March 18, 2020

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

Re: Docket No. FDA–2019-D-4964: FDA Draft Guidance, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO thanks FDA for developing this additional guidance on demonstrating substantial evidence of effectiveness. BIO understands that the new guidance is intended to be complementary to the 1998 guidance entitled *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*[1] by reflecting FDA's current thinking on trial designs, endpoints, and analysis, and the Agency's longstanding flexibility when considering the types and amount of evidence for demonstrating effectiveness.

In this letter we provide key areas that we request FDA to consider when finalizing the Guidance as well as redline edits that we hope will help clarify some of FDA's points.

I. The Guidance Should be Combined with Existing FDA Guidance on Effectiveness.

BIO believes that the new Draft Guidance provides important information for drug developers, especially given the advances in science and regulatory science since the publication of the 1998 Guidance.[2] However, BIO strongly encourages FDA to consolidate the content of the 1998 Guidance and the new content introduced in the 2019 Draft Guidance into a new, single, revised draft guidance. In several parts of the new Draft Guidance, FDA refers to sections of the 1998

[1] FDA Guidance on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.
[2] FDA Guidance on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

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Guidance on the same topic and currently two guidance documents on the topic requires Sponsors, reviewers, and other stakeholders to refer across two documents for the totality of FDA's thinking on a given issue. Furthermore, FDA will soon be adding to the Agency's overall guidance on substantial evidence of effectiveness when it publishes the forthcoming Draft Guidance on use of real-world evidence to support safety and effectiveness determinations.[3] At that time, there will be three guidances on this topic when arguably there should be, at most, two (one within the context of clinical studies and one within the context of non-interventional studies). By doing so, industry and FDA staff would have a single document to reference rather than two complementary guidances on the same topic, minimizing confusion and promoting clarity around FDA's current thinking on the state of the science. Consolidating the 1998 and 2019 guidance would also allow FDA to update the examples in the 1998 guidance with more recent examples. Additionally, over the last 20 years, FDA has increased transparency of the Agency's review and decision-making process by posting comprehensive action packages on FDA's website. More recent case examples where a comprehensive action package is available would enhance stakeholder understanding of FDA's thinking on this issue.

II. The Guidance Should More Clearly Indicate FDA's Flexibility Around Data and/or Evidence from a Range of Sources for Demonstrating of Substantial Evidence for Effectiveness.

BIO appreciates FDA's reference to the use of real-world-data/real-world evidence (RWD/RWE) in the context of demonstrating evidence for effectiveness; however, other significant and robust sources of data also could be leveraged to inform, compliment, or make more substantial the weight of evidence of effectiveness. For example, sponsors often have a range of study data going many decades and spanning multiple populations. These data may or may not have been powered to examine certain outcomes as a primary endpoint but may have incorporated other secondary endpoints or analyses that could inform or help support a determination of effectiveness. Likewise, where data collected in randomized controlled clinical trials were not deemed adequate at that time, or may have fallen short of a historic, prescriptively predetermined endpoint; nonetheless, these data could be useful in confirming or supporting a determination of effectiveness. Data captured in studies conducted outside the U.S., outside of an IND, also could be considered and included in support of an application and may be more rigorous or analogous to traditionally accepted randomized controlled clinical trial data than RWD. BIO strongly believes that all available and appropriate data should be leveraged to inform decisions about effectiveness, and we encourage FDA to indicate that in the final version of the Draft Guidance.

BIO also requests that FDA make it clear in the final version of the Guidance that while RWD/RWE can be used within the context of confirmatory studies, RWD/RWE also has the potential to be leveraged as evidence for effectiveness. Additionally, in many cases real-world evidence may better reflect safety and efficacy in the real-world setting. Especially as regulatory science discussions around RWD/RWE continue to advance and pilot programs help us understand the power of RWD, the guidance should not be overly limiting the uses of RWD/RWE which could limit the Agency's ability to later conclude that RWE can have a broader role in FDA's conclusion of substantial evidence of effectiveness. BIO notes that FDA is currently working through

[3] FDA PDUFA Reauthorization Performance Goals and Procedures, Fiscal Years 2018-2022.

considerations on the use of RWE to meet FDA's evidentiary standard and looks forward to the required draft guidance on the use of RWE to support efficacy and safety determinations.

III. The Guidance Should Include Reference to the Use of Patient Experience Data in the Context of Demonstrating Substantial Evidence for Effectiveness.

Over the last several years through PDUFA V, PDUFA VI, and 21st Century Cures, the Agency has shown a strong commitment to supporting patient input, and the requirement in law that it explain its accounting for patient experience data in the context of the benefit-risk framework and statement of patient experience. BIO notes that the draft guidance describes the subjective nature of patient- and clinician-reported outcomes (PRO/ClinRO). BIO encourages FDA to provide additional context regarding PROs and ClinROs to describe their potential value and contribution to FDA's overall conclusion on substantial evidence of effectiveness. While these tools involve some element of subjectivity, they are recognized as an appropriate method by which to gather relevant data regarding patients' experiences with diseases and treatments, including how patients feel and function. When these data are captured by reliable and well-defined tools and analyzed and interpreted according to pre-specified and scientifically sound methods, patient reported outcomes (PROs) and other assessments from clinicians and caregivers can provide a reliable evaluation of a treatment's clinical benefit. BIO believes these endpoints can serve as a rich source of data regarding the patient experience that provides information that is distinct from and complementary to what can be obtained with more traditional objective endpoints. Therefore, BIO recommends that FDA provide more detail to describe how patient experience data, specifically COAs are considered in the totality of evidence assessment. For example, it would be helpful for FDA to address under what circumstances COA data would be influential in FDA's conclusion of substantial evidence of effectiveness. BIO requests that FDA confirm in the final version of the Guidance that COAs can contribute to the demonstration of substantial evidence of effectiveness, under appropriate circumstances. Additionally, BIO recommends that the Draft Guidance reference other types of patient input in the context of drug development, review, or subsequent approval. While we understand that this Draft Guidance is addressing data used to inform determinations of "substantial evidence," a lack of reference to other types of patient experience data may cause stakeholders to conclude that FDA does not view those data types as important for drug review. BIO requests that FDA confirm in the final version of the Guidance that patient experience data (e.g., COAs, patient preference information, and other data on a patients' lived experience) is always considered relevant for the development of outcomes measures and review, including benefit-risk assessments and/or determinations of substantial evidence for effectiveness.

IV. The Guidance Could Benefit from Examples that are Relevant to the Center for Biologics Evaluation and Research (CBER)-Regulated Products.

While BIO appreciates the examples that FDA has included throughout the Draft Guidance, it does appear that the majority of the examples are Center for Drug Evaluation and Research (CDER)-regulated examples. Given that the Draft Guidance is applicable to both CDER and CBER-regulated products, BIO requests that FDA consider incorporating more examples to better illustrate how the Draft Guidance applies to CBER-regulated products.

V. The Guidance Should Reflect Flexibility with Respect to the Full Range of Therapies and Patients.

Generally, the guidance reflects FDA's willingness to be more flexible in certain contexts, especially for rare and life threatening or severely debilitating conditions which is appreciated. However, we request that FDA incorporate discussions of rare diseases through the Draft Guidance, rather than just in the section focused on determination of substantial evidence of effectiveness for rare diseases.

BIO also requests that FDA acknowledge flexibility with respect to the full range of therapies and patients. Patients suffering from chronic, potentially more common illnesses, for instance, also should benefit from newer/ better therapies, or more informed treatment regimens, based on new uses of available data. To this end, BIO requests that FDA elaborate on how flexibility may be applied to a wide rage of diseases and therapies.

Finally, BIO also believes that the Guidance would be strengthened if there was an additional section that addressed flexibility pertaining to modalities of certain therapies (e.g. gene therapy products). In particular it would be helpful if FDA referenced, as relevant, the final guidance documents pertaining to gene therapies that were released earlier in 2020[4] and provided additional detail regarding clinical trials designs, including use of external controls and adaptive trials or master protocols.

BIO appreciates this opportunity to submit comments regarding FDA's Draft Guidance, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

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

[4] FDA Cellular and Gene Therapy Guidances.

SPECIFIC COMMENTS

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I. INTRODUCTION		
Entire document	The guidance uses "effectiveness" throughout. However, "efficacy" and "effectiveness" are important and serve distinct purposes (e.g., efficacy from clinical trials is an estimate of the expected effectiveness of the drug in the patient population). This distinction should be discussed early in the document.	BIO requests that FDA include reference to both "effectiveness" and "efficacy" as well as the distinctions between the two terms in the final version of the guidance.
Lines 67-68	In this section FDA indicates that "*For drugs granted accelerated approval, FDA requires post-approval trials to verify the predicted clinical benefit.*"	BIO encourages FDA to describe more clearly the instances in which FDA might allow post-approval studies to include other confirmatory evidence (e.g., RWE) in addition to clinical trial data to provide substantiation of experimental results. In addition, we request that FDA describe in the guidance the envisioned timelines for the required post-approval trials relative to the accelerated approval; for instance, whether the post-approval trials should be on-going in the context of accelerated approval, or can be initiated later, post-approval.
II. STANDARDS		
Lines 125-126	In this section FDA indicates that "*Under specific circumstances, however, FDA has considered a large multicenter trial that has certain characteristics to satisfy the legal requirement for substantial evidence of effectiveness (discussed in Section II.C.3 of the 1998 guidance and Section IV.A.2).*"	Most trials for obtaining substantial evidence of effectiveness are large multicenter or multi-regional trials. Currently, for most trials, the center effect is either not considered in the analysis model or treated as a fixed effect in the model. BIO requests that the final version of the guidance reflect this. BIO also notes that, although substantial evidence of effectiveness is interpreted as the overall evidence based on data of all patients in the trials, there could be heterogeneity for treatment effects across regions. There are outcome trial examples where the overall treatment effects for the all studies are positive while the observed US treatment effects are numerically negative. Guidance

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		for dealing potentially this kind of issues could be provided. For example, it may be helpful to discuss the appropriate regional (or US) sample size that is large enough to reduce the chance of observing negative regional (or US) treatment effect (ICH E17).
A. Statutory standards		
B. Scientific basis for the statutory standards		
III. THE QUALITY OF CLINICAL EVIDENCE TO ESTABLISH EFFECTIVENESS		
Lines 181-184	In this section FDA indicates that "*Although randomized double-blinded, concurrently controlled superiority trials are usually regarded as the most rigorous design, as discussed further below, five types of controls are described in section 314.126: placebo concurrent control, dose-comparison concurrent control, no treatment concurrent control, active treatment concurrent control, and historical control (a type of external control).*"	BIO requests that FDA also recognize in this section the use of concurrent controls that also leverage historical control data to reduce the sample sizes of the studies. In this kind of design, the amount of historical data used can be dynamic and depend on the consistency of the historical control data and concurrent control data.
A. Trial designs		
Lines 226-229	In this section FDA indicates that "*For these reasons, external control designs are usually reserved for specific circumstances, such as trials of diseases with high and predictable mortality or progressive morbidity (e.g., certain malignancies or certain rare diseases) and trials in which the effect of the drug is self-evident (e.g., general anesthetics)*."	BIO notes that the wording "*are usually reserved*" may discourage the use of innovation in diseases other than those described here, even in situations where improved external controls and improved methodologies to address bias may be available. Therefore, we propose replacing "*are usually reserved*" with "*have usually been reserved.*" We also recommend adding a sentence to this section that indicates that "*Advancements in technology are anticipated to allow us to address the listed challenges and extend the use of external controls to other diseases*."
Lines 231-240	In this section FDA indicates that "*Despite the limitations of externally controlled trials compared with concurrently controlled trials, strong support for effectiveness can emerge*	The language in this section is more stringent than what FDA currently applies in practice in the oncology space. Currently, for "disease where spontaneous regression is not observed," FDA has not required an "external control", where for example, tumors do not ever shrink

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	from externally controlled trials, especially when (1) the natural history of a disease is well defined, (2) the external control population is very similar to that of the treatment group, (3) concomitant treatments that affect the primary endpoint are not substantially different between the external control population and the trial population, and (4) the results provide compelling evidence of a change in the established progression of disease. Such results could include partial or complete response in a disease where spontaneous regression is not observed, or stabilization or improvement in function in a disease where progressive functional decline is well documented to occur over the duration of the treatment period in the trial."	spontaneously. In diseases where tumors do not shrink (or spontaneous recovery is known to be extremely unlikely), a control group, randomized or external, to demonstrate this is usually not required. BIO requests that FDA explicitly indicate in the guidance that in diseases where it is accepted that spontaneous regression does not occur that controls may not be required.
Lines 240-242	In this section the FDA indicates that "*Another example of where there is strong evidence of drug effectiveness is reversal of clinical signs and symptoms following a toxic exposure or overdose after administration of a drug antidote,*" however, a design that demonstrates a reversal of signs of toxic exposure by an antidote is not an externally controlled trial.	BIO requests that the adjacent text be included in a separate paragraph devoted to within subject designs other than cross over.
B. Trial endpoints		
Lines 266 and 61	Patient reported outcomes (PROs) are briefly mentioned in the Introduction (Line 61) with little to no elaboration in the Endpoint Section (Line 266).	As patients are more involved in their healthcare decisions, and patient perspectives are becoming more of an expected component in regulatory decision making, it is critical to explicitly include patient perspectives as evidence to demonstrate effectiveness from patient perspective. Recent FDA guidance has begun to emphasize the important of patient perspectives in endpoint development for specific

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		diseases.[5] BIO requests that FDA provide additional detail regarding how patient's perspectives can inform clinically meaningful endpoint selection.
Line 266	In this section FDA indicates that "*One of the characteristics of an adequate and well-controlled clinical investigation is that "the methods of assessment of subjects' response are well-defined and reliable." Such a method of assessment can be a clinical endpoint or, where appropriate, a surrogate endpoint.*"	This section does not reference the evaluation of the impact of adherence/persistence in taking medicines on clinically meaningful outcomes in real-world setting. BIO requests that in the final version of the guidance FDA include discussion around the impact of adherence in taking medications on clinically meaningful outcomes.
Lines 272-275	In this section FDA indicates that "*Although the statutory standard for effectiveness does not refer to particular endpoints or state a preference for clinical endpoints over surrogate endpoints, it is well established that the effect shown in the adequate and well-controlled clinical investigations, must be, in FDA's judgment, clinically meaningful.*"	We suggest that FDA discuss both "clinical relevance" and "clinical meaningfulness" in this section. FDA must determine that the chosen endpoint is clinically relevant to the disease setting in accordance with its statutory authority and then assess whether the effect (i.e., magnitude) observed on the endpoint is clinically meaningful. We request clarification on how FDA weighs this assessment as part of the benefit-risk framework and approval decision, particularly in circumstances where the primary efficacy endpoints have been met and are clinically relevant. We recommend that the Agency also provide an example in a disease setting that illustrates both terms in FDA's judgment. Such an example could be based on a previously proposed endpoint for a specific disease area (without revealing the product) that was rejected on the basis of being not being clinically relevant or the effect on the endpoint not being clinically meaningful.
C. Statistical considerations		
Lines 285-288	In this section FDA indicates that "*The uncertainty about the findings from each trial should be sufficiently small and the findings*	BIO appreciates and agrees with FDA acknowledging that using a posterior probability is an appropriate statistical method, but we

[5] FDA Draft Guidance on Mucopolysaccharidosis Type III (Sanfilippo Syndrome): Developing Drugs for Treatment.

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	should be unlikely to result from chance alone, as demonstrated by a statistically significant result or a high posterior probability of effectiveness."	suggest making reference to this as a Bayesian method explicit rather than referring to it in a footnote.
IV. THE QUANTITY OF CLINICAL EVIDENCE TO ESTABLISH EFFECTIVENESS		
A. Meeting the substantial evidence standard based upon two adequate and well-controlled clinical investigations		
1. Two adequate and well-controlled clinical investigations		
2. One adequate and well-controlled large multicenter trial that can provide substantial evidence of effectiveness		
Lines 342-350	In this section FDA indicates that "*Reliance on a single large multicenter trial to establish effectiveness should generally be limited to situations in which the trial has demonstrated a clinically meaningful and statistically very persuasive effect on mortality, severe or irreversible morbidity, or prevention of a disease with potentially serious outcome, and with other characteristics described below, and confirmation of the result in a second trial would be impracticable or unethical. For example, conducting a second trial after a strongly positive trial had demonstrated a decrease in post-infarction mortality, or prevention of pertussis would generally present significant ethical concerns. Repetition of positive trials showing only symptomatic benefit would generally not present the same ethical concerns."* It is unclear whether this is in the context of new drug approvals exclusively or also in the context of new indications for drugs that are already approved.	BIO requests that FDA explicitly state whether this section is separate from the guidance under Lines 419-422 ("One adequate and well-controlled clinical investigation on a new indication for an approved drug…") or whether Lines 342-350 could also apply to approvals for new indications for already approved drugs.

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Lines 353-357	In this section FDA indicates that "*In addition to the expectation that the single trial is large and multicenter, there should be no single trial site that is the main contributor to the observed effect, either by virtue of having a much bigger effect or many more patients than other sites; these characteristics help address concerns about bias and chance findings associated with a single trial.*" Assessing the effect of a relatively small number of patients enrolled at one site in the context of many sites could be challenging. Considerable variation in site-level results may be present simply by random chance and abetted by multiplicity. In addition, there is frequently little guarantee of the comparability of patients across sites.	BIO recommends that FDA consider attenuating the statement with a consideration for patient comparability and that the context of sample sizes both within sites and the number of sites should play a role in this consideration.
Lines 363-365	In this section FDA briefly references patient-reported and clinician-reported outcomes as subjective endpoints and indicates that "*Moreover, an effect on a meaningful, objective endpoint, such as certain imaging endpoints, may complement a more subjective endpoint, such as a clinician- or patient-reported outcome*."	While BIO acknowledges that PROs and ClinROS involve some element of subjectivity, they are recognized as an appropriate method by which to gather relevant data regarding patients' experiences with diseases and treatments, including how patients feel and function. BIO requests that FDA acknowledge here that despite their subjective nature, when these data are captured by reliable and well-defined tools and analyzed and interpreted according to pre-specified and scientifically sound methods, PROs and other assessments from clinicians and caregivers can provide a reliable evaluation of a treatment's clinical benefit. We believe that this will help to promote consistent adoption of these approaches across the Agency.
Lines 371-373	In this section FDA indicates that "*Analysis of the results of such trials for consistency across important patient subgroups can address*	In the setting of two adequate and well-controlled clinical investigations, meta-analysis approaches should be allowed for subgroup analyses to increase the subgroup sample sizes for more

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	concerns about generalizability of findings to various populations in a manner that may not be possible with smaller trials or trials with more narrow entry criteria."	robust subgroup results. BIO requests that FDA explicitly state this in the updated version of the guidance.
Lines 376-380	In this section, FDA indicates that "*For example, the multicenter trial may sometimes be appropriately analyzed as "multiple trials" within a single trial. An example is a 4-arm ("2×2 factorial") trial (placebo, drug A, drug B, and drug A + drug B) in which the effectiveness of drug A could be supported by two controlled comparisons if the combination of drug A + drug B is superior to drug B alone and drug A is superior to placebo."*	Generally, multiplicity adjustments are only performed within a study. Within the context of the adjacent language, it is not clear as to whether FDA is recommending that multiplicity adjustments also be performed across "multiple trials". BIO also believes that the example provided does not clearly align with the concept discussed in the guidance.
B. Meeting the substantial evidence standard based on one adequate and well-controlled clinical investigation plus confirmatory evidence		
1. One adequate and well-controlled clinical investigation on a new indication for an approved drug, supported by existing adequate and well-controlled clinical investigations (s)		
2. One adequate and well-controlled clinical investigation supported by data that provide strong mechanistic support		
3. One adequate and well-controlled clinical investigation with compelling results, supported by additional data from the natural history of a disease		
Lines 458-459	In this section FDA indicates that "*In certain circumstances, FDA accepts one adequate and well-controlled clinical investigation that has generated compelling results as the basis to demonstrate effectiveness, when the single trial is supported by additional data from the natural history of the disease that reinforce the very persuasive finding,*" however FDA does not include information regarding considerations for variability historical data.	BIO recommends that the Agency clarify this statement by stating that unless historical data can be characterized as comparable in its conduct (e.g. another clinical trial conducted under similar circumstances), the historical data should simply qualitatively inform what null values can be considered for a one-sample test of the current study.

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4. One adequate and well-controlled clinical investigation of the new drug, supported by scientific knowledge about the effectiveness of other drugs in the same pharmaceutical calls		
C. Meeting the substantial evidence standard for a new population or a different dose, regimen, or dosage form, based on reliance of FDA's previous findings of effectiveness of an approved drug when scientifically justified and legally permissible		
Entire Section	BIO appreciates that the Draft Guidance indicates that effectiveness of a new dosage form or dosing regimen many be demonstrated by the effectiveness trial(s) on the original dosage form or regimen but believe that flexibility should also apply to new routes of administration.	BIO requests that FDA provide detail in the final version of this guidance on how the Agency will consider regulatory flexibility in what constitutes substantial evidence for the registration of a new route of administration.
V. EXAMPLES OF CLNICAL CIRCUMSTANCES WHERE ADDITIONAL FLEXIBILITY MAY BE WARRANTED		
Lines 508-685	The guidance could specifically address opportunities for flexibility with regard to gene therapy products. Gene therapy products have inherent qualities that make them candidates for additional flexibility.	BIO requests that FDA consider including an additional subsection within this section, to note that additional flexibility may be warranted in some instances on the basis of the modality of the product.
Lines 520-536	In this section FDA indicates that "*FDA experts may 'fairly and responsibly' rely on study designs that produce less certainty in some circumstances…FDA would not, however, find it responsible to rely on such design choices in other situations in which, for example, the drug will be used for a less serious disease and greater certainty about benefits and risks is needed, or in cases where designs providing more certainty are possible.*" The current wording suggests that the considerations – 1) a drug for a less serious disease and greater certainty about benefits and	We believe FDA's intent is that in the context of a drug for a less serious disease where greater certainty of the benefit-risk assessment may be needed, FDA would be less willing to accept alternate study designs when a design providing more certainty is possible. To this end, we suggest the following edit for increased clarity: "FDA experts may 'fairly and responsibly' rely on study designs that produce less certainty in some circumstances…FDA would not, however, find it responsible to rely on such design choices in other situations in which, for example, the drug will be used for a less serious disease**,** ~~**and**~~ greater certainty about benefits and risks is needed, **and** ~~**or**~~ in cases where when designs providing more certainty are ~~**possible**~~ **feasible and ethical**."

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	risks is needed and 2) cases where designs providing more certainty are possible – are considered separately.	
A. When the disease is life-threatening or severely debilitating with an unmet medical need		
Footnote 29	This footnote refers to the FDA guidance on expedited programs but is vague. Furthermore, unmet medical need is an important enough term in drug regulation that this reference to the guidance where unmet medical need is further defined should be part of the body rather than a footnote.	We suggest that FDA delete the footnote and refer to the Agency's discussion of unmet medical need in the expedited program guidance in Section V.A of the new draft guidance where "life-threatening" and "severely debilitating" are defined.
1. Trial Design		
Lines 571-573	In this section FDA indicates that "*While a randomized placebo-controlled trial can provide more definitive evidence of a small treatment effect than any other kind of trial of the same size, there are instances when this design and other concurrently controlled superiority designs may not be feasible or ethical.*"	BIO requests that FDA consider including examples of when a randomized placebo-controlled trial may not be feasible or ethical for a serious disease where treatment is available but could be improved. For example, we recommend that FDA cite their guidance on placebos and blinding in oncology[6] which was finalized last year and recognizes that placebo-controlled trials are unethical in cancer clinical trials where treatment is available, and also describes when blinding is not appropriate in these settings. We would ask FDA to extend this flexibility to include serious diseases beyond oncology where treatment is available but could be improved upon or in patients who have exhausted all available therapy.
Lines 573-576	In this section FDA states, "*In such settings, other trial designs, such as non-inferiority trials or externally controlled trials can be acceptable if they provide substantial evidence of*	BIO requests that FDA expand this section to include a discussion on alternative designs such as enrichment, adaptive, and N-of one or where each patient serves as his or her own control.

[6] FDA Guidance on Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drugs and Biologics.

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	effectiveness (see discussion of noninferiority design and external control in Section III.A).”	
2. Trial Endpoints		
3. Number of Trials		
4. Statistical considerations		
Lines 604-608	In this section FDA indicates that *“A typical criterion for concluding that a trial is positive (showed an effect) is a p value of < 0.05 (two sided). A lower p value, for example, would often be expected for reliance on a single trial. For a serious disease with no available therapy or a rare disease where sample size might be limited, as discussed further below, a somewhat higher p value – if prespecified and appropriately justified – might be acceptable.”* While a p value of 0.05 is not a statutory or regulatory requirement, we agree that in situations of high unmet need or a rare disease, it is appropriate to prespecify a higher p value. However, FDA should go beyond frequentist methods in diseases where there is a high unmet need. FDA notes earlier in the document that substantial evidence can also be achieved using a Bayesian method to demonstrate a high posterior probability of drug effect.	BIO requests that FDA address both frequentist and Bayesian methods in Section V.A.4. BIO also requests that more specific guidance on the level of rarity for flexibility in the p-value would be helpful. Additionally, this guidance should cross-reference the Expedited Pathways guidance to ensure the definition of “available therapy” is being used consistently. To this end, BIO requests that FDA state that all diseases affecting fewer than 200,000 people in the US would be allowed additional consideration in terms of p value.
B. When Diseases are Rare		
Lines 612-677	General comment on classification of rarity for purposes of flexibility.	Challenges in demonstrating effectiveness in a population of 200,000 may be different than in a population of 2,000 or even 2. We recommend the guidance reflect the need for a continuum of flexibility that considers the rarity of the population or sub-population. FDA should exercise discretion to apply flexibility as necessary to address

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		challenges associated with demonstrating effectiveness across the spectrum of rarity.
1. Trial design		
Line 639	In this section, FDA indicates "*a single-arm trial with an external control is an appropriate option*"	BIO requests FDA to further develop this section, specifically to include additional guidance, with examples, on situations when FDA will consider alternative trial designs such as single arm trials with an external control, a placebo group from a study used to approve another drug, or a delayed active drug enrollment such that subjects can act as their own control.
Lines 640-641	In this section FDA indicates that "*The ability of these or other trial designs to generate substantial evidence of effectiveness is dependent on the specifics of each situation.*" Extrapolation of efficacy between various age subsets is an important mechanism to provide substantial evidence of effectiveness.	BIO recommends FDA add information on extrapolation of efficacy between various age subsets and how this can provide substantial evidence of effectiveness in the rare disease population.
Lines 643-646	In this section FDA indicates that "*Sponsors of drugs intended for rare diseases should consider designing their first-in-human trial to be an adequate and well-controlled clinical investigation that has the potential, depending on the trial results, to provide part of the substantial evidence of effectiveness to support a marketing application.*" The use of the word "should" seems to indicate that FDA has experience with first-in-human trials for rare disease drugs being designed for purposes of product registration.	BIO requests that FDA provide an example where a first-in-human trial was designed to be an adequate and well-controlled investigation that contributed to a demonstration of effectiveness. We specifically request additional guidance, with examples, on situations when FDA will consider alternative trial designs such as single arm trials with an external control, a placebo group from a study used to approve another drug, or a delayed active drug enrollment such that subjects can act as their own control. BIO also requests that FDA expand this section to include that for rare diseases, depending on the clinical trial results, FDA may consider one trial to be sufficient to provide substantial evidence of effectiveness to support a marketing application.

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2. Trial endpoints		
Lines 652-655	In this section FDA states, "*In cases where utilizing clinical endpoints is not feasible because changes in symptoms and disease status occur too slowly to be measured in a clinical trial of reasonable duration, surrogate endpoints may be considered.*"	BIO recommends that this section is further developed, specifically with further consideration given to other endpoints beyond surrogate endpoints. For rare diseases those that are very low prevalence and heterogenous in nature, novel approaches are required. For example, Multi-Domain Responder Index (MDRI) that allowed translation of multiple clinical measures into a combination responder endpoint have been used to assess using minimally important difference (MID) thresholds without penalizing for non-assessable endpoints in a heterogeneous patient population. Each subject then acted as his/her own control. Examples such as this would be helpful to include in this section of the Draft Guidance.
Lines 655-656	In this section FDA states, "*It will be particularly important to understand the pathophysiology and natural history of the disease to help identify potential surrogate endpoints.*"	BIO requests that FDA add a reference to the guidance on natural history studies in rare diseases.[7]
3. Number of trials		
4. Statistical considerations		
Lines 672-677	The draft guidance notes, "*FDA may interpret the substantial evidence standard flexibly considering the harmful consequences of false negative and false positive results and the amount of evidence that can practically be acquired,"* but does not mention how a p value would be considered, particularly one that may not definitively meet a positive effect of <0.05. It is critical to explicitly address this in the guidance since achieving a p-value of <0.05 (although not a statutory or regulatory	To enhance the understanding and complexity of clinical trial development for rare diseases as discussed in this draft guidance, we recommend the following addition to the end of line 677: "Statistical approaches to evaluate treatment for rare diseases should consider... S**trongly trending results in favor of experimental treatment may also be considered to establish effectiveness**." And

[7] FDA Draft Guidance: Rare Diseases: Natural History Studies for Drug Development.

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	requirement) remains a key consideration by the agency in assessing the effectiveness of the experimental treatment in rare diseases.	We recommend that line 674 "amount of evidence that can practically be acquired" be amended to read: "**the totality of** ~~**amount**~~ of **the** evidence that can practically be acquired'.
C. When conducting a human efficacy trial is not ethical or feasible		