

September 21, 2026

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

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FDA-2019-D-4964; Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products; Revised Draft Guidance for Industry

Dear Dockets Management Staff:

We appreciate the opportunity to comment on the Food and Drug Administration's ("FDA" or "the Agency") revised draft guidance, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (June 2026) ("Draft Guidance"). We submit these comments building on recommendations set out in our white paper, *A Blueprint for FDA: Recommendations to Improve Innovation and Access* (Sept. 2025) ("White Paper"),^[1] which addressed several issues that bear on the evidentiary pathways by which sponsors can demonstrate substantial evidence of effectiveness.*

We commend FDA for advancing a framework that gives sponsors clearer direction on how a single adequate and well-controlled clinical investigation, together with confirmatory evidence, can satisfy the statutory substantial evidence standard. We write to recommend five refinements that we believe would strengthen the Draft Guidance:

1. Clarify its terminology on "regulatory flexibility" to avoid creating misconceptions regarding how it applies the statutory standard of substantial evidence of effectiveness;
2. Provide more affirmative guidance on the appropriate use of external controls — including when and how externally controlled trials can support a finding of substantial evidence — rather than framing external controls primarily in terms of their limitations;
3. Explicitly encourage novel trial designs — including master protocols and adaptive designs — as tools for use in pivotal trials and confirmatory evidence;
4. Incorporate patient preference information ("PPI") as a tool for trial design — including endpoint selection and the calibration of success criteria; and
5. Address rare disease-specific considerations in its discussion of external controls.

We address each recommendation below.

* The opinions expressed herein represent those of the authors and do not represent the positions of any of their affiliated organizations, including the University of Southern California or USC Schaeffer.

Comment 1: FDA Should Clarify Its Terminology on “Regulatory Flexibility” to Avoid Creating Misconceptions Regarding How It Applies the Statutory Standard of Substantial Evidence of Effectiveness

Section 505(d) of the Federal Food, Drug, and Cosmetic Act (“FD&C Act”) defines substantial evidence as:

evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.[2]

Section V of the Draft Guidance, titled “Regulatory Flexibility,” states that FDA “exercises flexibility in applying the standard in certain critical settings,” reflecting “the awareness that in certain critical settings a somewhat greater uncertainty about effectiveness may be warranted” (Draft Guidance at 13). We strongly support FDA’s use of the Draft Guidance to describe and reaffirm the agency’s approach to demonstrating substantial evidence of effectiveness. We are concerned, however, that describing this approach as “regulatory flexibility” could inadvertently create the misconception among sponsors, payors, or the public that FDA is applying a lower or different standard of effectiveness in some circumstances.

We agree with the statement in the Draft Guidance that “whether the disease is rare or common, fatal or less severe clinically, substantial evidence of effectiveness must be demonstrated” (Draft Guidance at 14). The statutory standard itself does not change based on the therapeutic context. Rather, consistent with longstanding FDA practice, the question of whether the available evidence satisfies that standard necessarily requires FDA to consider the circumstances in which the drug is being developed and evaluated. Those circumstances may include, for example, the severity of the disease, the availability of therapeutic alternatives, and the ethics or feasibility of particular study designs.

We recommend that FDA update its terminology to clarify this approach:

- Replace the term “Regulatory Flexibility” with terminology that more accurately conveys that FDA considers the relevant context in determining what evidence is sufficient to satisfy the statutory substantial evidence standard; and
- Add an explicit clarifying statement at the outset of Section V stating that the approach described in that section applies to the sufficiency and type of evidence FDA will consider in assessing whether the statutory standard has been met, and does not alter, lower, or waive the substantial evidence standard itself.

Comment 2: FDA Should Provide More Affirmative Guidance on the Appropriate Use of External Controls

The Draft Guidance discusses externally controlled trials — trials that rely on natural history and/or external control arms (“ECAs”) in place of, or alongside, a randomized concurrent control — in Section III.A (Draft Guidance at 5) and again in Section V.B.1 (Draft Guidance at 14). In both places, the discussion focuses primarily on the conditions under which comparability between an external control and the trial population may be doubted. The Draft Guidance identifies factors relevant to whether an externally controlled trial can support a conclusion of effectiveness, but it offers comparatively little affirmative discussion of when and how sponsors can design externally controlled trials to meet these conditions.

This gap is not unique to this Draft Guidance. As we discussed in our White Paper, FDA’s separate draft guidance on externally controlled trials similarly “focuses on the limitations and complexities of using ECAs, with little to no discussion of when and how ECAs can be beneficially deployed, or the benefits of using existing data when possible.”[1] (at 79) That approach risks discouraging sponsors from pursuing externally controlled designs even in circumstances where FDA’s own approval history shows they can succeed: one analysis of FDA and EMA approvals from 1999 to 2014 found that a substantial number of indications — including many for which no randomized trial was ever conducted for any indication — were approved without a randomized controlled trial. This Draft Guidance is a natural and important place for FDA to give sponsors more affirmative direction on how externally controlled data can serve as, or contribute to, that confirmatory evidence.[3, 4]

We recommend that FDA:

- Supplement Sections III.A and V.B.1 with illustrative examples of externally controlled trial designs that have satisfied, or would be expected to satisfy, the factors it identifies;
- Cross-reference and align the Draft Guidance with FDA’s draft guidance on externally controlled trials,[5] so that sponsors and reviewers have a single, consistent account of how external controls can support confirmatory evidence under both documents; and
- Clarify how an external control arm may be used in connection with a master protocol — an approach currently carved out of the scope of FDA’s draft guidance on master protocols.[6]

Comment 3: FDA Should Explicitly Encourage Novel Trial Designs

The Draft Guidance’s discussion of trial design briefly acknowledges “adaptive design elements” as one of several factors affecting the strength of evidence (Draft Guidance at 6), but does not otherwise discuss master protocols, platform trials, or other novel trial designs as tools for generating the confirmatory evidence needed to support a single-trial pathway. We believe this is a missed opportunity. Master protocols — including basket, umbrella, and platform designs — allow sponsors to study multiple products, populations, or disease states within shared infrastructure, which can help deliver advances to patients more rapidly and efficiently. FDA has already invested in programs and guidance to support these designs, including the Complex Innovative Trial Design Meeting Program and guidance on innovative methods such as adaptive designs and master protocols.[6, 7]

We recommend that FDA amend Section III.A, and Section IV.A.1 where relevant, to explicitly discuss how evidence from master protocols and other novel trial designs can serve as, or contribute to, either the single pivotal trial or the confirmatory evidence supporting it — consistent with our White Paper’s recommendation that FDA “expand its efforts to facilitate novel trial designs”[1] (at 68) and more clearly explain how the evidence such designs generate fits into its evidentiary frameworks.

Comment 4: FDA Should Incorporate Patient Preference Information as a Tool for Trial Design

Patient preference information (PPI) (defined as, qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or outcomes) is critical to incorporating the patient perspective into regulatory decision-making, but it is not discussed anywhere in the Draft Guidance.

FDA has developed a substantial framework for using PPI to inform medical device development over the past decade, most recently finalizing its guidance, *Incorporating Voluntary Patient Preference Information over the Total Product Life Cycle*, in March 2026.[8] Congress directed FDA to expand the use of patient experience data, including PPI, across the Agency’s work in the 21st Century Cures Act.[9] The Agency has an opportunity through this Draft Guidance to encourage greater use of PPI.

PPI is directly relevant to at least two topics the Draft Guidance already addresses:

- **Endpoint selection.** The Draft Guidance identifies endpoint selection as a key design element affecting the strength of evidence, and states that “[u]se of a clinical endpoint is preferred when feasible” (Draft Guidance at 5). Quantitative PPI can help sponsors and FDA identify which endpoints are most meaningful to patients, and can help establish a “crosswalk” between patient-prioritized outcomes and endpoints that are feasible to measure in a trial — including through case studies co-authored by one of the undersigned.[10, 11]

- **Trial design and success criteria.** The Draft Guidance states that FDA may accept “a significance level higher than the common one-sided 0.025 level” in certain circumstances, and that the choice of success criteria should account for “the consequences of false positive and false negative conclusions” (Draft Guidance at 14–15). Quantitative PPI — including Bayesian decision-analytic methods already developed and published for both oncology and Parkinson’s disease trials — offers a transparent, patient-centered method for making that determination, by systematically weighing the consequences of a false approval against the consequences of a false rejection based on what patients themselves are willing to accept.[12, 13]

We recommend that FDA revise Sections III.A and V.B.1 to identify PPI explicitly as a tool that sponsors can use, and should discuss with FDA early in development, to inform endpoint selection and the calibration of statistical success criteria. This would extend to drugs and biologics the same encouragement FDA has already given medical device sponsors, consistent with our White Paper’s recommendation that FDA “expand its approach of encouraging patient perspectives in medical device applications to all medical products.”[1] (at 80)

Comment 5: FDA’s Discussion of External Controls Should Address Rare Disease-Specific Considerations

Section V.A recognizes that disease rarity, along with severity and unmet need, is a relevant clinical consideration in assessing what evidence is sufficient to demonstrate substantial effectiveness (Draft Guidance at 14). Rare disease development is also where externally-controlled designs are most often necessary, given that patient populations may be too small to support a traditional concurrent control, and withholding an already available or promising therapy from a control arm can be especially difficult to justify ethically.[14, 15] Yet neither the Draft Guidance’s discussion of external controls (Sections III.A and V.B.1) nor FDA’s separate draft guidance on externally-controlled trials directly addresses rare disease as a distinct context, and FDA’s draft guidance on natural history studies for rare disease likewise contains only a brief discussion of using natural history data as an external control.[16]

We recommend that FDA use this Draft Guidance, or a cross-referenced revision to its external controls and natural history guidance documents, to provide rare disease-specific considerations for the use of external controls — including how master protocols can be used to generate shared external control data across multiple rare disease development programs.[17]

Conclusion

We appreciate FDA's efforts to give sponsors clearer guidance on the pathways available to demonstrate substantial evidence of effectiveness, and we believe the recommendations above would further that goal by making the Draft Guidance more precise about the statutory standard, more affirmative in describing beneficial uses of modern trial design and evidence-generation tools, and more consistent with FDA's guidance elsewhere. We would welcome the opportunity to discuss these comments further with FDA staff.

Respectfully submitted,

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Endnotes

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