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September 21, 2026

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Docket No. FDA-2019-D-4964; 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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Agency's Draft Guidance, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products.*

BIO is the premier biotechnology advocacy organization representing biotech companies, industry leaders, and state biotech associations in the United States and more than 35 countries around the globe. BIO members range from biotech start-ups to some of the world's largest biopharmaceutical companies – all united by the same goal: to develop medical and scientific breakthroughs that prevent and fight disease, restore health, and improve patients' lives. BIO also organizes the BIO International Convention and a series of annual conferences that drive partnerships, investment, and progress within the sector. Learn more at bio.org.

BIO strongly supports FDA's efforts to provide additional direction regarding the substantial evidence standard and to recognize advances in science, trial methodologies, disease understanding, and the increasing availability of high-quality data sources. We particularly welcome FDA's acknowledgement that substantial evidence may be established through an evidentiary framework tailored and adapted to indication and therapy, including one adequate and well-controlled clinical investigation supported by confirmatory evidence where appropriate. This approach appropriately recognizes that evidentiary considerations should be aligned with the specific characteristics of the disease, patient population, and therapy under evaluation and reflects a 'fit-for-purpose' approach to evidence generation.

Overall, we believe the draft guidance represents an important step toward facilitating efficient drug development while maintaining FDA's longstanding statutory standard for demonstrating effectiveness. We also support the Agency's recognition that the strength of evidence should be evaluated based on the totality of the available scientific evidence rather than through a rigid, one-size-fits-all approach.

As FDA finalizes the guidance, however, BIO encourages the Agency to further enhance predictability, transparency, and consistency in the application of the framework across review

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divisions, therapeutic areas, and development settings. While we generally support the flexibility reflected in the draft guidance, sponsors will benefit from greater clarity regarding how the one adequate and well-controlled trial plus confirmatory evidence framework will be applied in practice, including:

- The evidentiary concepts that support that framework, including confirmatory evidence and highly persuasive trials.
- The role of statistical considerations, prior evidence, external controls, natural history data, and real-world evidence in assessing the totality of effectiveness.
- The application of flexibility in rare diseases and other settings where traditional development paradigms may be impractical.
- How this guidance should be interpreted alongside existing FDA guidances and policies.
- And the relationship between the effectiveness framework and broader drug development considerations, including safety database requirements and global development programs.

Additional clarity in these areas would improve regulatory predictability, facilitate efficient development planning, promote consistent implementation across review divisions, and preserve FDA's ability to exercise scientific judgment based on the specifics of an individual development program.

BIO respectfully offers the following recommendations for FDA's consideration, which are discussed in greater detail in the General Comments section and accompanying line-by-line comments below. We appreciate FDA's engagement on this important topic and welcome the opportunity to further support the Agency as it finalizes the guidance.

Sincerely,

/s/
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General Comments – BIO Key Recommendations
BIO appreciates the overall direction of the draft guidance and its acknowledgement that substantial evidence of effectiveness may be established through evidentiary frameworks that are appropriately tailored and adapted to the indication, patient population, and therapy under evaluation. We believe this recognition reflects a fit-for-purpose approach to evidence generation that can support efficient and scientifically rigorous drug development. To further enhance the guidance's predictability, consistency, and practical implementation, we respectfully provide the following recommendations for FDA's consideration.

1. Increase Predictability and Consistency of Regulatory Application
BIO strongly encourages the FDA to consider providing additional direction and predictability regarding how FDA evaluates evidence of effectiveness. This would greatly benefit the final guidance, and help sponsors anticipate how evidentiary standards will be applied across review divisions, disease areas, and product classes.

Specifically, we recommend the following:

- Provide additional examples demonstrating application of the framework in different development settings. Such examples may include:
    - A single study with confirmatory evidence approach leveraged to pursue comparative claims against an active comparator in labelling.
    - A phase 2 (e.g., proof of concept and dose ranging) studies to serve as confirmatory evidence.
    - An adequate and well-controlled clinical investigation in each of two related, unapproved indications serving as confirmatory evidence for the other indicating, thereby supporting concurrent approval of the drug for both indications.
- Clarify factors that increase or decrease evidentiary strength.
- Describe how review divisions are expected to apply the framework consistently while maintaining their fit-to-purpose approach to evaluating evidence of effectiveness.
- Consider public workshops, case studies, or additional implementation materials following publication of the final guidance, as well as further training for FDA reviewers.

Greater transparency would improve development planning and reduce uncertainty while preserving FDA's scientific flexibility.

2. Clarify the One-Trial Plus Confirmatory Evidence Framework
The draft guidance would benefit from additional explanation regarding how sponsors should determine the appropriate evidentiary strategy for a particular development program, including when FDA would expect:

- Two adequate and well-controlled trials;
- One adequate and well-controlled trial plus confirmatory evidence; and

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- Other ‘fit-for-purpose’ adaptive approaches described throughout the guidance.

In particular, sponsors would benefit from greater clarity regarding the factors that FDA considers most important in determining the appropriate evidentiary strategy for a given development program.

BIO encourages the FDA to provide:

- Additional examples of successful evidence packages, including the applicable therapeutic context.
- Illustrative scenarios where one-trial approaches may be appropriate for a given therapeutic context.
- Greater transparency regarding factors that influence evidentiary expectations.

3. Clarify Confirmatory Evidence and Highly Persuasive Trial Concepts

Building on the need for greater clarity regarding the one-trial plus confirmatory evidence pathway, several evidentiary concepts central to the draft guidance would benefit from additional explanation, including what constitutes "strong" or "early-phase" confirmatory evidence, "same pharmacological class," "prior probability of effectiveness," and a "highly persuasive" trial. As these concepts may significantly influence development strategy, sponsors require a clearer understanding of how FDA interprets them and how they contribute to a determination of substantial evidence. In addition, the discussion of "highly persuasive" trials introduces potential uncertainty regarding whether FDA is establishing a new evidentiary category within the one-trial framework. Greater clarity would be helpful regarding whether these concepts reflect a flexible, overall weight-of-evidence approach, in which the strength of evidence from a single trial influences the amount and nature of confirmatory evidence needed, or whether FDA intends a more specific evidentiary framework. While BIO members support FDA's ability to consider the strength of a study's findings when evaluating evidence of effectiveness, the introduction of separate terminology may inadvertently create misunderstanding regarding the applicable evidentiary standard. Therefore, BIO suggests FDA consider the following:

- Develop and include a glossary for key evidentiary terms.
- Clarify the factors that contribute to a determination that a trial is considered "highly persuasive" and consider incorporating those attributes into the broader discussion of evidentiary strength rather than establishing a distinct evidentiary category.
- Provide examples of acceptable confirmatory evidence packages, including circumstances in which various data sources may contribute individually or collectively to support a determination of effectiveness.
- Clarify how multiple sources of confirmatory evidence are evaluated within a totality-of-evidence framework when supporting substantial evidence of effectiveness.

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This approach would preserve regulatory flexibility, improve transparency and predictability, and help avoid unintended interpretations by external stakeholders regarding the applicable standard for demonstrating substantial evidence of effectiveness.

4. Expand Practical Guidance for Rare Disease Drug Development
The guidance appropriately recognizes situations where additional flexibility may be warranted. However, many of the challenges described as exceptional circumstances are routine features of rare disease drug development. For instance, sponsors developing therapies for rare diseases often face small, fixed patient populations that make multiple adequate and well-controlled trials impractical. These programs frequently rely on natural history data, face challenges with concurrent control groups, and depend more heavily on biomarker and translational evidence to support effectiveness.

Based on these reasons, we would appreciate further clarification of how flexibility may be applied in these settings, including discussion of:

- Trial design considerations.
- External controls and natural history data.
- Statistical considerations in small populations.
- Integration of biomarker and translational evidence, as well as application of biological plausibility.

These clarifications would improve the practical utility of the guidance for programs where evidentiary challenges are inherent to the disease context.

5. Provide Additional Clarity Regarding Statistical Considerations and Evidence Sources
The draft guidance discusses significance levels, prior probability of effectiveness, Bayesian approaches, and totality-of-evidence considerations. At the same time, external controls, natural history studies, and real-world evidence are increasingly important components of development programs, particularly in rare diseases and serious conditions. Together, these concepts form an important part of evidence generation but may be interpreted inconsistently across sponsors and review divisions without additional clarification.

BIO recommends FDA provide additional discussion regarding the framework and factors FDA may consider in evaluating the strength of evidence needed to support regulatory decision-making, including the role of statistical considerations and alternative evidence sources:
<u>Statistical Consideration</u>

- Circumstances and factors FDA may consider when determining whether significance thresholds more stringent than conventional levels may be expected, while maintaining flexibility for case-specific considerations.
- The role of prior probability of effectiveness in assessing evidence.

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- Acceptable application of Bayesian approaches.
- How statistical considerations are integrated into broader evidence assessments.

Evidence Sources

- Examples illustrating acceptable use of external controls, natural history studies, and real-world evidence.
- Factors supporting the reliability and relevance of alternative evidence sources.
- Considerations for bias mitigation when using external controls or real-world data.
- How real-world evidence, natural history data, and prior knowledge and accumulated scientific understanding, including information related to target biology and mechanism of action, may contribute to confirmatory evidence packages and the overall strength-of-evidence assessment.

Greater transparency in these areas would assist sponsors in prospectively designing fit-for-purpose evidence generation strategies and development programs that align with FDA expectations.

6. Clarify Interaction with Existing FDA Guidances

Sponsors would benefit from additional discussion regarding how this guidance should be interpreted alongside existing FDA guidance documents addressing confirmatory evidence and real-world evidence guidances, as well as other therapeutic area-specific evidentiary recommendations. Specifically, this draft guidance mentions replacing older related guidances from 1998 and 2019, however, does not detail how it coincides with the 2023 draft guidance on *'Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence.'*

Clarification would reduce potential misinterpretation when other related guidances describe evidentiary expectations as well.

7. Acknowledge Global Development and Safety Considerations

We support FDA's recognition that substantial evidence may be established efficiently. However, in practice, the number and size of trials are frequently influenced by considerations beyond efficiency alone. For example. sponsors often conduct additional studies to address safety database requirements, global regulatory expectations, multiregional development strategies, and other scientific or operational considerations.

Given these considerations, BIO encourages FDA to clarify that sponsors may elect to conduct multiple adequate and well-controlled trials to address broader development needs, including safety, global regulatory, and scientific considerations, without implying a preference for one evidentiary approach over another.

BIO Line-by-line Edit Suggestion Table

Line #	Line to	Section	Comment and rationale	Proposed changes / recommendation
49	52	I	Anticipated approach to substantial effectiveness should be discussed no later than end-of-phase-2 but final decision made at review of MA	Design and conduct of a study consistent with FDA advice provided during early interactions be considered adequate to demonstrate substantial evidence when the primary analysis is met.
50	52		The FDA guidance states "When meeting with FDA, sponsors should provide a scientific justification for their proposed approach. Ultimately, whether substantial evidence of effectiveness has been demonstrated will depend on FDA's review of the marketing application "however, early discussion between the FDA and Sponsor should inform and align upon the determination made at the time of review of the marketing application.	We suggest the following addition: Ultimately, whether substantial evidence of effectiveness has been demonstrated will depend on FDA's review of the marketing application, *"but early discussions between FDA and the Sponsor should aim to align on evidence needed to demonstrate effectiveness."*
113		III.A	We support FDA recognizing a range of designs and endpoints for use where appropriate but are concerned that framing clinical endpoints as "preferred" and surrogate endpoints as "an alternative that requires justification" in the context of the current draft guidance could be read to narrow the Agency's acceptance of surrogate endpoints and, by extension, affect the acceptance of accelerated approval. Accelerated approval based on either a surrogate or intermediate clinical endpoint is a necessary approval pathway in a variety of context appropriate scenarios including for slow degenerative diseases, monogenic diseases or conditions where a therapy is intended to target the underlying genetic mutation, and in rare diseases where the study populations are small. In addition, accelerated approval, like traditional approval, requires a demonstration of substantial evidence of effectiveness, such that the basis for approval is the same regardless of the endpoint chosen. We are concerned that, for rare-disease and genetic-medicine programs, the practical obstacles to relying on a single adequate and well-controlled trial often arise not from endpoint choice but from related design and analysis expectations, including the expectation of a concurrent within-trial control arm, the degree of statistical persuasiveness expected of a study population whose size is limited by disease prevalence, and halting or stopping rules that may not suit the underlying disease biology, which differs materially between progressive loss-of-function conditions and gain-of-function conditions.	We recommend FDA revise section III.A, Trial Design of the current draft guidance, to reflect that endpoint choice be driven by disease context and the available science, and that for both traditional and accelerated approval the trial should be designed to demonstrate substantial evidence of effectiveness on the most appropriate endpoint. The guidance should not state a preference for either clinical or surrogate endpoints. We further recommend FDA recognize that, for rare diseases and genetic medicines, the feasibility of a single-trial approach frequently turns on trial-design and analysis expectations rather than endpoint choice, and accordingly that FDA: (i) confirm that a concurrent within-trial control arm, including a non-intervention or placebo arm, is not invariably required where disease biology, ethics, or well-characterized natural history make such an arm impracticable or inappropriate; (ii) apply the statistical-persuasiveness expectation in a manner that accounts for study populations whose size is limited by disease prevalence; and (iii) tailor halting and stopping-rule expectations to the underlying disease mechanism, recognizing that progressive loss-of-function conditions and gain-of-function conditions raise different considerations We also suggest the FDA to kindly provide worked examples applying its existing considerations for externally controlled trials, such as natural-history and population comparability, endpoint ascertainment, and bias-mitigation, since the guidance does not currently include any concrete examples of how those considerations would be satisfied in practice.

				Additionally, we recommend FDA add examples of successful external controls (illustrating uses and bias-mitigation methods) and update the Externally Controlled Trials draft guidance for alignment and commends FDA for removing the "usually reserved for" language. We also note, beyond rare diseases, there are likely other situations where flexibility is warranted.
115	113		The portion of this section focused on the choice of control group does not discuss the situation in which a treatment arm is compared to a fixed benchmark (performance goal).	Suggest adding a paragraph on designs that compare a treatment arm with a justified performance goal in single-armed trials, including justifications such as reasons for not randomizing and large of treatment effect.
128	130	III.A	It is unclear why NI studies facilitate collection of long-term controlled data for benefit–risk assessment (implying superiority studies do not)	Please clarify this point
134	134	III.A	It is unclear what the untested assumptions in non-inferiority trials	Please state one or more of the assumptions, for example, "*…that the untested assumptions* (such as [constancy and …]) *hold*"
137	149	III.A	Weaknesses (bias) associated with the use of external controls are highlighted along with conditions in which they may overcome such biases but there is no specific reference to methods that can mitigate bias and quantify uncertainty. It would be useful to include reference to randomized trials with augmented controls that mitigate some of the mentioned drawbacks of the externally controlled trials such as "high potential for bias"	Include reference to randomized trials with augmented controls that mitigate some of the mentioned drawbacks of the externally controlled trials. We recommend the following addition: *"Sophistication in methodological approaches aimed at mitigating bias continues to evolve with the potential to confront some of the inherent biases which may be at play when combining externally sourced patients with trial patients. Examples of these include clone censoring weighting to address immortal time bias, use of negative controls to assess the presence of unmeasured confounding, and inverse probability of censoring weighting to mitigate informative censoring and augmented controls, among others."*
149	156	III.A	The guidance gives 6 criteria for externally controlled trials to have "support for effectiveness" (middle of Section III.A). One criterion is that the estimated treatment effect be "so large that it is unlikely to be fully attributable to bias." This is often difficult to ascertain in the design stage. Adaptive approaches could be used instead.	We suggest the following edit*: "Since this is often difficult to ascertain in the design stage, adaptive approaches (such as an external control that changes to a randomized design) would be recommended to handle cases where it is not entirely clear whether bias is "unlikely" to fully explain externally controlled results."*
162			It is worthwhile to include in this paragraph, after the word "(MACE)" and before "and patient reported outcomes", the reference to prioritized (hierarchical) composite endpoints based on generalized pairwise comparisons, e.g. win-ratio, win odds ratio, total net benefit, DOOR.	We suggest adding the text in italics in the 162 line, "…adverse cardiovascular events (MACE), *hierarchical composite endpoints based on generalized pairwise comparisons*, and patient reported outcome (PRO)…."
186	188		This is the only paragraph in which Adaptive Designs are mentioned in the guidance (with the reference #23). It will be useful to provide clarity by stating separately in a sentence that Adaptive Designs may be accepted to provide a single A&WC trial.	An adaptive clinical trial can be accepted as the single adequate and well-controlled trial for demonstrating substantial evidence of effectiveness, provided it meets all regulatory and scientific requirements [with reference to 23].

192	193	III	Quality trial conduct requires maintenance of blinding trial participants and investigators to treatment assignment	Include discussion of evaluator blind endpoint collection and other remedies for biased endpoints like 6MW or complex platforms where double dummy approaches are not ethical or feasible (e.g. neurosurgical delivery of gene therapy treatments
207		III.C	We welcome explicit recognition of Bayesian approaches and of flexibility in the significance level but seeks predictability on when FDA will expect a level more stringent than one-sided 0.025.	We recommend FDA describe, with examples, the factors (e.g., pretrial probability of effectiveness) that would lead it to expect a more stringent significance level and affirm that Bayesian designs agreed with FDA at the design stage are an acceptable path to substantial evidence. Additionally, and consistent with our related recommendation in Section IV.A.2, we recommend FDA revise Section III.C to specify that, in rare diseases where trial size is constrained by disease prevalence, the prespecified significance level is one input into a totality-of-evidence assessment rather than a dispositive threshold. Where strong mechanistic and biomarker evidence establishes a high pretrial probability of effectiveness (for example, a genetic medicine that corrects the causal mutation), FDA should recognize that a totality assessment integrating effect magnitude, cross-endpoint consistency, dose and exposure-response, and natural-history comparison can support a conclusion of effectiveness even where a single p-value threshold is not met.
236	253	III.D	The guidance mentioned Bayesian alternatives such as the posterior probability of effectiveness alongside p-values (start of Section III.D). It seems that Bayesian and frequentist approaches are both accepted.	Will be helpful to have examples of how flexible the Bayesian approach is and how the Bayesian success criteria can be formulated.
239	241		The guidance states, "To contribute to a demonstration of substantial evidence of effectiveness, it is well established that the effect shown in the adequate and well-controlled trial must be, in FDA's judgment, clinically meaningful." This statement nor the associated references does not provide clarity for sponsors to determine FDA's view of clinical meaningfulness. As the sponsor is expected to discuss and align on the development plans with the Agency, what constitutes "clinical meaningfulness" may naturally be discussed at that time.	To contribute to a demonstration of substantial evidence of effectiveness, it is well established that the effect shown in the adequate and well-controlled trial must be, in FDA's judgment, clinically meaningful. Clinical meaningfulness should be a point of discussion in early engagements between FDA and Sponsors. We also encourage FDA to consider mechanisms for sharing their thoughts on demonstration of clinical meaningfulness.
248	259		If the primary endpoint is not met, hierarchical and sequential testing does not allow for additional endpoints to be formally tested for statistical significance.	We suggest removing the strikethrough text in this sentence, "The persuasiveness of the trial results also depends ~~on the findings for additional relevant endpoints, as~~ consistency across endpoints that reflect distinct and meaningful aspects of health can increase confidence in results."
255	268	III.E	We support recognizing that early-phase, mechanistic, and external data inform the prior probability of effectiveness and thus the evidence needed. We seek assurance this assessment will be applied transparently and consistently rather than as a subjective barrier.	We recommend FDA provide examples for how the "prior probability of effectiveness" will be assessed, to support predictable and consistent application across review divisions.

			While the guidance appropriately recognizes that early-phase studies, mechanistic understanding, and external information contribute to the overall assessment of effectiveness. However, it does not distinguish between biomarkers used as surrogate endpoints and biomarkers used to demonstrate target engagement, pharmacodynamic activity, biological plausibility, dose selection, or restoration of normal biology. Mechanistic biomarkers are critical components of the totality of evidence even when they are not intended to serve as surrogate endpoints. Greater clarity would improve predictability for sponsors developing therapies that directly address well-characterized molecular defects or known mechanistic inadequacies. Furthermore, the guidance appropriately recognizes that the overall development program contributes to the assessment of effectiveness. However, additional clarity would be valuable regarding how FDA integrates complementary evidence from multiple sources when evaluating the strength of evidence supporting an adequate and well-controlled trial. Sponsors would benefit from greater transparency regarding how mechanistic, pharmacodynamic, natural history, and other supportive evidence contribute to the overall determination of substantial evidence.	We also request the FDA clarify that mechanistic biomarkers that demonstrate target engagement, pharmacodynamic activity, restoration of protein or enzyme function, or correction of downstream disease biology may contribute to the overall assessment of effectiveness independent of whether they are validated surrogate endpoints. We also recommend providing examples illustrating how such evidence contributes to the totality-of-evidence framework in mechanism-based therapies. Lastly for this section, we recommend FDA clarify that confirmatory evidence may be generated from multiple complementary components of a single development program and evaluated collectively within a totality-of-evidence framework. Illustrative examples demonstrating how mechanistic, pharmacodynamic, exposure-response, natural history, and extension-study data may collectively strengthen evidence of effectiveness would improve regulatory predictability.
266	268	III	Original text: *"Such information is relevant because the probability of erroneous conclusions of effectiveness depends on the prior probability of effectiveness, the power, and the type I error probability."* To maintain consistency of terminology and in keeping with other FDA guidance, we suggest introducing Context of Use as a relevant consideration here to reinforce that evidence should be judged according to the question it is intended to answer.	We recommend adding the following sentence at the end of line 268: *"The relevance and contribution of each source of evidence should be considered within its Context of Use as part of the overall development program."*
305	338	IV.A.1	The current organization suggests that a single pivotal trial need not be "highly persuasive" when coupled with "strong" confirmatory evidence. This section also does not include some examples of confirmatory evidence listed previously (e.g., mechanistic data).	Please clarify the approach that Agency will take to evaluate when single pivotal trials must be highly persuasive." Please also clarify in a separate section what FDA considers as constituting "strong" confirmatory evidence and the considerations that inform acceptance of different forms of evidence. We also encourage FDA to discuss whether and how multiple forms of confirmatory evidence can be pooled together to collectively form a strong confirmatory evidence package.
305	306	IV.A.1	*"Evidence from an adequate and well controlled trial plus a source of strong confirmatory evidence"*	We recommend defining "Strong confirmatory evidence" in a glossary since this appears to be a subclass of confirmatory evidence and new terminology
308	312	IV	Sources of strong confirmatory evidence	We request the FDA to provide insight on whether a randomized controlled phase 2a (proof of concept) study may also contribute to

				strong confirmatory evidence, as well as on whether a randomized controlled phase 2b (dose ranging) study may also contribute to strong confirmatory evidence supplementing a single well controlled trial as confirmatory evidence.
325	327	IV.A.1	Trial data for related indications *"... or a different but closely related disease*....etc	We recommend clarifying "closely related", including examples as well as the level of evidence that is needed (including mechanistic evidence) to determine that these diseases are "closely related" diseases.
337			The strength of confirmatory evidence depends not only on observed results from a rigorous design with high data integrity, but also on residual uncertainty.	We encourage the FDA to provide more specific recommendations, especially in the context of programs that include analysis of RWD sources external to the RCT, regarding assessment of: Sensitivity analyses, quantitative bias analysis, robustness assessments, and triangulation across data sources.
338	339	IV.A.2	Early phase confirmatory evidence. *"Evidence from a highly persuasive adequate and well-controlled trial plus early-phase confirmatory evidence"*	We recommend including "early-phase confirmatory evidence" in a glossary since this appears to be a subclass of confirmatory evidence and new terminology
338		IV.A.2	Consistent with our recommendation in Section IV.A that FDA fold the elements of a "highly persuasive" trial into the general description of confirmatory evidence, we request greater transparency around the Agency's thinking on significance-level expectations for a single trial supported by comparatively early-stage confirmatory evidence (e.g., when $p<0.01$ or more stringent applies) and on how the pretrial probability of effectiveness drives it.	Consistent with our recommendation to fold these considerations into the general description of confirmatory evidence rather than into a potentially separately labeled category, we recommend FDA describe the significance-level criteria that apply when a single trial is supported by comparatively early-stage confirmatory evidence, including how the pretrial probability of effectiveness informs the expected significance level, so sponsors can plan single-trial programs with confidence. We recommend FDA state that a single trial can be "highly persuasive" based on the totality of evidence rather than solely by achieving a more stringent statistical significance level such as $p<0.01$. While this principle should apply across all disease areas, it is particularly important for rare diseases, where population size is often constrained by disease biology. Tying "highly persuasive" primarily to the significance level disadvantages rare diseases with small populations, including where persuasiveness instead derives from effect magnitude, consistency across primary and secondary endpoints, dose and exposure-response, biomarkers that measure the biological source of the disease, and comparison to well-characterized natural history. We recommend FDA: (1) state that statistical significance is one factor among several in assessing whether a single trial is highly persuasive across disease areas, while recognizing that the relative importance of different evidentiary elements may vary by disease context; (2) add worked examples of "highly persuasive" single trials from a range of therapeutic areas, including rare diseases, and

				(3) confirm that a totality determination applied across endpoints is available where a rigid endpoint-by-endpoint significance requirement would not fit the disease context. We further recommend FDA recognize that endpoint characteristics, and not only population size, can make a fixed significance threshold an incomplete measure of persuasiveness. Where the primary endpoint is subject to substantial placebo response or rater variability, as in many neuropsychiatric conditions, a meaningful portion of the observed variability reflects measurement noise rather than uncertainty about the drug's effect, so an otherwise effective therapy can be structurally disadvantaged relative to indications with objective endpoints. In those settings, we recommend FDA weigh assay sensitivity, responder-level analyses, and biomarker-supported effect confirmation as part of the highly-persuasive-trial determination, rather than relying on a fixed significance threshold alone. Separately, we recommend FDA confirm whether Section IV.A.2 is intended to subsume the extremely persuasive single-trial pathway available without confirmatory evidence under the 2019 guidance, since the current draft consistently requires early-phase confirmatory evidence even for the most persuasive single-trial results (lines 385–387). If so, we ask FDA to address how prior approvals obtained on that basis should be understood going forward. We also recommend FDA (1) add examples of "highly persuasive" adequate and well-controlled trials across a broad range of designs, and (2) apply existing multiregional-trial standards for U.S. applicability while maintaining flexibility on what counts as "sufficient" U.S. patient representation.
346	379	IV.A.2	The bullets in subsection A.2 should be broadened. It would generally be assumed that a design that is generalizable and relevant to practice in the US would be needed in either A.1 or A.2 but the location only in A.2 suggests its only in situations where an applicant is relying on ph2 data as their confirmatory evidence. The same can be said for other bullets in this section.	Consider listing these bullets in an earlier subsection and then only speaking to nuances that may differ or apply between subsection A.1 or A.2.
352	355	IV.A.2	On pg 11 FDA discusses scenarios where early-phase confirmatory evidence may be appropriate. These conditions seem too narrow and may not be appropriate to allow for many rare diseases. For example, FDA describes the condition of a "clinically meaningful primary endpoint, such as irreversible morbidity or mortality" – the example provided (irreversible morbidity or mortality) lies on one extreme and is very narrow.	Please provide wider range of examples. The example provided is very limited in application.

357	362	IV.A.2	The text indicates that "a single trial with hypothesis testing at the common one-sided 0.025 significance level may not adequately limit the probability of false positive effectiveness conclusions."	It would be helpful to provide more information about when this is the case and what alpha is likely acceptable. Please provide scenarios when a one sided 0.025 significance level may not adequately limit the probability of false positive effectiveness conclusion, as well as the acceptable alpha in these cases
385	386	IV.A.2	"*The single trial is adequately designed to provide highly persuasive results, it is expected that the available **early-phase information** used to support proceeding to such a trial may be able to provide sufficient confirmatory evidence."*	A better understanding of what is meant by "early-phase information" would be helpful.
392		IV.B	We strongly support FDA's acknowledgment that sponsors may elect more than one trial and that nonidentical trials can be more persuasive. We recommend FDA affirm in the guidance that a two-trial program chosen for legitimate scientific or strategic reasons will not be viewed unfavorably by the Agency.	We recommend FDA state that its assessment of substantial evidence does not turn on why a sponsor elected to conduct more than one adequate and well-controlled trial, so that a program is not disadvantaged whether the additional trial reflects scientific considerations, business strategy, or the requirements of other regulatory authorities
426		IV.C	We welcome the pathway to leverage an approved drug's known effectiveness for a new population, dose, regimen, route, or dosage form. We request that the Agency provide additional insight into their thinking on the interaction with 505(b)(2)/right-of-reference and on evidence expectations for extrapolation.	We recommend FDA provide additional examples and clarify the evidentiary and 505(b)(2)/right-of-reference considerations that apply when leveraging known effectiveness for new populations, doses, regimens, routes, or dosage forms.
441			Clarification needed on changes in administration methods or delivery device) under the same route of administration	We recommend FDA clarify that, for changes in the method of drug administration using the same route of administration (e.g., prefilled syringe to autoinjector for subcutaneous administration), established effectiveness from the original administration method may be relied upon without requiring new clinical efficacy studies or dedicated clinical PK comparability studies, provided there is adequate scientific evidence demonstrating that any differences in pharmacokinetic profiles are not expected to result in clinically meaningful differences in effectiveness or safety. The effectiveness of the original product should be considered applicable when exposure-response understanding, pharmacology, and other relevant scientific evidence provide a sound basis to conclude that effectiveness and safety will be maintained despite differences in delivery characteristics. Examples may include transitions from vial-and-syringe administration to prefilled syringes, or from prefilled syringes to autoinjectors, or on-body injection delivery systems. Therefore we recommend FDA further clarify that additional clinical effectiveness, or safety studies would generally not be expected in these circumstances.
445			Additional clarity would be helpful regarding whether safety from RWE could potentially be sufficient to inform in the scenario described when effectiveness of a new dose, regimen, route of administration, or dosage form may be demonstrated by the trial(s) that used the original dose,	We suggest adding text in italics at the end of this sentence, "In this case, although no new effectiveness or pharmacodynamic data may be needed, additional safety data *from clinical trial or analysis of fit-for-purpose RWD may still be needed."*

			regimen, route of administration, or dosage form + pharmacokinetics data.	
470	496		The structure of the previous guidance made for easier reading and comprehension. The current draft provides little insight into contexts for which different forms of flexibility may be more or less appropriate.	Consider adding discussion on clinical circumstances where additional flexibility as was done in previous guidance (i.e., life-threatening or severely debilitating diseases with unmet need, rare diseases, diseases where studies are highly impractical or unethical).
470		V.A	We support a holistic assessment of severity, unmet need, and rarity. We recommend FDA confirm that flexibility is available for serious chronic diseases with meaningful unmet need, not only for rare or life-threatening diseases.	We recommend FDA specify that regulatory flexibility can apply across a spectrum of serious conditions, including prevalent serious chronic diseases with meaningful unmet need, and is not limited to rare or life-threatening diseases. *Although the guidance's severity, unmet-need, and rarity factors are structured independently, its illustrative examples lean heavily toward rare and life-threatening conditions; an explicit textual confirmation would remove the ambiguity this practical emphasis can otherwise create.* We also recommend FDA extend regulatory flexibility to indications where the primary endpoint is inherently labile or placebo-responsive (for example, many psychiatric and pain conditions), such that endpoint-driven variability, rather than disease severity or rarity, is the principal source of evidentiary uncertainty.
472	482	V 14	Clinical circumstances where flexibility may be warranted include rare and debilitating diseases that lack therapies.	Suggest adding special considerations for epidemics and outbreaks (i.e., animal rule or in vitro models as confirmatory evidence).
500		V.B.1	We welcome flexibility in significance level and design where appropriate but needs it to be predictable and reliable at the planning stage so it can be built into program design.	We recommend FDA commit to documenting agreed flexibilities (e.g., significance level, use of external controls) in formal meeting minutes so sponsors can rely on them and apply such flexibilities consistently across review divisions.
509			Include an example in which the Bayesian approach is used and the reliance on exchangeability between external and current data may add to the uncertainty about effectiveness.	As another example, when adopting a Bayesian design and analysis with a prior distribution based on external data, the degree of uncertainty will depend on the accuracy of the assumption of exchangeability between current and external data, as well as on the method used to discount the external data (see Bayesian Guidance Document)
523			Include the possibility of using the posterior probability of effectiveness as a measure of certainty about effectiveness. Reference the Bayesian Guidance and Proschan, M.A., Dodd, L., Price, D. 2016. Statistical Considerations for a Trial of Ebola Virus Disease Therapeutics, ***Clinical Trials.*** doi:10.1177/1740774515620145	As another example, when a Bayesian design and analysis is used, the trial success may rely on a high posterior probability of effectiveness. Instead of adopting the 97.% threshold that mirrors the common one-sided 0.025 significance level, a different threshold for success may be acceptable in some cases
536		V.B.2	We support flexibility to use natural history and real-world data/evidence as confirmatory evidence and recommend alignment with FDA's existing RWE/RWD guidances.	We recommend FDA cross-reference its RWE/RWD guidances and clarify the reliability and relevance criteria for using natural history and real-world data as confirmatory evidence, including what documentation or methodological showing would demonstrate that such data is distinct from any data used as the trial control.

				We also recommend FDA clarify that in certain circumstances RWE can serve as substantial evidence of effectiveness on its own (or combined with other data), not only as confirmatory evidence, with examples
538	570	V15	Sources of confirmatory evidence	Clarify whether compassionate use or managed access data be used as supportive data. The text jumps immediately from mechanistic evidence to RWD. We recommend providing additional text how phase 1b and 2a studies may contribute to the weight of confirmatory evidence. Also including the relevance of larger phase 2 studies (i.e. 2b dose ranging) as confirmatory evidence as well would be beneficial to final guidance.
542	549	V.B.2	FDA appropriately recognizes that mechanistic evidence may serve as confirmatory evidence for therapies targeting diseases with well-understood biology. However, additional clarity would be valuable regarding therapies that directly correct a known molecular defect, particularly in monogenic diseases. For these programs, the integration of target engagement, restoration of protein or enzyme activity, correction of downstream metabolic abnormalities, and durable pharmacodynamic effects may substantially strengthen confidence in the observed clinical benefit. Similarly, demonstration of durable treatment effects through longitudinal within-patient follow-up provides important evidence supporting the persistence and reproducibility of treatment benefit.	We recommend FDA expand this section to describe how integrated mechanistic evidence—including target engagement, restoration of protein or enzyme function, pharmacodynamic biomarkers, correction of downstream disease biology, and durability of biological and clinical effects—may strengthen confirmatory evidence for therapies targeting well-characterized monogenic diseases. We further recommend FDA provide examples illustrating how durability of treatment effect and consistent longitudinal within-patient responses contribute to the overall assessment of substantial evidence.
549	549	V.B	We acknowledge and support that FDA may exercise flexibility with respect to the sources and strength of confirmatory evidence. However, the guidance does not expressly acknowledge that mechanistic evidence can be generated through a range of evolving, scientifically relevant approaches, including human models, new approach methodologies, and translational assays. Such evidence can help establish biological plausibility, demonstrate target engagement or pathway modulation, and provide context for interpreting clinical findings. Explicitly recognizing this role would encourage sponsors to use the most scientifically appropriate evidence for the question at hand.	We suggest adding the following sentence at end of last paragraph: *"Mechanistic evidence from scientifically relevant experimental approaches may strengthen interpretation of clinical findings and contribute to the overall assessment of effectiveness."*
559	561		Expanding the mention of RWD use to cover both effectiveness and safety, from a practical aspect, would improve the utility of this section for sponsors. Only mentioning safety in section VI is disjointed when considering program design.	We suggest adding the text in italics in the middle of this sentence, "Whether an RWD source may be appropriate to provide confirmatory evidence depends on several factors, such as the reliability and relevance of the RWD source for its proposed use *(effectiveness and/or safety to inform the benefit-risk assessment)* and, when relevant, the

				appropriateness of the study design and the use of appropriate prespecified statistical methods and analyses."
573		VI	We agree that safety-database requirements are independent of the number of effectiveness trials, and that meeting the effectiveness standard with a single trial does not reduce safety expectations. This is a principal reason the patient and cost savings from a one-trial approach are more modest than often assumed: savings come largely from eliminating redundant control arms (on the order of 17 to 25%), not from reducing active-treatment exposure.	We recommend FDA state explicitly that the effectiveness framework does not alter safety-database expectations (e.g., ICH E1A; disease-specific exposure requirements) and acknowledge that safety and benefit-risk needs, not the effectiveness standard alone, frequently drive the size, duration, and number of trials in a development program.
582	584	VI	Need for additional safety data in the setting of sufficient efficacy data.	The *Benefit-Risk Assessment for New Drug and Biologic Products* guidance could provide additional clarity regarding this situation. For example, if additional safety data are needed, it would be helpful to understand whether these data could be generated through a less complex study design focused primarily on safety, without collecting additional efficacy data. Illustrative examples of approaches that could fulfill such safety requirements would be valuable.