April 27, 2026

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

Re: Docket No. FDA-2026-D-1256: Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause.

Dear Sir/Madam:

The International Society for Pharmacoepidemiology (ISPE) respectfully submits the following comments in response to the FDA draft guidance, "Considerations for the Use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause," issued jointly by the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) in February 2026 (Docket No. FDA-2026-D-1256). ISPE is an international organization dedicated to advancing the health of the public by providing a global forum for the open exchange of scientific information, collaboration, and the development of new epidemiologic research methods, policy, education, advocacy, and leadership for the field of pharmacoepidemiology. ISPE commends FDA for developing this framework as an important step toward addressing the unique epidemiologic and methodological challenges inherent in rare disease drug development, and we offer the following recommendations to strengthen its rigor, clarity, and practical applicability.

Sincerely,
International Society for Pharmacoepidemiology

Executive Summary of ISPE Comments

The focus of this guidance on individualized therapies targeting specific genetic conditions with a known biological cause is especially relevant to rare and ultra-rare diseases, where patient populations are small, phenotypically heterogeneous, and frequently defined by narrow molecular or genotypic subgroups. In these settings, randomized controlled trials and conventional control arms are often impractical or ethically challenging, increasing reliance on alternative evidentiary approaches to characterize disease progression and contextualize treatment effects.

Across sections, the guidance presumes the availability of well-characterized untreated natural history data, it is unclear whether within-person or population data is acceptable in addition to when a well-designed external control study, implementing causal inference methods, are acceptable versus contextualization more generally.. In many rare disease settings, however, truly

untreated populations are infeasible or non-representative because patients commonly receive heterogeneous standard of care (SOC), including off-label, supportive, or evolving therapies. We recommend that the guidance explicitly acknowledge these realities and allow the use of SOC-treated cohorts, hybrid external controls, and contemporaneous real-world data (RWD) as potential comparators, with appropriate attention to population comparability and outcome definition, and use of causal inference methods to address confounding and time-related bias.

We strongly encourage the Agency to further define terms (e.g., "well-characterized natural history," "reasonably characterized," and "robust") and to clarify evidentiary considerations for within-patient comparisons, external controls, and extrapolation across genetic variants or subpopulations, particularly as biological or phenotypic heterogeneity increases. Greater transparency regarding expectations for prespecification of estimands, index dates, eligibility criteria, analytic plans, sensitivity analyses, and bias assessment would support interpretability and reproducibility, especially in ultra-small samples where individual design choices can meaningfully influence conclusions.

Pharmacoepidemiology and RWE should play a central role in both pre- and post-approval evidence generation. Observational lead-in periods and natural history studies should be designed to support meaningful clinical comparisons, for example by emulating key features of the intended interventional contrast ("target trial" approach), with epidemiologic expertise incorporated early in study planning. Confirmatory evidence should more explicitly recognize the role of RWE derived from registries, external cohorts, and longitudinal follow-up conducted alongside or external to clinical trials, with biomarkers used where their relationship to clinical benefit is biologically and clinically well justified.

Post-marketing expectations would benefit from further clarification, including the role of registries, long-term safety and effectiveness evaluation, global data sharing, and how post-approval evidence may contribute to reassessment of benefit-risk, continued authorization, or potential labelling expansion. Finally, ISPE encourages the Agency to acknowledge the global nature of rare disease evidence generation and to consider how high-quality non-U.S. data, common data standards, and international collaboration may complement U.S-based evidence within the broader Agency RWE framework.

The following table presents ISPE's detailed comments and recommended language changes, organized by section and line number of the draft guidance. New suggested text is bolded in the suggested changes column.

Detailed Comments

Type of Comment	Section	Line Number	Comment	Suggested Changes
Major: Methodological	I	30	The bullet references a "well-characterized natural history in an untreated population" but does	Consider modifying the bullet wording to: "**Using contemporary, well-**

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			not address whether standard-of-care (SOC) data may also support the plausible-mechanism framework. In many rare diseases, untreated data may be infeasible or non-representative of the target rare disease population because most patients receive SOC. We recommend that the guidance explicitly state whether the data would only come from the patient's history or whether summarized data from an external population can serve as the comparator or benchmark. If the data can come from an external population, consider clarifying that these data should be contemporary where feasible; if only non-contemporary data are available, justification of comparability and assessment of temporal bias would be provided.	**characterized untreated disease natural history data or SOC treatment data (if effect size is expected to be substantial) from the patient's pre-treatment period or from a target population as an external comparator, as appropriate and available**"
Major: Methodological	II	104-106	The guidance states that substantial evidence of effectiveness may rely on: "a single adequate and well-controlled clinical investigation with confirmatory evidence." The Agency is recommended to reference the suggested confirmatory evidence in lines 180-185.	In lines 104-106, the following wording changes are suggested: "The Agency anticipates that substantial evidence of effectiveness for individualized therapies could be established based on a single adequate and well-controlled clinical investigation with confirmatory evidence **as discussed in Section III.A**."
Minor: Regulatory	II	114	The term "reasonably characterized" as it pertains to understanding natural history of disease would benefit from further clarification. The Agency should consider briefly defining what constitutes a reasonable characterization of the disease in the untreated state.	The guidance should consider briefly define what is considered a reasonable characterization of a disease in the untreated state. Consider adding illustrative examples on line 114, such as: "(**e.g., molecular or genetic disease characteristics, clinical manifestations, and/or information on disease progression).**"
Major: Regulatory	II	114-121	There are multiple clarifications that are needed in this section: • The criteria for relying on within-patient comparisons are not provided, including whether the natural history should be stable or predictable leading up to treatment and whether the	Suggest revising the sentence to clarify the Agency's intent : "**In patients for whom the natural history of the disease can be reasonably characterized, a single-arm clinical investigation that evaluates each patient's change from**

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			large, rapid effect is unlikely under versus the patient's baseline natural history • When an external natural history comparator cohort is used, the guidance is recommended to reference the causal methods to address confounding and time-related bias	**baseline following treatment may be sufficient to constitute an adequate and well-controlled clinical investigation necessary to support approval/licensure. External natural history data should be considered for comparisons to support or in place of within-person comparisons, as appropriate."**
Major: Methodological	II	114-121	The guidance assumes availability of a well-characterized "natural history of the disease in the untreated state," which is often not feasible or representative in rare diseases where most patients are treated with a SOC.	The guidance may consider clarifying how sponsors should proceed when a non-treatment approach for the disease is outdated relative to current clinical practice or is not representative of the target population, including if an individual or population receiving SOC can be used for comparative evidence.
Major: Methodological	II	149-156	The guidance permits extrapolation across variants or product variants without specifying the criteria used to assess generalizability or the boundaries beyond which extrapolation may no longer be appropriate or what evidence is needed. Greater clarity would improve consistency and predictability in applying the plausible mechanism framework.	Add language to clarify how the Agency will assess the appropriateness of extrapolating prior evidence to additional variants under a shared plausible mechanism. Such as: **"When extrapolating prior evidence to support additional product variants under a shared plausible mechanism, the Agency will consider similarity in mechanism of action, role in disease pathophysiology, anticipated clinical effect, and safety considerations. As differences across variants increase, including differences in downstream biological effects, disease manifestation or progression, or potential safety risks, reliance on prior evidence alone may be less appropriate, and additional supportive nonclinical, clinical, or observational information may be informative."**
Moderate: Regulatory	II	113-121,	This section should reference the Draft Guidance for Industry: Rare Diseases: Natural History Studies	Add a reference to the end of the sentence for the Draft Guidance for Industry: Rare Diseases:

Type of Comment	Section	Line Number	Comment	Suggested Changes
			for Drug Development (March 2019)	Natural History Studies for Drug Development (March 2019)
Major: Methodological		113-116 469-472	The Agency describes an external control if adequate, can be used for clinical investigation. However, in ultra-rare settings, where causal inference methods may be inappropriate (i.e., the sample size is small), a well-designed external control study, implementing causal inference methods, are not feasible.	It is recommended that the Agency provides more clarity around how external natural history may be used (i.e., contextualization).
Minor: Editorial	III.A	173	Reference to Section III.B for effectiveness criteria is inconsistent with the content of that section. In the regulatory pathway section, the draft states that substantial evidence may be provided "in accordance with the criteria discussed in section III.B. of this guidance," but section III.B is the Nonclinical section, whereas the evidence standard described seems to be tied to the Clinical discussion.	It is recommended that the cross-reference be changed from Section III.B to Section III.C.
Major: Methodological	III.A	176-178	The requirement for results to be "robust to exclude chance findings" is not defined. . The FDA should consider recommending that sponsors show whether effects are unlikely due to chance by demonstrating consistency across related endpoints, durability over time, alignment with pre-treatment trajectory (as applicable), and sensitivity analyses under alternative assumptions or comparator constructions.	Consider modifying the wording to: "FDA recognizes that an adequate and well-controlled clinical investigation in this context will include a small sample size; therefore, investigation results should be robust to exclude chance findings that may incorrectly suggest effectiveness. **Robust evidence may include, as appropriate, consistency across related endpoints, durability of effect over time, alignment with pre-treatment disease trajectory where applicable, and consistency of findings in sensitivity analyses exploring alternative assumptions or comparator constructions**."
Major: Regulatory	III.A	180-186	Biomarkers and mechanistic evidence are positioned as confirmatory evidence without clear limits relative to clinical outcomes. If biomarkers are used as confirmatory evidence, sponsors should justify their link to clinical benefit and whether they are validated (traditional approval) or	Consider adding a bullet that states: "**If biomarkers and target engagement are used as confirmatory evidence, evidence should be provided on the link to clinical benefit and whether the biomarker is validated to predict benefit (traditional approval) or reasonably likely to predict**

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			reasonably likely to predict benefit (accelerated approval). The Agency is recommended to caution that target-engagement or mechanistic plausibility alone is not clinically interpretable confirmatory evidence.	**benefit (accelerated approval). Other outcomes may provide supportive evidence (e.g., symptom or functionality changes or survival)**."
Major: Regulatory	III.A	180-186	FDA lists potential sources of data for confirmatory evidence. Although this is not intended to be a comprehensive list, it would be helpful/consistent to explicitly include real-world data sources in this list as a potential source of confirmatory evidence. More information is needed on the circumstances under which each clinical or nonclinical data source may serve as confirmatory evidence.	Wording is recommended to clarify that evidence for using the different data sources as confirmatory evidence: "Confirmatory evidence would likely come from clinical or nonclinical data sources **and evidence should be provided on why these data sources are sufficient. Data sources supporting confirmatory evidence may include but are not limited to**:…" Suggest adding a bullet after these lines on real-world data e.g., "**Natural history data, disease registries, or other real-world data sources that contextualize observed treatment effects**".
Major: Regulatory	III.A	180-186	The Agency is recommended to explicitly link to/reference Rare Disease Evidence Principles (RDEP) in this section.	Please consider adding an explicit link to RDEP: https://www.fda.gov/industry/fda-rare-disease-innovation-hub/cdercber-rare-disease-evidence-principles-rdep
Moderate: Regulatory	III.A	194-203	Lines 194–203 describe post-marketing data collection at a high level and references Section III.B. However, Section III.C (lines 608-609 and lines 617-632, in particular) referring to long-term safety studies is recommended to be added as a reference for this statement.	Please consider adding a reference to Section III.C in line 198.
Minor: Editorial	III.C	429-437	This paragraph could be enhanced by clarifying what is meant by "as soon as the potential study participants are identified."	Consider adding this additional text: "**Sponsors should identify clinically meaningful outcomes and biomarkers that are relevant to the disease and, where feasible, systematically collect such data prior to initiation of the individualized**

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				therapy. Sponsors should initiate data identification/collection early in development."
Moderate: Methodological	III.C	461	The text requires standardized, pre-specified assessments for clinical efficacy, safety, and biomarkers but does not address whether an external control will be used. We recommend that the protocol also pre-specify the decision to include an external control.	Consider adding this additional text: "Protocols should be designed with standardized, pre-specified assessments of clinical efficacy and safety outcomes and relevant biomarkers. **Where an external control is intended, the protocol should also pre-specify the decision to include an external control and the proposed data source."**
Moderate: Methodological	III.C	464	The text requires pre-specified analysis plans for data compared to a control but does not address how external controls should be integrated. We recommend specifying the integration method for any external control in the pre-specified analysis plan.	Consider adding this additional text: Analysis plans for data compared to a control **(including the method for integrating external control into the analysis)** should be pre-specified.
Moderate: Methodological	III.C	466-467	Observational lead-in periods are recommended but more information is needed on how data collected during these periods will support valid causal comparisons.	Consider adding this additional text: "It is recommended that data be collected in an observational period prior to the initiation of the treatment to establish a lead-in baseline. **Specifically, the lead-in period should be aligned with the intended treatment comparison, including clear specification of time zero, covariate assessment windows prior to treatment initiation, and consistent outcome assessment schedules to ensure appropriate temporality and comparability between groups."**
Major: Methodological	III.C	469-471	We recommend that that Agency consider allowing natural history data from patients treated with SOC when the new individualized treatment has aa large anticipated effect since many rare disease patients will receive SOC, and untreated patients may be unrepresentative.	Consider adding this additional text: In general, the disease under study will have a well-characterized natural history in the untreated **or standard of care** population, as feasible. This natural history data may serve as an external control if it is adequate to allow for the treatment effect to be reasonably

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				distinguished from natural variability in the phenotype of the disease.
Moderate: Methodological	III.C	557	The draft guidance includes the bullet "Consider collecting multiple types of outcomes to evaluate for treatment effects" - which is too high level to be actionable.	Consider this revised paragraph: "Consider collecting multiple types of outcome **(e.g., clinical outcomes, functional measures, biomarkers, and patient-reported outcomes), as appropriate for the disease and mechanism, to support interpretation of treatment effects and consistency of evidence.**"
Moderate: Methodological	III.C	575-580	For individualized therapies, traditional RCT-based surrogate endpoint validation is often not feasible. In these settings, incorporating within-patient longitudinal assessments and supportive RWE may provide important additional context for evaluating biomarker relevance.	Consider adding this text to the end of the bullet: **"In addition, this determination may also consider within-patient longitudinal consistency, including assessment relative to lead-in baseline data, and, where available, supportive RWD from patients with sufficiently similar pathophysiology as external contextual evidence."**
Moderate: Methodological	III.C	608-609	The Agency only mentions that long-term follow-up studies for delayed reactions may be required for GE. However, long-term follow-up studies may be relevant to other individualized therapies and should assess safety data beyond delayed adverse events. This bullet is recommended to be modified to include details regarding long-term follow-up studies that may be warranted.	Consider adding this text: "Long-term follow-up studies **may be required for GE or other individualized products for the collection of data on safety outcomes, including delayed adverse reactions**."
Major: Regulatory	III.C	619-632	While FDA anticipates limited pre-approval safety data and mentions PMRs/PMCs, we recommend that the Agency provide more guidance on: • Expectations for long-term follow-up, especially when repeated dosing or variant expansion occurs • Use of real-world data sources (registries, EHR, global data sharing)	The Agency may consider adding the following considerations to the Post-marketing section: • **Sponsors should consider incorporating pharmacoepidemiologic methods and real-world data sources, such as patient registries, electronic health records, or other fit-for-purpose data systems, to support**

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			.	**post-marketing evaluations.** • **Expectations for the duration and scope of long-term follow-up may vary based on factors such as disease severity, durability of treatment effect, repeated dosing, or expansion to additional variants. The long-term study duration should be proportionate to the biological mechanism of risk and informed by accumulated clinical and post-marketing safety data.**
Minor: Editorial	III.C	429-437; 468-486; 619-632	The guidance extensively references rare disease and clinical trial guidance but does not explicitly cross-reference FDA's RWE and observational study guidance, despite relying on natural history data, external controls, and post-marketing observational follow-up.	The Agency may consider explicitly cross-referencing relevant FDA RWE and observational study guidance in Section III.C (e.g., lines 429-437 and 468-486) and in the Post-marketing considerations section (lines 619-632) to reinforce consistency and clarify expectations. Relevant examples include: • Considerations Regarding the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products • Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products • Rare Diseases: Natural History Studies for Drug Development