NATIONAL HEALTH COUNCIL

September 22, 2026

Kyle A. Diamantas, JD
Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products; Revised Draft Guidance for Industry [FDA-2019-D-4964]

Submitted electronically via regulations.gov

Dear Acting Commissioner Diamantas:

The National Health Council (NHC) appreciates the opportunity to provide comments on the Food and Drug Administration's (FDA's) revised draft guidance, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. The revised guidance addresses a foundational question for patients, caregivers, researchers, and medical product developers: how FDA will determine whether evidence is sufficiently rigorous and persuasive to establish that a therapy works. It also recognizes that the evidence reasonably available to make that determination may vary across diseases, populations, and development programs. The NHC supports FDA's effort to provide a more integrated and contemporary explanation of the substantial evidence standard. We also support the Agency's recognition that advances in scientific understanding and the availability of high-quality data can permit efficient approaches to evidence generation without changing the statutory standard for effectiveness.[1]

The NHC unites nearly 200 national organizations—including leading patient groups, research institutions, providers, caregivers, and businesses across the health care sector—to drive patient-centered health policy. Representing 200+ million Americans with chronic diseases and disabilities, the NHC strengthens its members' collective influence to expand access to quality, affordable, and equitable health care. The NHC fosters collaboration to shape policies that reflect the needs of patients. Across this membership, there is a shared interest in an FDA evidentiary framework that is scientifically rigorous and predictable enough to support efficient development. The framework should also be responsive to circumstances in which conventional development approaches may be impracticable or fail to capture the outcomes that matter most to patients.

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[1] U.S. Food and Drug Administration, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Draft Guidance for Industry (June 2026), 1.

The NHC particularly supports the draft guidance's recognition that the strength of evidence is not determined solely by the number of studies conducted. Instead, it depends on the design, conduct, analysis, and clinical and statistical persuasiveness of the evidence considered in the context of the overall development program. We also appreciate FDA's explicit acknowledgment that trial designs should produce information relevant to patients and prescribers in clinical practice; that eligibility criteria should reflect the intended-use population; that enrollment, retention, and assessment approaches can improve generalizability and reduce participant burden; and that the primary endpoint should be meaningful to patients. These concepts are important because a technically successful development program can still provide limited value to patients if the population studied differs materially from the population expected to use the therapy or if the trial measures outcomes that do not reflect the effects patients prioritize. Avoidable participation burdens can also prevent important segments of the patient community from enrolling or remaining in a study.[2]

Summary of Recommendations

- More explicitly connect the substantial evidence framework to FDA's patient-focused drug development (PFDD) guidances and explain how patient experience data can inform judgments about endpoint relevance, clinical meaningfulness, acceptable uncertainty, feasibility, and the overall clinical context.

- Clarify that determinations of what is "clinically meaningful" should, where appropriate, be informed by evidence about what patients consider a meaningful benefit, including data from patient-reported and other clinical outcome assessments, alongside the clinical, statistical, and other evidence relevant to the particular development program.

- Expand the discussion of representativeness and participant burden to recognize their effects on the applicability of evidence and, in some circumstances, its strength, as well as the value of early engagement with patients and patient organizations on eligibility criteria, visit schedules, endpoint assessments, retention, and trial feasibility.

- Preserve and further explain regulatory flexibility for serious diseases, rare diseases, conditions with substantial unmet need, and other circumstances in which conventional evidence generation may be infeasible or may unnecessarily delay access, while making clear that such flexibility should be scientifically justified, transparently applied, and directed toward producing interpretable evidence of meaningful benefit.

- Clarify the circumstances in which natural history data, registries, real-world data (RWD), mechanistic evidence, and other sources may serve as confirmatory

[2] U.S. Food and Drug Administration, Demonstrating Substantial Evidence of Effectiveness, 4–6.

evidence, including how patient organizations can contribute fit-for-purpose data and evidence infrastructure.

- Improve transparency and consistency in FDA's application of the guidance across review divisions by describing the factors that drive evidentiary expectations, documenting key scientific judgments, and encouraging early and iterative sponsor engagement when nontraditional approaches are contemplated.

- Add a stronger cross-reference to FDA's benefit-risk and PFDD frameworks so that the guidance more clearly explains how uncertainty about effectiveness is considered alongside disease burden, available alternatives, patient tolerance for uncertainty, and the consequences of delaying an effective therapy.

Patient Input Should More Explicitly Inform Clinical Meaningfulness and Evidentiary Strength

The revised guidance appropriately states that an effect demonstrated in an adequate and well-controlled investigation must be clinically meaningful to contribute to substantial evidence of effectiveness. It also recognizes that the clinical meaningfulness of an effect depends on both the relevance of the endpoint and the magnitude of the estimated treatment effect. The NHC encourages FDA to build on this foundation by stating explicitly that judgments about clinical meaningfulness should, where feasible, be informed by systematic evidence about what patients consider meaningful in the context of the disease and treatment under study. The distinction between statistical significance and clinical meaningfulness makes patient experience data particularly valuable when FDA is evaluating whether an observed treatment effect represents a meaningful benefit. These data can help establish whether the endpoint reflects an important aspect of health and whether the magnitude or the nature of change would matter in patients' lives.[3]

FDA has made substantial progress in establishing methodological expectations for collecting patient experience data, identifying what is important to patients, selecting or developing fit-for-purpose clinical outcome assessments, and incorporating those assessments into endpoints for regulatory decision-making. The NHC has supported that work because meaningful patient engagement can both inform the selection of a particular patient-reported outcome measure and shapes development priorities, protocol design, eligibility criteria, recruitment and retention strategies, interpretation of treatment effects, and benefit-risk judgments. The final substantial evidence guidance should therefore cross-reference the PFDD guidance series more directly and explain that patient input is relevant to several of the judgments described throughout this

[3] U.S. Food and Drug Administration, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, 8.

document, including endpoint selection, clinical meaningfulness, feasibility, acceptable uncertainty, and interpretation of the overall evidence.[4,5]

FDA could operationalize that principle by encouraging sponsors to describe the patient evidence used to support the selection and interpretation of key endpoints. This would be particularly valuable in development programs involving serious disease, substantial heterogeneity, rare conditions, or outcomes that are difficult to interpret without context. One example of such approach is the NHC's Patient-Centered Core Impact Sets (PC-CIS) Blueprint, which guides the creation of PC-CIS, which are standardized, patient-derived and patient-prioritized lists of the most important impacts of a disease and its treatments on patients and their families and caregivers. The Blueprint illustrates how a structured process for identifying patient priorities can inform what researchers measure and help address the recurring disconnect between the impacts that matter most to patients and the information routinely collected in research and care. FDA need not prescribe any single method, but the final guidance could encourage sponsors to use fit-for-purpose approaches that demonstrate a clear line from patient experience to the concepts measured and, ultimately, to the interpretation of benefit.[6]

Representativeness and Participant Burden Are Central to the Usefulness of Evidence

The NHC appreciates FDA's statement that trial designs should provide information relevant to patients and prescribers in clinical practice and that eligibility criteria should reflect the intended-use population, with exclusion criteria used only when scientifically justified. The draft further recognizes ways to improve participation and generalizability, including enrollment and retention practices, contemporary standards of care, approaches that reduce visit and endpoint-assessment burden, and selection of a primary endpoint that is meaningful to patients. These provisions are well aligned with FDA's December 2025 guidance on enhancing participation in clinical trials, which encourages broader enrollment across demographic and non-demographic

[4] National Health Council, "NHC Comments on PFDD: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making," July 5, 2023, https://nationalhealthcouncil.org/letters-comments/nhc-comments-on-pfdd-incorporating-clinical-outcome-assessments-into-endpoints-for-regulatory-decision-making/.

[5] U.S. Food and Drug Administration, "FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making," accessed September 4, 2026, https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

[6] National Health Council, "A Blueprint for Developing Patient-Centered Core Impact Sets (PC-CIS)," accessed September 4, 2026, https://nationalhealthcouncil.org/a-blueprint-for-developing-patient-centered-core-impact-sets-pc-cis/.

characteristics so that study populations more closely reflect the patients likely to use an approved product.[7,8]

The final guidance should make clear, however, that representativeness and burden are not peripheral operational considerations. They can affect the interpretability and applicability of trial results as well as the strength of the resulting evidence, when participation burdens contribute to differential attrition, missing data, or other sources of bias. Overly restrictive eligibility criteria can leave uncertainty about effectiveness in clinically important populations; burdensome visit schedules, travel requirements, assessment procedures, or treatment logistics can produce differential dropout and missing data; and study procedures that are disconnected from routine clinical practice can make it more difficult to understand how an observed benefit will translate to the intended-use population. FDA already acknowledges elsewhere in the draft that extensive dropout and missing data can undermine an otherwise rigorous randomized trial. The NHC encourages FDA to connect these concepts more explicitly and to recognize that patient input early in protocol development can help identify avoidable sources of burden before they affect enrollment, retention, or data quality.

Patient organizations can be particularly valuable partners in this work because they can contribute disease-specific knowledge about diagnostic pathways, care settings, treatment burden, common comorbidities, caregiver responsibilities, transportation or technology barriers, and the practical feasibility of proposed study procedures. Sponsors and researchers can work with patient organizations to capture this type of data through patient experiment mapping. For example, the NHC's Patient Experience Mapping Toolbox provides project-planning and data-collection resources to support this process and document the patient journey and the effects of disease and treatment on daily life. The final guidance should encourage sponsors to establish partnerships with patient organizations and use fit-for-purpose methods early in study planning so that patient input can influence core study design .[9]

Regulatory Flexibility Should Be Preserved, Patient-Informed, and Transparently Applied

The NHC strongly supports the draft guidance's recognition that regulatory flexibility should be retained and may be necessary in certain critical settings. In such settings, a somewhat greater degree of uncertainty about effectiveness may be warranted when

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[7] U.S. Food and Drug Administration, Enhancing Participation in Clinical Trials—Eligibility Criteria, Enrollment Practices, and Trial Designs: Guidance for Industry (December 2025), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-participation-clinical-trials-eligibility-criteria-enrollment-practices-and-trial-designs.

[8] U.S. Food and Drug Administration, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, 5–6.

[9] Oehrlein EM, Schoch S, Majercak K, Gressler LE, Costantino R, and Perfetto EM, on behalf of the Patient Experience Mapping Working Group, Patient Experience Mapping Toolbox (Washington, DC: National Health Council, 2021), https://nationalhealthcouncil.org/additional-resources/patient-experience-map/.

weighed against the risk of rejecting or delaying an effective therapy. It also identifies disease severity, unmet need, and rarity as relevant clinical considerations that should be evaluated holistically. For patients with serious, progressive, life-threatening, or rare diseases, the consequences of delay can be substantial and, in some settings, irreversible. The evidentiary framework should therefore allow FDA to exercise sound scientific judgment when conventional development programs are infeasible, unethical, or disproportionate to what is needed to reach a reliable conclusion about effectiveness.[10]

The final guidance should avoid framing flexibility primarily as a departure from an otherwise preferred evidentiary model. Instead. It should explain more directly that the statutory standard can be satisfied through different evidence configurations when the totality of the evidence is sufficiently persuasive. That distinction is important. Flexibility should not mean that evidence is accepted without adequate scientific justification, but rigor should not be equated with a fixed number of trials, a single preferred design, or uniform statistical conventions that may not fit the clinical context. FDA's 2023 rare disease guidance similarly recognizes the need to tailor development programs to disease-specific challenges, including small populations, limited natural history information, heterogeneity, and the need for early engagement with the Agency.[11]

The NHC also encourages FDA to more explicitly consider patient perspectives when determining how much uncertainty may be acceptable in a given setting. Patients living with severe disease and few or no treatment options may reasonably value earlier access despite greater uncertainty, while patients in other settings may prioritize greater certainty regarding the magnitude or durability of benefit. FDA notes that its approach to flexibility has been reinforced by interactions with patients and caregivers who have expressed willingness to accept less certainty in exchange for earlier access. The final guidance should build on that observation by encouraging the use of systematic patient preference information, PFDD evidence, listening-session findings, externally led PFDD meeting reports, and other fit-for-purpose sources when those data can inform the relevant tradeoffs.[12]

The same balance between flexibility and rigor underlies NHC's recent comments on drug repurposing. In those comments, we emphasized the importance of pathways that can address significant unmet need while maintaining an evidence framework adequate to support informed regulatory and clinical decision-making. In both contexts, the objective is an evidentiary approach that reliably identifies meaningful benefit and makes full use of scientifically appropriate sources of evidence. Requirements that add

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[10] U.S. Food and Drug Administration, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, 13–15.

[11] U.S. Food and Drug Administration, Rare Diseases: Considerations for the Development of Drugs and Biological Products: Guidance for Industry (December 2023), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-considerations-development-drugs-and-biological-products.

[12] U.S. Food and Drug Administration, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, 13.

time or burden without materially improving the certainty needed for regulatory decision-making should be avoided.[13]

Confirmatory Evidence Should Accommodate High-Quality RWD, Natural History Data, and Patient-Organization Evidence Infrastructure

The draft provides useful clarity regarding the use of one adequate and well-controlled clinical investigation plus confirmatory evidence, including circumstances in which related trial data, mechanistic evidence, natural history data, registries, and other RWD sources may contribute to the evidentiary package. The NHC supports approach, which is particularly important in rare diseases and other settings where conducting multiple conventional trials may be infeasible, where patient populations are small, or where high-quality longitudinal data already exist outside a traditional trial.[14]

The final guidance would benefit from additional examples showing how expectations for confirmatory evidence vary based on the persuasiveness of the adequate and well-controlled investigation and with clinical context. Sponsors and patient communities would benefit from understanding, for example, when a disease registry that was not created for regulatory purposes could nevertheless become sufficiently fit for purpose to contribute confirmatory evidence; when natural history information can be used as confirmatory evidence without also serving as the external control for the pivotal investigation; how FDA evaluates multiple individually limited but directionally consistent sources of evidence; and what documentation is necessary when evidence comes from patient organizations, academic networks, or other non-sponsor sources.

The NHC has previously encouraged FDA to continue developing clear, transparent expectations for RWD and real-world evidence (RWE) and to engage patient organizations in that work. Patient groups and other stakeholders must be able to generate and assess useful, high-quality RWD for these sources to be used successfully in regulatory decision-making. FDA's final 2024 guidance on electronic health record (EHR) and medical claims data appropriately emphasizes relevance and reliability when such data are proposed to support regulatory decisions. The substantial evidence guidance should reinforce this fit-for-purpose approach and recognize that patient organizations may contribute to evidence generation through registries, natural history studies, patient experience research, endpoint-development efforts, and longitudinal disease infrastructure.[15,16]

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[13] National Health Council, "NHC Responds to FDA RFI on Drug Repurposing," June 11, 2026, https://nationalhealthcouncil.org/letters-comments/nhc-responds-to-fda-rfi-on-drug-repurposing/.

[14] U.S. Food and Drug Administration, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, 9–16.

[15] U.S. Food and Drug Administration, Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products: Guidance for Industry (July 2024), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory.

The NHC also encourages FDA to maintain a fit-for-purpose approach that recognizes the complementary strengths and limitations of different data sources. Claims and EHR data can provide important information at scale, while other sources may be necessary to capture symptoms, functional effects, caregiver burden, treatment burden, or other outcomes that are central to patients. Depending on the regulatory question, a strong evidentiary package may therefore draw on or link traditional clinical data, RWD, natural history information, and patient-generated or patient-reported evidence. The final guidance should preserve methodological flexibility while clearly articulating expectations for relevance, reliability, transparency, prespecification where appropriate, and the management of bias and missingness.

FDA Should Promote Predictability and Consistency Without Constraining Scientific Judgment

Because the guidance is intentionally principles-based, its usefulness will depend heavily on how consistently the principles are applied across review divisions and development programs. The NHC supports FDA's recommendations that sponsors discuss their proposed approach to demonstrating substantial evidence early in development and no later than the end-of-phase 2 meeting, and that approaches relying on one adequate and well-controlled investigation plus confirmatory evidence be discussed before the pivotal trial is initiated. Early engagement can prevent avoidable development delays. Sponsors must make consequential decisions regarding trial design, evidence generation, and investment well before a marketing application is submitted. Clear and durable FDA feedback is therefore particularly important when a development program will rely on an innovative design, a single adequate and well-controlled investigation with confirmatory evidence, RWE, or another context-specific application of regulatory flexibility. The value of early engagement is reduced if sponsors receive materially different expectations across review teams or if the basis for an evidentiary judgment becomes clear only late in development.[17]

The final guidance should therefore provide additional examples or a decision framework illustrating the factors that most often drive FDA toward different evidentiary expectations, including the persuasiveness of prior evidence, disease understanding, magnitude and durability of effect, endpoint characteristics, representativeness, feasibility of replication, availability and quality of confirmatory evidence, and the clinical consequences of a false-positive or false-negative conclusion. Any such framework need not be a rigid scoring system. A transparent framework can preserve scientific judgment while making the Agency's reasoning more understandable to sponsors, patients, researchers, and the broader public.

The NHC also encourages FDA to consider how to communicate major evidentiary judgments after approval. Where an application relies on one adequate and well-

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[16] National Health Council, "NHC RWE, EHR and Medical Claims Comments," November 29, 2021, https://nationalhealthcouncil.org/letters-comments/nhc-rwe-ehr-and-medical-claims-comments/.

[17] U.S. Food and Drug Administration, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, 2, 9.

controlled investigation plus confirmatory evidence, a less conventional trial design, or another context-dependent application of regulatory flexibility, the NHC encourages FDA to use its existing review-document transparency mechanisms to explain the principal scientific considerations supporting its determination. Doing so would help patients, clinicians, sponsors, and researchers better understand how the Agency applies the substantial evidence standard across different development contexts and would provide useful precedent for future programs.

The Guidance Should More Clearly Connect Effectiveness, Safety, and Patient-Informed Benefit-Risk Assessment

The draft appropriately notes that substantial evidence of effectiveness is necessary but not sufficient for approval and that FDA must also determine that a drug is safe for its intended use and that its benefits outweigh its risks. Although a detailed discussion of safety and benefit-risk is outside the scope of this guidance, the NHC recommends a stronger cross-reference to FDA's benefit-risk framework and to the role of patient input in understanding the clinical context. Evidentiary flexibility regarding effectiveness cannot be evaluated in isolation from the seriousness of the disease, the availability and limitations of existing therapies, the risks of treatment, the risks of no treatment, and the outcomes that patients value.[18]

FDA's 2023 Benefit-Risk Assessment guidance explains that the therapeutic context, evidence of benefits and risks, and uncertainty are considered together in regulatory decision-making. The final substantial evidence guidance should make clear that FDA considers this broader context and, where available and appropriate, by patient experience and preference information when determining whether to accepting greater uncertainty about effectiveness. This would help connect the guidance to the patient-focused framework FDA has developed over the last decade and would reinforce that efficiency and flexibility remain anchored in a patient-centered assessment of whether the evidence is adequate for the intended use.[19]

Conclusion

The NHC appreciates FDA's effort to modernize and clarify its recommendations for demonstrating substantial evidence of effectiveness. The revised guidance provides a strong foundation by focusing on the total strength of the evidence, recognizing multiple scientifically valid pathways to satisfy the statutory standard, and preserving flexibility where the clinical context warrants it. As FDA finalizes its guidance, the NHC encourages the Agency to make the patient role more explicit throughout the evidentiary framework; to more clearly connect clinical meaningfulness, representativeness, feasibility, and acceptable uncertainty to patient experience; to expand practical guidance regarding RWD, natural history data, and other confirmatory evidence; and to

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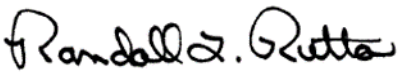
[18] U.S. Food and Drug Administration, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, 2, 16–17.

[19] U.S. Food and Drug Administration, Benefit-Risk Assessment for New Drug and Biological Products: Guidance for Industry (October 2023).

strengthen transparency regarding how these principles are applied across review programs. These changes would preserve rigorous standards while helping ensure that the evidence FDA relies on is not only statistically and scientifically persuasive, but also relevant to the patients who will ultimately make decisions about whether and how to use an approved therapy.

Please do not hesitate to contact Jennifer Dexter, Senior Vice President, Policy & External Affairs, or Shion Chang, Assistant Vice President, Policy & Regulatory Affairs, if you or your staff would like to discuss these comments in greater detail.

Sincerely,



Randall L. Rutta
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