



The professional society for health
economics and outcomes research

Improving healthcare decisions

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Docket Number: FDA-2019-D-4964

Dear U.S. Food & Drug Administration (FDA):

ISPOR—The Professional Society for Health Economics and Outcomes Research - is
pleased to respond on behalf of its membership to your consultation titled

**“Demonstrating Substantial Evidence of Effectiveness for Human Drug and
Biological Products – Draft Guidance for Industry”**

ISPOR is a scientific and educational society with many of its members engaged in
evaluating health technologies, including pharmaceuticals, medical devices, and other
interventions. ISPOR membership includes nearly 18,000 individual and chapter
members from more than 100 countries worldwide. The number of individual members
in the US exceeds 2,500. Our membership is uniquely diverse and represents a variety
of stakeholder perspectives, including research organizations, academia, payers, patient
groups, government, healthcare professionals, health technology assessment bodies, and
the life sciences industry. ISPOR also publishes peer-reviewed scientific journals,
develops internationally recognized Good Practices Reports, and convenes scientific
conferences to communicate healthcare evidence to decision makers worldwide.

The response to this consultation was led by the ISPOR Scientific Initiatives Team and
Chief Science Officer Laura Pizzi. Comments were solicited from ISPOR’s Real-World
Evidence, Emerging and Orphan Therapies, Oncology, and Statistical Methods in
HEOR Special Interest Groups, as well as ISPOR’s Health Science Policy Council and
Health Policy Community of Interest. The attached document summarizes our
comments on specific provisions of the guidance.

ISPOR would be happy to answer any questions about our response, serve as a partner,
or participate in any follow-up consultations on the relevant items mentioned in the
document.

Sincerely,

Robert M. Abbott
CEO & Executive Director
ISPOR

Beth Devine, PhD, PharmD, MBA, MSc
President
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Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products – Guidance for Industry

On behalf of the members of ISPOR – The professional society for health economics and outcomes research, we appreciate the Food & Drug Administration’s (FDA) efforts in preparing draft guidance that will replace the 1998 guidance “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products” and acknowledges the advances in our understanding of biological processes and how the increasing availability of high-quality data have transformed the evidentiary landscape for drug development. ISPOR members have reviewed the draft guidance and identified 5 recurring themes for FDA’s consideration, including; (1) continuity with the existing 1998 guidance, (2) the importance of highly persuasive evidence and flexibility, (3) relevance of real-world data (RWD), real-world evidence (RWE), and non-interventional evidence sources, (4) transparency and pre-specification requirements, and (5) patient-centered considerations.

Continuity with 1998 and other existing guidance

In this new guidance, it is important that FDA clearly describes the changes that are adapted from earlier guidance documents, such as the 1998 original “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products”, the 2019 “Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products” and the 2023 “Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence” guidance document. Rationale for the choices and changes made to earlier guidance should be clearly documented, explained, and referenced.

Importance of highly persuasive evidence and regulatory flexibility

Generating effective evidence relies on the careful and intentional selection of analytical methods which are best suited to answer the research question with the available data. The FDA should remain flexible while maintaining consistent evidentiary standards in their acceptance and consideration of these methodologies, endpoints, and outcomes, with special attention given to causal inference methods, like external controls, and the evidence they generate as important factors that impact the strength of evidence effectiveness.

We also recognize that the growth of artificial intelligence (AI) here for evidence generation and synthesis for supporting effectiveness. We encourage the FDA to direct researchers to their 2025 draft guidance “Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products”¹ with balanced consideration for AI as an assistive tool.

Relevance of real-world data, real-world evidence, and other non-interventional evidence sources

Members noted that the current draft guidance does not address non-interventional evidence sources in the analysis of effectiveness. In research scenarios that evaluate the effectiveness of a drug or biological product for a rare disease, outcome, or other data-limiting scenario, the use of non-interventional evidence sources like real-world data (RWD) is necessary and should be explicitly acknowledged by the FDA in the guidance. The draft guidance should more clearly clarify that fit-for-purpose real-world evidence may contribute to substantial evidence beyond rare diseases or circumstances which warrant regulatory flexibility. Moreover, FDA should include sources of acceptable RWD sources, such as federated data networks, or other commercial databases, to support this.

Transparency and pre-specification requirements

Closely related to the relevance of RWD, RWE, and other non-interventional evidence sources, is the need for transparency in data sources, methodologies, and other research decisions. FDA should require documentation of the provenance and analytical role of each evidence source, including any overlap in patients, datasets, endpoints, time periods, or assumptions. Multiple correlated evidence sources should not be considered equivalent to independent corroboration. For example, to accept non-interventional evidence sources like RWD, it is important that clear and objective criteria for evidence expectations are provided by FDA, as well as equally clear and objective rationale from the researchers, such as with their endpoints and outcomes selection. Efforts like these promote transparency in real-world evidence results and support our earlier recommendation for FDA to provide examples of non-interventional evidence sources that would be accepted for the purposes of drug review. The HARmonized Protocol Template to Enhance Reproducibility (HARPER)², helps to create a shared understanding of intended scientific decisions through a common text, tabular and visual structure, and would be a welcome addition to this guidance for the purposes of promoting transparency.

Patient-centered approaches

FDA should more explicitly describe how patient-centered evidence can inform determinations of effectiveness. This includes identifying which outcomes matter most to patients, explaining why selected endpoints are clinically meaningful, and clarifying how patient experience data will be evaluated as part of the overall evidence package. FDA should encourage transparent use of patient-reported outcomes and related evidence, including clear disclosure of how this information will support regulatory decision-making, as well as where the data came from, such as direct from patient sources via digital health technologies and wearables. This longitudinal patient data should be integrated with existing data sources when doing so would improve the

interpretation of effectiveness over time. As with other considerations previously described, FDA should acknowledge when flexibility may be warranted for patient benefit, particularly in settings where there is no satisfactory alternative therapy or available evidence is limited. Relevant resources, including the ISPOR Good Practices Report on Quantitative Benefit-Risk Assessment in Medical Product Decision Making³, may help support consistent and transparent evaluation.

We acknowledge ISPOR members Candide Ahouehome, Nora Fayed, Mallik Greene, Ben Illigens, and Mannat Sharma for their assistance in assembling these comments as well as ISPOR staff Laura Pizzi, Chief Science Officer, and Madeline Shipley, Scientific Initiatives Manager.

References

1. Food and Drug Administration. *Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products: Draft Guidance for Industry and Other Interested Parties*. Food and Drug Administration; 2025, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-artificial-intelligence-support-regulatory-decision-making-drug-and-biological>.
2. Wang SV, Pottegård A, Crown W, et al. HARmonized Protocol Template to Enhance Reproducibility of hypothesis evaluating real-world evidence studies on treatment effects: A good practices report of a joint ISPE/ISPOR task force. *Value Health*. 2022;25(10):1663-1672. <http://doi.org/https://doi.org/10.1016/j.jval.2022.09.001>.
3. Tervonen T, Veldwijk J, Payne K, et al. Quantitative benefit-risk assessment in medical product decision making: a good practices report of an ISPOR Task Force. *Value Health*. 2023;26(4):449-460. <http://doi.org/https://doi.org/10.1016/j.jval.2022.12.006>.