involvement		
Study site and local data collection		
VI. DATA COLLECTION, STORAGE, AND DISSEMINATION		
Data Collection		

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Line 528	Data collection may use a different coding system from the eventual common data model. Accuracy of the mapping from one system to another is important.	BIO requests that the FDA provide greater detail on the requirements for acceptance of any mapping process that is used.
Data Storage		
Data Dissemination		
VII. HUMAN SUBJECT PROTECTIONS		
Confidentiality of Subjections and Data Protection		
IRB Review		
Informed Consent		
INTERACTING WITH FDA		
References		
Lines 672-673		We understand that Critical Path Innovation Meetings (CPIM) are not binding, however we ask the Agency to internally disseminate the discussions held at such meetings to ensure that reviewers who were not present at the CPIM meeting(s) are made aware of their conclusions in order to help advance rare disease drug development and registration.