



Dockets Management  
U.S. Food and Drug Administration (FDA)  
5630 Fishers Lane, Rm 1061  
Rockville, MD 20852

**Re: Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause (FDA-2026-D-1256)**

To Whom it May Concern:

Friends of Cancer Research (*Friends*) powers advances in science and policy that speed life-saving treatments to patients. *Friends* is committed to accelerating cutting-edge cancer care that extends and improves quality of life for patients. To accomplish this, we leverage groundbreaking collaborations, generate scientific evidence, and integrate patient input to shape public policy.

*Friends* appreciates the opportunity to provide comments on the draft guidance, “*Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause.*” This guidance represents an important step toward clarifying FDA’s thinking regarding the application of the plausible mechanism framework and in supporting more efficient and predictable application of approval pathways for individualized therapies while maintaining appropriate standards for patient benefit and safety.

Individualized therapies such as gene editing (GE) and antisense oligonucleotides (ASOs) represent transformative therapeutic approaches for treating patients with rare and ultra-rare genetic conditions, including n=1 scenarios. However, these therapies present unique challenges under traditional drug development and approval paradigms, particularly due to small patient populations, limited availability of robust natural history data, and the need for flexible yet rigorous approaches to evidence generation. The plausible mechanism framework reinforces that existing expedited programs remain the primary approval pathways, while clarifying how evidence generated in individualized contexts can support regulatory decision-making within existing standards rather than creating a parallel pathway

At the same time, the framework introduces important flexibility in how evidence may be generated (e.g., small sample sizes, external controls, and mechanistic or biomarker-based support), but additional clarity is needed regarding how evidentiary sufficiency will be assessed, particularly when traditional sources of statistical certainty are inherently limited.

We offer the following considerations in response to the draft guidance, with a focus on practical implementation, regulatory clarity, and product scalability across individualized and small-cohort applications.

## **1. Clarification of Regulatory Expectations Across the Full Product Lifecycle**

We commend the FDA for addressing opportunities for flexibility at the Investigational New Drug (IND) stage for individualized therapy products. However, additional clarity around Chemistry, Manufacturing, and Controls (CMC) expectations is needed across the full product lifecycle, particularly regarding the transition from IND to Biologics License Application (BLA)/New Drug Application (NDA) stages. For therapies with extremely small patient populations, traditional CMC requirements may not be feasible.

We recommend that the FDA:

- Allow iterative (rolling or staged) CMC submissions to reduce sponsor burden and support compressed clinical timelines.
- Clarify how CMC expectations scale as drug development progresses from n=1 applications to small cohorts, including whether approaches acceptable for n=1 INDs remain sufficient for platform-based expansion or whether additional validation is required at defined thresholds.
- Expand or clarify expectations in existing or updated guidance (e.g., the FDA’s gene therapy CMC guidance and/or ASO IND guidance),<sup>1,2</sup> including:
  - Defining acceptable CMC approaches.
  - Establishing clear guardrails for regulatory flexibility, including minimum quality standards.
  - Providing aggregated, de-identified case examples of flexible approaches.
  - Supporting ongoing public dialogue and post-implementation learnings to identify best practices and remaining barriers in transitioning from IND to BLA/NDA.

## **2. Defining “Well-Characterized” Natural History Data**

The guidance appropriately highlights the importance of natural history data but does not provide sufficient operational clarity on what constitutes a “well-characterized” dataset. Limitations in data quality and completeness, including missingness, may impact both

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<sup>1</sup>[Chemistry, Manufacturing, and Control \(CMC\) Information for Human Gene Therapy Investigational New Drug Applications \(INDs\) | Guidance for Industry](#)

<sup>2</sup> [IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations | Guidance for Sponsor-Investigators](#)

evidentiary sufficiency within the plausible mechanism framework and a sponsor's ability to meet this threshold. Additional clarification regarding the defining attributes of well-characterized data would be beneficial.

We recommend that the FDA:

- Provide clear operational definitions of well-characterized natural history data, including minimum data elements (e.g., disease progression metrics, variability thresholds, duration of patient follow-up).
- Acknowledge data limitations, including missingness and cross-cohort inconsistencies, and specify acceptable methodological approaches (e.g., statistical adjustment methods, cross-cohort harmonization, and federated data models) in cases where natural history data are incomplete, but the disease target is otherwise well-justified.
- Include case examples illustrating when natural history data were deemed well-characterized and insufficiently characterized.
- Encourage the development of standardized natural history data frameworks to guide data selection.
- Emphasize early FDA engagement to assess the suitability of natural history datasets and their integration into trial design.
- Clarify how treatment effects should be interpreted relative to natural history variability, including what magnitude or consistency of deviation from expected disease trajectory may be considered sufficient to support evidence of effectiveness.

### **3. Platform Trial Design and Assay Standardization**

We support the FDA's openness to platform protocols but recommend additional clarity to ensure scientific consistency and regulatory confidence. Platform approaches rely on validated and standardized assays, yet the current guidance provides limited detail on assay expectations.

We recommend that the FDA:

- Provide clear expectations for assay performance, including sensitivity, specificity, and validation requirements.
- Clarify expectations for assay comparability across variants within a platform.
- Share de-identified examples of assay validation and, where appropriate, recommended performance benchmarks.
- Clarify whether platform approaches are intended for single sponsor use or broader multi-sponsor application.
  - If broader use is anticipated, encourage mechanisms and incentives for assay standardization and sharing.

- Clarify how platform-based development approaches may support evidence generation across related variants.

#### **4. Data Leveraging Across Product Variants**

The guidance appropriately allows flexibility in nonclinical programs and highlights the role of new approach methodologies (NAMs). However, clearer expectations are needed regarding how data can be leveraged across individualized product variants, particularly as clinical experience accumulates.

We recommend that the FDA:

- Clarify principles for data leveraging, including which elements must be re-established for each variant and which may be extrapolated across variants.
- Define expectations for assessing on-target and off-target effects across variants.
- Encourage early FDA engagement on data leveraging strategies.
- Provide examples of acceptable cross-variant extrapolation, including required bridging data.
- Support the use of NAMs and *in vitro* systems where appropriate.
- Consider a risk-based approach to scaling from n=1 to a small cohort (e.g., minimal bridging for closely related variants, with more robust requirements as the genetic divergence from the anchor variant increases).
- More broadly, clarify how data generated across related product variants may be integrated within a platform-based framework to support efficient development.

#### **5. Post-Market Evidence Generation and Lifecycle Considerations**

Given the limited size of premarket datasets anticipated for individualized therapies, as noted in the draft guidance, post-market data collection will play an important role in further characterizing safety and, where applicable, confirming clinical benefit. However, the feasibility of traditional post-marketing requirements may be limited in ultra-rare or n=1 contexts.

We recommend that the FDA:

- Clarify expectations for post-marketing evidence generation, including the role of registries, observational follow-up, and real-world data sources.
- Provide guidance on how confirmatory evidence, particularly in the context of an accelerated approval, may be generated when replication in larger patient populations is likely not feasible.
- Consider approaches to longitudinal data collection that balance feasibility with the need to monitor long-term safety and durability of response.

*Friends* appreciates the FDA's leadership in putting forth this draft guidance, which reflects a significant commitment towards advancing individualized therapies. We look forward to collaborating with the FDA and other stakeholders to support effective implementation of the plausible mechanism framework for individualized and other therapies, while ensuring patient-centricity, scientific rigor, and regulatory clarity across the product lifecycle.

On behalf of Friends of Cancer Research

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Friends of Cancer Research