

October 16, 2015

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

RE: Docket No. FDA-2015-D-2818 Draft Guidance for Industry: Rare Diseases-Common Issues in Drug Development

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) appreciates the opportunity to provide feedback in response to the Food and Drug Administration's (FDA's) Draft Guidance for Industry, entitled "Rare Diseases: Common Issues in Drug Development" (Draft Guidance).¹

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.

General Comments

BIO shares FDA's goal of improving the efficiency and success of development programs that target the treatment or prevention of a rare disease. We agree that the issues encountered in this space "are frequently more difficult to address in the context of a rare disease," and thus, BIO appreciates the Agency's attention—in the form of issuing this Draft Guidance—to drug development challenges manufacturers face.² While we agree that therapies to treat rare diseases should be held to the same stringent regulatory approval standard imposed for therapies to treat more common conditions, BIO echoes the Agency's recognition that regulatory flexibility is all the more crucial to "creat[ing] successful drug development programs that address the particular challenges posed by each disease."³ Additionally, in the context of the Draft Guidance, BIO would like to reiterate that regulatory flexibility is necessary, but not entirely sufficient, to improve the efficiency and success of rare disease development programs. This flexibility must be provided uniformly throughout the Agency's review divisions to support rare disease drug development across therapeutic areas.

As an initial matter, BIO has four general comments pertaining to the Draft Guidance. First, we note that the introduction and background sections of the Draft Guidance would benefit from a concise identification of the major categories of challenges that face rare disease drug developers. These include, but are not limited to, the difficulties in recruiting patients and in adhering to the standard drug development paradigm. To balance the recitation of challenges, however, BIO asks the Agency to devote similar focus

¹ FDA. 2015. *Rare Diseases: Common Issues in Drug Development Guidance for Industry; Draft Guidance*, available at: <u>http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-</u>

<u>gen/documents/document/ucm458485.pdf</u>. ² <u>Id</u>. at lines 21-23.

³ <u>Id</u>. at lines 76-78.



to identifying mechanisms that have the ability to, or are likely to, help overcome these challenges. Second, we note that the Draft Guidance identifies a series of general concepts and issues involved in drug development for both common and rare diseases, not always highlighting the challenges posed specifically for rare diseases. The Final Guidance should focus more narrowly on the aspects of common challenges in drug development that are exacerbated by the small patient populations with which Sponsors deal in developing rare disease therapies. Third, in that same vein, BIO recommends that the Agency consider the Draft Guidance as a piece of the broader body of guidance and rules that guide and govern rare disease drug development. In doing so, we ask FDA to work with stakeholders to consider what gaps in this broader structure remain. As part of this effort, BIO asks FDA to consider identifying aspects of drug development that prove particularly challenging where the target is a pediatric rare disease as well as potential mechanisms to address these challenges. Fourth, BIO asks FDA to reiterate at the beginning of the Final Guidance that it supports early and frequent communication with Sponsors developing rare disease therapies given the challenges and the need for tailored regulatory flexibility. We believe FDA also should reiterate the opportunities for informal meetings between the Agency and Sponsors to facilitate a more efficient approval process.

I. Natural History Studies

A. Timing and Necessity of Natural History Studies

In the Draft Guidance, FDA emphasizes the importance of natural history studies as critical context for early stages of drug discovery through clinical trial design. However, we note that prospective longitudinal natural history studies may last several years and development programs for investigational therapies for rare diseases typically operate on a more accelerated timeframe. If a Sponsor is expected to have significant natural history data early in development, this expectation potentially could result in a delay in the development of novel therapies, and, in turn, in future access to promising therapies for patients with serious or life-threatening rare diseases. To address this concern, BIO asks the Agency to recommend early and more frequent communication between Sponsors and FDA to receive tailored guidance with regard to the timing of any planned natural history studies for a specific rare disease. If the Agency is able to identify high-level, broad considerations with respect to timing, it would be helpful to Sponsors if FDA included examples in the Final Guidance or within an accompanying reference appendix. In addition, to reflect the balance between the utility of natural history data and the challenges associated with conducting this type of study, FDA should consider clarifying that natural history studies are not required but may be useful under a number of circumstances—including, for example, to inform endpoint selection or trial design, and/or as a run-in or historical control in cases where few trials have been conducted in a rare disease. Sponsors would further benefit from examples—that do not necessarily focus on a specific disease state or therapeutic area—of the advantages and disadvantages associated with natural history studies in different rare disease drug development constructs.

BIO also asks FDA to comment on other potential alternative approaches to generate background disease information besides lengthy longitudinal natural history studies. For example, cross-sectional survey studies in a broad range of patient severities can provide useful disease background information as well as support the selection of outcome measures. Along these same lines, Sponsors also would benefit from examples of flexibility in the use of such alternative approaches in a rare disease context.



B. Use of Natural History Data as a Historical Comparator

FDA also notes that while historical controls have been used in clinical development programs of rare diseases successfully, in general the challenges associated with doing so are significant. The Draft Guidance goes on to identify an example of a guiding criterion for Sponsors that are considering the feasibility of utilizing a historical comparator: "studies using historical controls are credible only when the observed effect is large in comparison to variability in disease course (e.g., substantial improvement in outcome is observed with treatment in a disease that does not naturally remit)." Through this characterization, it can be interpreted that FDA is discouraging the use of historical comparators, thus we ask FDA to provide clarification on this point in the Final Guidance. To the extent that the Agency is discouraging the use of historical comparators, BIO is concerned that this position may not take into account the fact that the ability to employ historical comparators in a clinical development program—including as a run-in or historical control—is a motivating factor for Sponsors to invest the significant resources required to conduct natural history studies for many rare diseases. Further, as more becomes understood about the natural history of a disease, historical comparators should not be discouraged as they may provide an avenue to support drug development and approval particularly when it is unethical or infeasible to employ a placebo control group. To address this, BIO has recommended changes to the guidance text that identifies the potential to utilize natural history data as historical controls in rare disease studies (see Appendix, lines 153-155), thus broadening the focus of this section beyond the use of natural history as only "critical background information."⁴

Similar to FDA's draft guidance for Duchenne muscular dystrophy, BIO believes FDA should provide examples of the circumstances under which externally controlled studies would be persuasive and considered adequate and well controlled.⁵ We also recommend that FDA encourage early communication with Sponsors so that the Agency can clarify issues related to the consideration of using a historical comparator on a case-by-case basis, including, for example: (1) the scope and magnitude of the potential/likely observed effect; (2) selection of patients (e.g., well matched with respect to disease severity, age, type and sensitivity of supportive care); and (3) a comparison of endpoint data. BIO understands that there can be great variability in disease course, but the more knowledge that is gained through natural history studies, the better patient characteristics can be matched to minimize variability and increase credibility when such data serve as an external control.

Moreover, we appreciate FDA's example of a situation in which a historical control may be feasible. In fact, given the success of several development programs in employing

⁴ Draft Guidance at lines 138-141.

⁵ In FDA's Draft Guidance on Duchenne Muscular Dystrophy, the Agency notes that "In some circumstances, however, trials using external controls, such as historically controlled trials, may be considered adequate and well-controlled, and may provide or contribute to evidence of efficacy to support approval" and that "For externally controlled studies to be persuasive, detailed evidence should be presented that the study design and conduct adequately controlled for bias. For example, it would be critical to establish that the control group was well-matched across key baseline and prognostic variables, including age, baseline value of the primary efficacy measure and other measures of disease stage, type and intensity of supportive care, dose and duration of corticosteroid or other concomitant pharmacotherapy, and genotype, among others" (*see* FDA. 2015 (June). Duchenne Muscular Dystrophy: Draft Guidance, p. 5, available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM450229.pdf).FDA should consider whether this language could serve as a template for acknowledging, and providing examples of, the circumstances under which externally controlled studies would be persuasive and considered adequate and well-controlled.



this methodology, BIO requests additional clarity in the Final Guidance—or in a subsequent, relevant Agency guidance—regarding when consideration of a historical control is appropriate. This is particularly important for studies in rare diseases for which the use of a placebo control group might be unethical, and/or no approved therapy exists. The Agency also should identify existing methods to improve the ability to utilize historical controls, including but not limited to propensity scores and instrumental variable analyses. As part of this effort, FDA should consider providing examples of known and unknown covariates, which would be useful to Sponsors.

Furthermore, BIO requests that the Agency include a discussion on, and examples of, the acceptability of retrospective studies using patient data from electronic medical records (EMRs) and/or claims database to capture clinical and outcomes information, including demographics and socioeconomic status, comorbidities, changes in concomitant medications, clinical and laboratory measurements, and outcomes. Given the inherent challenges of rare disease drug development—specifically, the limited feasibility of conducting a longitudinal prospective natural history study for a rare disease—effective utilization of EMRs and claims database could be used to obtain data on a wide spectrum of patients, help generate hypotheses for additional research, and may identify potentially meaningful associations to clinical measures/outcomes to serve as potential endpoints in development. As such, we request that FDA, in the Final Guidance, discuss its perspective on the context in which clinical associations generated from EMRs and claims database for a rare disease program could be used to define efficacy endpoints.

C. Data Inputs for Natural History Studies

FDA identifies considerations associated with the duration, scope, and type of data collection in the Draft Guidance, but does not address issues of data quality with regard to natural history studies. BIO notes that the quality of data obtained through observational studies can vary widely, and without the proper controls in place, this can result in misinterpretation of the data that can negatively impact how the data can be used in the clinical development of a rare disease therapy. Examples of needed controls include detailed pre-specification of the protocols governing data handling, entry, and analysis. Given the importance of data quality, BIO recommends FDA encourage Sponsors to communicate with the Agency early, and through such interactions, we request that FDA identify expectations with regard to these studies. BIO also asks the Agency to include high-level, broad text in the Final Guidance that speaks to the practical scope of such expectations.

In discussing the data included in natural history studies, FDA also notes that "natural history studies include patients across as wide a spectrum of disease severity and phenotypes as possible...[to] allow identification and better characterization of disease phenotypes for which therapy development may be more feasible or needed."⁶ However, we do not believe that the Draft Guidance provides sufficient context for choosing a continuous range of phenotypes versus distinctly separable phenotypes. For example, while these data may be helpful in justifying separate dosing, other potential benefits are unclear. In the Final Guidance, BIO recommends that FDA address these issues by recommending that Sponsors meet with the Agency to discuss the specifics of a clinical development program such that FDA can provide tailored guidance. We also ask FDA to consider what high-level guidance can feasibly be provided to Sponsors on these issues in the Final Guidance, or in

⁶ <u>Id</u>. at lines 131-133.



future guidance, including in the form of examples included in the guidance or as a reference appendix.

With regard to FDA's discussion of retrospective versus prospective natural history study design, BIO recommends that the Agency more comprehensively address issues related to the choice of study design in the Draft Guidance. For example, BIO agrees with the Draft Guidance that prospectively designed trials are generally better than their retrospective alternatives. However, we ask FDA nonetheless to highlight some of the benefits and disadvantages of the latter. For example, retrospective study designs may allow a Sponsor to use the resulting data to inform drug development decision making more quickly; alternatively, the standard of care used in a retrospective study may be outdated in comparison to the clinical environment into which a new rare disease therapy may be launched. In expanding the discussion of the merits of prospective versus retrospective study design over the other may impact the appropriateness of using the resulting data as a historical comparator (e.g., consider the example provided, in which a retrospective study design results in the use of a currently-outdated standard of care: in this case, the use of data from this study as a historical comparator may be inappropriate).

II. Disease Pathophysiology and Identification and Use of Biomarkers

In this section of the Draft Guidance, FDA focuses almost exclusively on the role of biomarkers for proof-of-concept (POC) and for study design purposes. BIO has concerns with this limited focus, discussed in more detail below. However, with respect to the focus on biomarkers for POC and study design, BIO asks FDA to provide additional comment on identifying early markers and responses that could be used in adaptive and enrichment designs in the Final Guidance. For example, additional guidance with respect to considerations for developing and validating relevant biomarkers to assess efficacious product concentrations in animal species, and the use of this information to guide clinical study design and efficacy endpoint selection, would be useful to Sponsors.

As previously noted, BIO asks FDA to provide guidance in this section with respect to the use of biomarkers as surrogate endpoints, an important aspect of the timely and efficient development of drugs for rare diseases. At a minimum, FDA should encourage Sponsors to meet with the Agency early in development to discuss the approval pathway to be able to provide tailored guidance based on an individual clinical development program. As is feasible, we also ask FDA to provide additional, broader examples of the use of biomarkers as surrogate endpoints and intermediate clinical endpoints in the context of Accelerated Approval. We make this recommendation based on Congress's direction to FDA to consider how to apply Accelerated Approval to rare disease drug development specifically, paired with the current lack of guidance on FDA's perspective on challenges with doing so and examples of overcoming such challenges.

Additionally, while the Draft Guidance notes the potential for biomarkers to be utilized to identify early markers and responses that could be used in adaptive and enrichment designs, FDA stops short of including a discussion of how this can be accomplished. BIO recommends that the Agency include such a discussion, and where feasible, additional broad direction to Sponsors on this issue in the form of examples provided in the text of the Final Guidance, a reference appendix, or a future guidance. In doing so, FDA should consider employing more complex examples than those included in



the Draft Guidance—such as a pathophysiologic process that slowly re-establishes over time or one that varies by disease phenotype—to reflect the circumstances with which Sponsors are often presented. Also as part of revised or new guidance, FDA also should encourage Sponsors to consult with the Agency early in the development process to discuss these issues. Finally, FDA references existing draft guidance on these issues, but we note that additional details are necessary to understand how the Agency believes this guidance can be applied in the rare disease drug context.

III. Nonclinical Studies

BIO notes that FDA's focus in this section is limited to toxicology studies. While we appreciate guidance focused on this topic, and have several related recommendations discussed in detail below, as an initial matter we ask the Agency to consider including guidance related to carcinogenicity studies as well. At a minimum, Sponsors can benefit from an understanding of FDA's perspective with regard to when carcinogenicity studies are warranted and whether it would be acceptable to consign such a study to a Sponsor's postmarketing commitments, as has been the case in the oncology space.

As noted above, FDA identifies several general issues related to design, scope, and timing of toxicology studies in this section of the Draft Guidance. In response to the draft text, BIO offers several comments. First, the Agency notes that it "may apply additional flexibility in evaluating development programs for drugs to treat serious and life-threatening disorders."⁷ BIO notes that such flexibility is not only important in the context of the marketing application, but that it also can support conducting clinical trials and trial extensions for patients who respond to treatment. To illustrate such additional flexibility, BIO requests that FDA provide examples in the Final Guidance, including with regard to the Agency's expectations for nonclinical data that support a marketing application. However, since we realize that the scope and extent to which flexibility can be applied will vary by disease, at a minimum we ask FDA to encourage early communication with Sponsors such that the latter are able to receive guidance tailored to their specific situation.

Second, with regard to nonclinical studies, FDA also notes that "information from previous nonclinical and human use has the potential to decrease the amount of new toxicology data needed."⁸ While FDA indicates that it considers factors such as the "*diverse* biology and structure of drugs and biologicals," (emphasis added) the Agency does not specify whether, and under what general circumstances, toxicology data can reasonably be inferred from such data for a different compound that uses the same or similar platform (e.g., using the same oligonucleotide or protein format) and the same dose route as the clinical candidate, or whether this information must come from studies with the clinical candidate in question.^{9,10} BIO asks the Agency to consider what general parameters on this issue may be able to be included in the Final Guidance or in future guidance more narrowly tailored to this issue.

Third, the Agency states that while toxicology testing in an animal model of disease can, and in some circumstances should, be performed, this cannot be done in lieu of testing

⁹ Ibid.

⁷ <u>Id</u>. at lines 268-269

⁸ <u>Id</u>. at lines 261-262.

¹⁰ Note: To the extent that this may include cross-referencing across sponsor applications, BIO notes that such an effort is **only** acceptable after the sponsors agree to cross-referencing.



in normal healthy animals.¹¹ However, this statement contradicts guidance provided by FDA earlier this year addressing "Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment[,]" relevant because enzyme replace therapies (ERTs) frequently are used to treat rare diseases.¹² In the ERT Draft Guidance, the Agency states that "... studies conducted in animal disease models deficient in the targeted enzyme are preferable to using healthy animals in assessing the pharmacodynamic activity — and, in some cases, the toxicology of ERT products."¹³ Considering that in some cases the value of toxicology testing in normal healthy animals is unlikely to yield any information that would be relevant to the clinical population to be treated, BIO asks FDA to reconcile the text in the Draft Guidance with that of the ERT Draft Guidance to clarify that the Agency will consider the need for testing in healthy animals on a case-by-case basis.

Finally, BIO also asks the Agency to provide additional clarification with respect to the "limited circumstances" referenced in the Draft Guidance in which "FDA may apply additional flexibility in evaluating the development programs for drugs to treat serious and life-threatening disorders."¹⁴ We recommend a line edit to this section of the Draft Guidance because we believe this clarification would be helpful to Sponsors since there are a myriad number of serious or life-threatening diseases without existing treatments where the FDA has required toxicology studies. The criteria, however broad, that separate the latter circumstances from the former are important for Sponsors to understand, both to be able to plan for the need to conduct toxicology studies and as context in advance of initial meetings with the Agency (e.g., criteria may address the chance of off-target toxicity and/or the extent to which the drug target has been characterized).

IV. Efficacy Endpoints

In general, BIO appreciates the Agency's inclusion of considerations with regard to identifying efficacy endpoints in this guidance. As a general comment, either in the Final Guidance or in future guidance more narrowly focused on endpoint identification and selection, BIO urges FDA to provide significantly more detailed guidance on improving and focusing approaches to endpoint validation specific to the development of a therapy for a rare disease. We agree with the Agency's flexibility and judgement of "substantial evidence" to modify or derive endpoints; however, there is often limited information and patient population size to validate clinical instruments and measures according to standard validation, reliability, feasibility processes and standards. Clarification on "validity, reliability, and feasibility" requirements in the context of rare disease is needed.

In this section of the Draft Guidance, FDA notes that Sponsors should consider a myriad of issues, including "which aspects of the disease are meaningful to the patient and might also be affected by the drug's activity." BIO strongly supports the recognition of the importance of considering endpoints that are meaningful to patients, which is in alignment with the Agency's ongoing patient-focused drug development initiatives. In fact, as part of these initiatives, FDA also has encouraged the use of patient reported outcomes (PROs) in clinical trials. To facilitate this recommendation, BIO urges the Agency to comment on the potential for novel PRO endpoints as the basis for label claims in the Final Guidance, at least

¹¹ Draft Guidance at lines 253-255, 276-280.

 ¹² FDA. 2015 (May). Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment, available at: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm446569.pdf.
¹³ Id. at lines 145-149.

¹⁴ Draft Guidance at lines 268-272.



at a high level, until such time as the Agency defines the standards of evidence needed for inclusion of PROs in the label. The Agency also may want to encourage Sponsors to identify and discuss with FDA any proposed novel endpoints that are directly relevant to patients (whether PROs or other patient-centric data that describe function directly but are reported through other mechanisms, such as through patient advocacy organizations or foundations).

In describing the succession of foci for clinical investigations—first on safety assessments, then to quide dose selection, and finally to determine efficacy and safety-FDA appears to suggest that development programs should conduct successive clinical trials. However, BIO notes that the general, sequential, and segregated template of Phase 1, followed by Phase 2, followed by Phase 3 clinical studies is not generally applicable in the rare disease context. As just one example of the challenges this model presents, there are limited patient populations available to participate in rare disease-focused clinical trials, often making such successive trials infeasible. To address this reality of rare disease drug development more comprehensively, BIO recommends that FDA include a discussion in the Final Guidance about the use of alternative trial designs to overcome this challenge. For example, similar to the discussion in Section IV on biomarkers, FDA should reference enrichment and adaptive studies in the context of identifying efficacy endpoints in order to further highlight the challenges of conducting traditional adequate and well-controlled studies in the rare disease population.¹⁵ We also recommend that FDA identify the potential for flexibility in clinical trial design more broadly in the Final Guidance or future guidance more narrowly tailored to this issue. For example, FDA should offer guidance to Sponsors with respect to the degree to which the Agency demands dose selection be optimized in preapproval studies, requirements for the validation of a PRO instrument for a rare disease population, and/or flexibility in the proof of sensitivity, specificity, and clinical meaningfulness of primary endpoints in very small patient populations.¹⁶

In addition, Sponsors would benefit from a more thorough discussion of the inclusion of relevant clinical endpoints. In particular, FDA should consider addressing the inclusion of relevant clinical endpoints that may not have reached statistical significance by the time of the primary analysis for the relevant biomarker or other outcome measure, but are nonetheless clinically meaningful and demonstrate a positive trend such that the totality of the data can support an approval (e.g., with post-marketing requirements to provide the clinical outcome data at an appropriate data cut point). Consider the following example: a Sponsor has established a primary biomarker-specific endpoint (e.g., the reduction in a substrate) with secondary clinical outcomes-based endpoints (e.g., survival). At the point in time of the primary biomarker readout (e.g., time of the primary analysis), the secondary outcomes measures are trending in a positive direction but have not reached statistical significance. In this example, while the biomarker(s) alone may not be sufficient for approval, when supplemented by the trend in clinical outcomes endpoints, the totality of the data is sufficient for an approval in a rare disease setting. Thus, to the extent that a Sponsor's circumstance fits these, and potentially other FDA-defined parameters, BIO believes that the result of allowing the inclusion of these clinically relevant endpoints would result in an earlier full approval than could otherwise be expected in the absence of this flexibility. This could mean significant relief for rare disease patients without other treatment options. However, additional Agency guidance is necessary on this subject to

¹⁵ <u>Id</u>. at lines 399-401.

¹⁶ Sasinowski, F. J. 2011. *Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs*. NORD, available at: <u>http://nordphysicianguides.org/wp-content/uploads/2012/02/NORD-study-of-FDA-approval-of-orphan-drugs.pdf</u>.



inform Sponsors in this position and to establish a basis, and context, for Sponsor-Agency discussions on specific clinical development programs. At a minimum, FDA should reiterate support for early Sponsor communications with the Agency to be able to receive tailored guidance based on the Sponsor's specific situation.

Finally, BIO believes that Sponsors would benefit from guidance with respect to the use of modeling and simulation to guide dose/dose regimen selection with limited data, otherwise omitted in the Draft Guidance. We encourage FDA to include a high level discussion of this issue in the Final Guidance, including any examples the Agency believes are particularly instructive to Sponsors in this space, and/or to address associated issues in future guidance more narrowly tailored to this issue.

V. Evidence of Effectiveness and Safety

In its discussion of sufficient evidence of effectiveness and safety, FDA identifies design features that an adequate and well-controlled study must include, the last of which is "methods of analysis adequate to assess effects of treatment (e.g., an appropriate statistical analysis plan)."¹⁷ BIO appreciates the need for rigorous study design to evaluate whether a drug is effective and safe. We also agree, and appreciate the Agency's recognition, that "the investigation of potential drugs for the treatment of rare diseases is challenging, and study approaches used in common diseases are not always feasible for rare diseases."¹⁸ However, given this assertion, we recommend the Agency include—in the Final Guidance or future guidance more narrowly tailored to this issue—examples of flexibility that FDA would consider in the context of rare disease drug development to satisfy standards for effectiveness and safety, including the application of innovative statistics additional examples of the appropriate application of innovative statistics (e.g., Bayesian statistics) to rare disease drug development. Such a discussion would aid Sponsors in understanding the potential application of these state-of-the-art methods to improve the efficiency of rare disease drug development. FDA and individual Sponsors also should aim to identify these types of innovative statistical models early on in drug development, an effort that could serve as a level foundation upon which further Agency-Sponsor communication could proceed (e.g., based on the specifics of the population and the therapy). While the European Medicines Agency has openly encouraged the use of these innovative statistical techniques for rare disease drug development, FDA's assessment of how to appropriately utilize such statistical methods remains unclear.¹⁹

Additionally, in considering specific guidance on demonstrating sufficient evidence of safety and effectiveness, BIO asks the Agency to provide examples of, and clarity to its perspective on, the appropriate considerations a Sponsor should take into account in two particular instances. First, as a general theme of BIO's comments, we began this response to the Draft Guidance with a request for additional guidance on pediatric rare disease drug development in general. We reiterate this request, in particular, in this section, and ask for examples of mechanisms to overcome the challenges of demonstrating sufficient evidence of effectiveness and safety in pediatric rare disease drug development in the Final Guidance, or future guidance, given that these challenges often exceed those that exist for rare

¹⁷ Draft Guidance at lines 474-47512.

¹⁸ <u>Id</u>. at lines 517-519.

¹⁹ European Medicines Agency (EMA). 2007. *Guideline on Clinical Trials in Small Populations*. Committee for Medicinal Products for Human Use (CHMP), available at: <u>http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf</u>.



disease drug development in adults. Second, BIO asks FDA to provide examples of considerations Sponsors should take into account when including patients from clinical sites outside of the U.S., especially in non-developed countries. The need to aggregate clinical data from multiple sites, often including international sites, is a practical reality in rare disease drug development given the small patient populations involved. Specifically, to achieve statistical significance, Sponsors often must recruit patients from multiple countries, including from developing countries, in which significant numbers of patients with a rare disease reside.

BIO also applauds the Agency's "commitment to expediting the availability of drugs for serious diseases as soon as it can be concluded that the benefits of the drugs exceed their risks."²⁰ However, in the Final guidance, we ask FDA to consider providing additional specificity, in the form of examples, with respect to how severity of disease and the availability, or lack thereof, of alternative treatments are taken into account in the benefitrisk assessment for therapies that treat, or cure, rare diseases. In particular, FDA should provide greater clarity with regard to how it considers the risks of the rare disease itself if patients are treated with the current standard of care (especially in cases where there is no alternative treatment) and the level of tolerance for risk and uncertainty acceptable to patients with a specific rare disease. We understand that the Agency is working on a number of fronts to make its benefit-risk assessment more relevant to the specific disease/condition being studied, and ask that FDA more clearly identify the application of this work to rare disease drug development and continue to work with stakeholders to consider additional efforts on this critical topic specific to rare diseases.

VI. Chemistry, Manufacturing, and Controls

In this section of the Draft Guidance, FDA identifies the potential that there may be a transfer of manufacturing responsibilities after initial testing, a possibility that introduces the potential for unanticipated changes to drug characteristics. In the event that significant differences are identified in drug characteristics after such a change (compared to batches used in earlier studies), then additional nonclinical and clinical studies may be needed. BIO supports the principles of robust CMC plans FDA identifies in this section of the Draft Guidance. In considering the application of these principles in the rare disease context, we note that rare disease therapies may be manufactured in limited—and perhaps extremely limited—quantities based on the total supply and demand of the patient population and/or the static magnitude of rare disease population changes. The natural consequence of this reality is that there may be limited CMC data with regard to characterization and processes, to name a few. We believe it is important that the Agency identify how it will handle the issue of limited existing data, especially considering that the generation of additional data may significantly delay the availability of a novel therapy to patients who, in many instances, have no alternative options. FDA could address this important issue in the Final Guidance or in future guidance relevant to this narrower issue.

Furthermore, due to significant implications and the need to improve CMC validation process for application of accelerated programs, including rare disease and Orphan developments, we request the Agency provide a separate specific guidance on CMC recommendations for accelerated programs. In particular, such guidance should note the potential challenges in this space that are specific to rare disease drug development. This additional guidance would enable Sponsors – and particularly Sponsors of rare disease

²⁰ Draft Guidance at lines 500-504.



therapies – to better understand when and how to leverage prior platform experience and site/technologies knowledge to expedite CMC-validation with marketing application. In particular, the limited number of patient-exposure years for ultra-rare and rare diseases provide appropriate justification for a modified CMC-validation package from the standard requirements.

VII. Conclusion

BIO appreciates this opportunity to comment on the Draft Guidance for Industry "Rare Diseases: Common Issues in Drug Development." We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Respectfully submitted,

/s/

Kristin Viswanathan Director, Health Policy & Research Biotechnology Industry Organization

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Specific Comments

<u>SECTION</u>	<u>ISSUE</u>	PROPOSED CHANGE		
I. INTRODUCTION				
II. BACKGROUND				
III. NATURAL HISTORY STUDIES				
Lines 102-103:	The Draft Guidance states, "Understanding and implementation of critical elements in clinical study design, such as study duration and choice of subpopulations."	BIO suggests editing the text for clarity: "Understanding and implementation of critical elements in clinical study design, such as study duration, and choice of subpopulations, and appropriate control group."		
Lines 150-152:	The Draft Guidance discusses the potential use of natural history data as a historical comparator.	BIO suggests adding to the text as follows: "Longitudinal studies characterize the course of disease within individuals and better enable different phenotypes to be distinguished. <u>To the extent possible, the conduct and</u> <u>analysis of natural history studies should follow Good</u> <u>Clinical Practice guidelines. Furthermore, the Agency</u> <u>advises full transparency regarding what observational</u> <u>studies are being undertaken and the resulting findings."</u>		
Lines 153-155:	The Draft Guidance states, "The potential use of natural history data as a historical comparator for patients treated in a clinical trial is often of interest but the challenges associated with the use of historical controls are well recognized."	BIO suggests editing the text as follows: "The potential use of natural history data as a historical comparator for patients treated in a clinical trial is often of interest, but the challenges associated with the use of historical controls are well recognized. <u>However, as these</u> <u>populations are typically limited, historical controls from a</u> <u>natural history study can be considered in rare disease</u>		



SECTION	<u>ISSUE</u>	PROPOSED CHANGE		
		studies."		
IV. DISEASE PATHOPHYSIOLOGY AND IDENTIFICATION AND USE OF BIOMARKERS				
V. NONCLINICA	L STUDIES			
Lines 268-272	The Draft Guidance states, "FDA may apply additional flexibility in evaluating development programs for drugs to treat serious and life-threatening disorders. Under limited circumstances, clinical studies can proceed in the absence of standard toxicology studies; however, this approach should be well justified and is only appropriate for serious or life- threatening diseases where current treatments, if any, are inadequate."	BIO suggests editing the text as follows: "FDA may apply additional flexibility in evaluating development programs for drugs to treat serious and life- threatening disorders:- for serious or life-threatening diseases for which treatments are not available or are inadequate, as a general matter, it may be appropriate to permit clinical trials to commence based on less than usual nonclinical testing if scientifically justified. Under limited circumstances, clinical studies can proceed in the absence of standard toxicology studies; however, this approach should be well justified and is only appropriate for serious or life-threatening diseases where current treatments, if any, are inadequate."		
VI. EFFICACY ENDPOINTS				
Lines 399-401:	The Draft Guidance States, "Clinical outcome assessments are usually the basis of endpoints of adequate and well- controlled studies (section VII) that will provide the substantial evidence of effectiveness supporting marketing approval of the drug."	BIO suggests editing the text to read: "Clinical outcome assessments are usually the basis of endpoints of adequate and well-controlled studies (section VII) that will provide the substantial evidence of effectiveness supporting marketing approval of the drug. <u>In</u> <u>addition, enrichment and adaptive studies should be</u> <u>considered</u> ."		
VII. EVIDENCE OF EFFECTIVENESS AND SAFETY				



SECTION	ISSUE	PROPOSED CHANGE		
VIII. CHEMISTRY, MANUFACTURING, AND CONTROLS				