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December 18, 2023

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

Re: FDA-2023-D-2318; Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence

Dear Recipient:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the request for information and comments on the **Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence.**

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BIO appreciates FDA's release of this draft guidance as it provides additional details regarding the types of evidence could be considered confirmatory to support a single adequate and well-controlled (AWC) study and meet the statutory requirements for "substantial evidence" for approval. Along with FDA's 2019 *Demonstrating Substantial Evidence of Effective for Human Drug and Biological Products* guidance, this will help sponsors better understand how the Agency is interpreting their statutory authority and how scientific judgment is being applied in evaluating drug effectiveness.

While we acknowledge that FDA includes the basis of its regulatory decisions in summary approval documents, we note that it may be difficult to determine what sources of evidence supported a conclusion of substantial evidence of effectiveness. Therefore, we suggest that to increase transparency about its underlying rationale, the FDA should include a short statement in review summaries that clearly notes the types of confirmatory evidence that FDA considered in its determination that the evidentiary standard was met. This section can be built into an appendix to the guidance, similar to how FDA does in a Q&A guidance. This provides information shared relating to meeting "substantial evidence" criteria rather than individually searching through various summary basis of approvals.

Consistency and Harmonization with Other Guidance
As this draft guidance is complementary to the 2019 guidance, BIO suggests that this draft guidance (2023) can be further incorporated into the 2019 draft guidance to facilitate harmonization. This could be an opportunity to add examples like the ones we see in this 2023 guidance to the 2019 guidance in Section III, *The Quality of Clinical Evidence to Establish Effectiveness*, to help sponsors better understand the quality of evidence the FDA believes demonstrates substantial evidence.

Although several examples now exist, we note that the draft guidance lacks practical examples of cases where a single study plus confirmatory evidence supported approval decisions. We ask FDA to consider referencing practical examples on the FDA website where approval decisions were based on a single study plus different types and amounts of confirmatory evidence, with commentary about the acceptability of the approach as well as anonymized cases where approval was not supported. This could include links to publicly available review documents or publications. Older FDA guidance has provided some examples to illustrate where these approaches (i.e., 1-AWC) might be considered more appropriate than when they are not.

Lastly, BIO suggests FDA include the reference in footnote 2 of the 1998 guidance *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* to maintain clarification on the use of effectiveness and efficacy as they tend to be confused within the scientific community.

Practical Examples for Additional Considerations

The draft guidance clarifies that the strength of the confirmatory evidence will be evaluated relative to the robustness of the evidence from a single AWC trial. FDA suggested that the quantity of confirmatory evidence needed to support effectiveness, therefore, may vary across development programs and a highly persuasive single trial could potentially be supported by a lesser quantity of confirmatory evidence. We ask FDA to elaborate on the acceptable level of uncertainty regarding the quantity and quality of confirmatory evidence relative to the single trial. Specifically, we suggest that FDA better define, clarify or provide examples illustrating the types and amount of confirmatory evidence that might be sufficient to support a “highly” versus “less persuasive” adequate and well-controlled clinical investigation. The Agency should also provide insights on the range of flexibility in substantial evidence determinations, and cases where such flexibility may be appropriate. Such information will help sponsors understand the relationship between the strength and rigor required for confirmatory evidence relative to the single trial, and situations where uncertainty may be acceptable (e.g., severely debilitating diseases, high unmet needs).

In prior guidance, FDA has indicated that the rarity and seriousness of a disease and the availability of treatment (e.g., unmet medical need) help determine the acceptable level of uncertainty for an AWC study. We appreciate that FDA has acknowledged that the approach to establishing substantial evidence of effectiveness with a single AWC should consider the clinical context of the proposed therapy, including unmet need and the size of the patient population. We urge the Agency to explicitly recognize the need for flexibility to accept alternative lines of confirmatory evidence in rare diseases. In addition, we believe the guidance should provide additional descriptions of the types of evidence that are appropriate for determining substantial evidence of effectiveness based on the severity of the disease and/or degree of unmet need. We also suggest training review staff on the use of this guidance.

BIO is pleased that FDA included real-world evidence (RWE) as a type of confirmatory evidence that can, in appropriate circumstances, be used to substantiate one adequate and well-controlled clinical investigation to demonstrate substantial evidence of effectiveness. BIO recommends that to provide more clarity regarding the requirements for the use of RWE, FDA include examples of approved drugs that have successfully used confirmatory evidence, including RWE, to support approval across disease settings.

Lastly, BIO suggests FDA further expand on the use of early clinical data as confirmatory evidence and provide more examples (e.g. early ranging studies) as there are missing examples on early clinical data. Specifically, the FDA released a poster for the 2023 FDA Science Forum titled "FDA Confirmatory Evidence of Effectiveness Used to Support Non-Oncologic Rare Disease Novel Drug Marketing Application Approvals, CY 2020-2022" describes evidence from an additional clinical study (e.g., early proof of concept, dose-finding, and safety studies) as one of the most commonly used categories of confirmatory evidence in recent non-oncologic rare disease new molecular entities (NME) drug approvals. This use of additional clinical studies as confirmatory evidence is not described in this new guidance and would be helpful if mentioned. A public workshop on this topic could help reinforce the principles described in the guidance and would be beneficial for all stakeholders.

Sincerely,

/s/
Neil Ichiro Laruan
Manager, Science & Regulatory Affairs
Biotechnology Innovation Organization

LINE-BY-LINE RECOMMENDED EDITS

SECTION/ LINE	ISSUE	PROPOSED CHANGE
I.	**Introduction (Section 1)**	
II.	**Background and Scope**	
76 - 83	This guidance supplements the discussion in the 2019 Effectiveness draft guidance by providing further detail on the use of data drawn from one or more sources (e.g., clinical data, mechanistic data, animal data) to substantiate the results of one adequate and well-controlled clinical investigation. This guidance describes factors to consider when assessing whether a single adequate and well-controlled clinical investigation and confirmatory evidence are sufficient to demonstrate substantial evidence of effectiveness.	"This guidance supplements the discussion in the 2019 Effectiveness draft guidance by providing further detail on the use of data drawn from one or more sources **of confirmatory evidence** (e.g., clinical data, mechanistic data, animal data) to substantiate the results of one adequate and well-controlled clinical investigation. This guidance describes factors to consider when assessing whether a single adequate and well controlled clinical investigation ~~and~~ **in conjunction with** confirmatory evidence are sufficient to demonstrate substantial evidence of effectiveness"
89-91	"This guidance does not discuss the development paradigm in which, under certain circumstances, a single multicenter trial can satisfy the legal requirement for substantial evidence of effectiveness;" The 2019 draft guidance (IV.A.2) had a section dedicated to "One adequate and well-controlled large multicenter trial that can provide substantial evidence of effectiveness."	"This guidance does not discuss the development paradigm in which, under certain circumstances, a single ~~**multicenter**~~ **robust** trial can satisfy the legal requirement for substantial evidence of effectiveness;"
III.	**General Considerations Regarding Confirmatory Evidence and the Demonstration of Substantial Evidence of Effectiveness**	
131-139	This language brings up an important point about the quality of the data that comes from an adequate and well controlled clinical investigation	Add a sentence on line 139: "In a similar vein, highly persuasive data from an adequate and well controlled clinical investigation may indicate that a second adequate and well-

	and how that will impact the necessary confirmatory data. Going one step further, it may be accurate to say that highly persuasive data from one adequate and well controlled clinical trial may mean that there is not a need to do a second adequate and well controlled clinical trial. If data is more persuasive than expected it would be helpful to open the opportunity for meeting with the Agency at that point, which may not be the end-of-phase 2 meeting.	controlled clinical investigation may not be necessary, if the necessary confirmatory evidence has been collected."
141-146	"Sponsors must include in their marketing submissions a description and analysis of all data or information relevant to an evaluation of the safety and effectiveness of the drug product, from any source, foreign or domestic, to avoid selecting only those sources that favor a conclusion of effectiveness. The results of a clinical investigation or confirmatory evidence can be called into question by conflicting evidence unless there is a sufficient scientific justification that may explain the disparate findings."	It would also be beneficial to provide further clarification and examples of avoiding sources that favor a conclusion of effectiveness, particularly in the context of selection bias in RWD/RWE and preclinical experiments.
148-152	"When evaluating whether to approach establishing substantial evidence of effectiveness with one adequate and well-controlled clinical investigation and confirmatory evidence, sponsors should consider the clinical context for the proposed therapy. Disease- or condition-specific considerations (e.g., unmet need, size of the patient population) may be relevant to whether such an approach is appropriate."	It would be helpful to elaborate on when an adequate and well-controlled clinical investigation would be applicable, specifically in the context of orphan drug designation as a logical scenario for pursuing such an investigation. Including references to relevant FDA documents on this matter would enhance the document's completeness.
IV. Types of Confirmatory Evidence		
	Recommend that FDA acknowledges that confirmatory evidence could be derived from within an adequate and well-designed clinical trial. For	

	example, randomized withdrawal study or placebo cross-over to active treatment. Biological plausibility in the form of PD markers are relevant measures, as indicated in section B, to support totality of evidence and provides additional support for confirmatory evidence.	
A. Clinical Evidence from a Related Indication		
185 -122	"Under certain circumstances, evidence of effectiveness of a drug from a clinical investigation for a particular indication can provide confirmatory evidence of effectiveness to support approval of the drug in a different but closely related indication."	Consider whether results from another indication could be formally incorporated via Bayesian borrowing.
200-202	The scope of "degree of similarity between efficacy endpoints" is not clear, especially where the two target indications relate to different manifestations of a similar disease (e.g., psoriasis and psoriatic arthritis or SLE and lupus nephritis). In such cases the primary endpoints will almost certainly be different, but there is likely some alignment with secondary and other endpoints. While this may be implied, similarity between patient populations should be explicitly stated.	Recommend to request that FDA clarify the approach it intends to take to evaluate "the degree of similarity" with regard to endpoints "…the drug for a different indication, are the degree of similarity between the indications, **the degree of similarity between patient populations"**
B. Mechanistic of Pharmacodynamic Evidence		
224 (general comment)	There is no discussion of the use of quantitative system modeling to substantiate mechanistic evidence in a specific disease	Recommend to request that FDA address how quantitative system modeling can substantiate mechanistic evidence in a specific disease
224-287	Considering completeness, it may be worthwhile to mention ex-vivo evidence in addition to in vitro and in-vivo (Lines 224 and 287). Referring to FDA Guidance on Tissue Culture Media for Human Ex-Vivo Tissue could provide further guidance.	Include ex-vivo evidence in addition to in vitro and in-vivo. Cross-reference to FDA Guidance on Tissue Culture Media for Human Ex-Vivo Tissue.

240-242	The guidance is not clear with regard to how it sees a PD endpoint differing from a surrogate endpoint. Additional text may be needed to understand the use of mechanistic evidence to understand PD endpoint.	Recommend to request that FDA clarify whether surrogate endpoints (that could support either accelerated approval or full approval) can serve as confirmatory evidence. It will be helpful to have the text from footnote (11) incorporated into the main body in the lines 240-242 on the utilisation of mechanistic evidence as supportive data. This should include PK/PD and E/R data from controlled early clinical trials (e.g. Ph2 dose finding) that can provide substantial supportive information about modulation of biomarkers/pharmacodynamic endpoint in relation to more than one dose.
244	"… in vitro evidence in a relevant cell line…" This could be described more generically to include in vitro evidence of target binding as important confirmatory evidence. For instance, receptor occupancy as a measure of target engagement could be specified as a relevant example.	Include in vitro evidence of target binding, for example, receptor occupancy could be specified as a relevant example of confirmatory evidence.
266-270	"An ~~antisense~~ oligonucleotide directed at a specific gene variant or molecular genetic mechanism causing an inborn error of metabolism or genetic disease (e.g., overexpression of a gene leading to overexpression of an enzyme), where biochemical data in the target organ shows expected changes in gene expression (e.g., knockdown of the gene expression in the tissue and decreased enzyme activity)"	There are many established classes of oligonucleotides, besides ASOs, that achieve targeted knockdown; therefore, recommend removing the word "antisense".
272 - 274	"Nonclinical data demonstrating concentration-dependent… in a specific cancer type" This example emphasizes dose dependency as an important drug property in non-clinical data. It may be valuable to extend this point to clinical data, highlighting that a demonstrated dose-response in	Propose emphasizing dose dependency as an important drug property in clinical data in addition to non-clinical data.

	a dose-finding study could be crucial in deciding to pursue an adequate and well-controlled clinical investigation. Referencing exposure-response modeling could support this point.	
288-289	"Statistical approaches should be specified in advance, to limit erroneous conclusions resulting from multiplicity." It is unclear why pre-specification of statistical approaches can mitigate multiplicity issues.	Suggest FDA to clarify the relationship of multiplicity and pre-specification of statistical approaches.
289-294	Animal data (e.g., proof-of-concept data, pharmacological studies, toxicology studies) are used in drug development for a number of purposes, including to help characterize a therapy's pharmacodynamic effects (which may be done either in healthy animals or in animal models of disease, as appropriate); provide evidence of efficacy in an animal model of disease, using an endpoint that is intended to reflect or translate to a similar outcome in humans with disease; or profile drug toxicity.	"Animal data (e.g., proof-of-concept data, pharmacological studies, toxicology studies) are used in drug development for a number of purposes. These purposes include: helping to characterize a therapy's pharmacodynamic effects (which may be done either in healthy animals or in animal models of disease, as appropriate); to provide evidence of efficacy in an animal model of disease, using an endpoint that is intended to reflect or translate to a similar outcome in humans with disease; or to profile drug toxicity" Please see the suggested clarifications to improve readability in red. Additionally, the highlighted text is specific to use of animal data as confirmatory data while the rest of this sentence focuses on general uses for animal data. Suggest deleting.
C. Evidence from a Relevant Animal Model		
	No examples for rare diseases	While there are examples for antimicrobial agents and vaccines, BIO believes an additional example of a successful rare disease use would be beneficial. Perhaps an example from the FDA research, "Confirmatory Evidence of Effectiveness Used to Support Non-Oncologic Rare Disease Novel Drug Marketing Application Approvals, CY 2020-2022."

309 - 314	"Although animal models are useful in the preclinical stages of drug development, only a few such models may accurately predict human responses quantitatively or even qualitatively. Only models that have proved to be translational (i.e., prior drugs with the same intended clinical effect have been shown to have this effect observed in the animal model, with similar exposure-response) are likely to be considered as confirmatory evidence."	The guidance defines translational between animal and human disease extremely narrowly (and in a way that suggests it's only acceptable if some of the criteria relating to drugs in the same pharmacological class hold). Therefore, BIO recommend changing "i.e.," in parenthetical to "e.g.," as situations without approved precedence can be supportive (e.g., in recent example with eflornithine)
D. Evidence from Other Members of the Same Pharmacological Class		
	With the increasing clinical studies with combination therapy in oncology field, it would be valuable to have information on how monotherapy data could serve as confirmatory for combination data.	Recommend to request that FDA include guidance on the use monotherapy data from a similar drug class as confirmatory evidence to support a single adequate and well-controlled investigation of combination therapy for the same or related indication.
338-343	It is great to see that evidence from other members of the same pharmacological class is accepted as a type of confirmatory evidence. In addition to clinical trial data of the same pharmacological class, FDA should also acknowledge that the evidence from high quality RWD could provide sufficient evidence of safety, and in some cases, effectiveness.	Suggest to add: The evidence presented may include RWD sources (see III.F).
356	Clarification if unapproved drugs from a similar pharmacological class can be considered – like is considered under section A where 'two related, unapproved indications can serve as confirmatory evidence for the other indication'?	Recommend to request that FDA add a category of examples to take account of unapproved drugs under development in the same pharmacological class.
E. Natural History Evidence		
F. Real-World Data/Evidence		
	In either one of these sections (F & G), FDA should also consider commenting on evidence generated from routine medical practice, including off-label	

	use of drugs. Evidence of effectiveness and safety are often available in many RWD sources. They provide useful, and in many cases, early evidence of benefits or potential signal of risks for a licensed drug in another indication. FDA's OCE has as one of its various "Projects" titled Project Renewal that looks at expanding labelling based on longstanding medical practice that often includes use outside of what was initially approved.	
390	The Agency outlines Real-world Data/Evidence as one potential type of confirmatory evidence. However, unlike the sections describing other types of confirmatory evidence (e.g., clinical evidence, mechanistic, animal model, same pharmacologic class, natural history, expanded access), the RWD/E section does not outline potential examples/scenarios when RWD/E could provide confirmatory evidence.	Provide examples or scenarios where RWD/E may be acceptable as confirmatory evidence to: 1) maintain consistency with the other sections that do provide this information, and 2) to provide sponsors with concrete examples that could, in certain scenarios, be considered appropriate use of RWD/E to help guide decision making.
392-395	Pursuant to section 3022 of the 21st Century Cures Act[16] FDA developed a program to evaluate the potential use of real-world evidence to help support the approval of a new indication for a drug already approved under section 505(c) of the FD&C Act or to help support or satisfy post-approval study requirements[17].	On page 7 of "Framework for FDA's Real-World Evidence Program" (reference 17), Bayesian statistical models is mentioned as shown below. However, it is mentioned in the context of improving the efficiency of clinical trials. But Bayesian methods can also be used to generate real-world evidence especially in single arm clinical trial as shown in Wang, Chenguang, et al 2019. RWD can also be used to improve the efficiency of clinical trials, even if not used to generate RWE regarding product effectiveness. For example, RWD can help with: • Generating hypotheses for testing in randomized controlled trials • Identifying drug development tools (including biomarker identification)

		• Assessing trial feasibility by examining the impact of planned inclusion/exclusion criteria in the relevant population, both within a geographical area or at a particular trial site • Informing prior probability distributions in Bayesian statistical models • Identifying prognostic indicators or patient baseline characteristics for enrichment or stratification • Assembling geographically distributed research cohorts (e.g., in drug development for rare diseases or targeted therapeutics) "**In 2019, there was a publication by Wang, Chenguang, et al that combined Bayesian inference and propensity score methodology with majority of the authors from FDA. The power prior method was used as a Bayesian model. It would be very helpful to list these types of methods in the guidance document.**" Wang, Chenguang, et al. "Propensity score-integrated power prior approach for incorporating real-world evidence in single-arm clinical studies." Journal of biopharmaceutical statistics 29.5 (2019): 731-748.
400-405	Definitions - RWD and RWE are very similar to Guidance (Lines 527-530) Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products, but not identical.	Suggest aligning on definitions for consistency
407-411	"As noted above, confirmatory evidence can come from one or a variety of sources, including RWD sources. Whether an RWD source may be appropriate to develop RWE that serves as confirmatory evidence depends on several factors, including but not limited to the reliability and	"The approval is also significant because it reflects how a well-designed, non-interventional (observational) study relying on fit-for-purpose (i.e., reliable and relevant) real-world data (RWD), when compared to a suitable control, can

	relevance of the RWD source and, when relevant, the quality of the study design and the use of appropriate prespecified statistical methods and analyses." The guidance should recognize the potential strengths of RWE.	be considered adequate and well-controlled under FDA regulations." Propose providing examples of what is considered reliable and relevant or citing guidance that speaks to these factors with regards to RWD source. Propose providing examples of what may be considered quality study designs and examples of appropriate statistical methods and analyses or citing guidance that speaks to these with regards to RWD source. Rigorously designed non-interventional studies complement evidence from clinical trials; answer questions that cannot or will not be addressed in RCTs; more reflective of broad patient populations, settings of care, use, and outcomes of drug in actual clinical practice; provide evidence on long-term effectiveness/safety, outcomes in subpopulations, effectiveness in rapidly changing treatment landscape (vs. RCT snapshot in time)
G. Evidence from Expanded Access Use of an Investigational Drug		
	Section III.G could be expanded to clarify the considerations around using these data to expand what is known about a product, including ultimately how it can inform changes to labelling.	
415-450		Consider referencing the RWD/E guidance to the extent that this may be relevant when using expanded access as confirmatory evidence. Will provide useful information and clarity to sponsors wishing to use RWD/E from expanded access programs. Recommend adding more examples of how expanded access of an investigational drug could be used as confirmatory evidence

432-434	Although the purpose of expanded access is not primarily for research, if the patient outcome information collected under expanded access use of the drug is of sufficient quantity and quality to be highly persuasive, the information may be considered for use as confirmatory evidence.	Provide additional clarity on the "quantity and quality" of evidence from Expanded Access use of the drug that FDA is seeking to be used as confirmatory evidence. For example, would an incomplete set of data from some patients be acceptable and is the number of patients needed related to the prevalence of the disease or does it relate more to the strength of the data.
V. Process Considerations		
467-470	Discuss the confirmatory evidence they intend to use to demonstrate, in conjunction with one adequate and well-controlled clinical investigation, substantial evidence of effectiveness. Sponsors should describe the type (i.e., data source) and quantity of confirmatory evidence that will be included in their application.	Provide recommendations to discuss methodology or statistical approaches used in the generation of the confirmatory evidence.