



HHS Kicks Off Rare Disease Week with FDA Release of Draft Guidance on Plausible Mechanism Framework for Individualized Therapies

February 24, 2026

Reading Time : **1 min**

By: Anna K. Abram, Nathan A. Brown, Maddy L. Bolger

On February 23, 2026, the Food and Drug Administration (FDA) released a draft guidance entitled “Considerations for the Use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause.” This guidance is designed for targeted, individualized therapies for which randomized controlled trials are not practical due to a small patient population, and was previewed by the Commissioner in several public forums.

The guidance describes considerations for generating substantial evidence of effectiveness and evidence of safety for individualized therapies based on a plausible mechanism framework. The plausible mechanism framework outlines recommendations to help developers of individualized therapies generate sufficient clinical safety and efficacy data to demonstrate that a drug or biological product can be manufactured to meet regulatory quality standards.

The guidance specifically discusses genome editing and RNA-based therapies, but notes that the framework may apply to other types of individualized therapies. Criteria for the use of the plausible mechanism framework include:

- Identifying the disease-causing abnormality.
- Developing a therapy that targets the root cause or proximate biological pathway.
- Relying on well-characterized natural history data in untreated patients.
- Confirming successful target drugging or editing.

- Demonstrating improvement in clinical outcomes, disease course or biomarkers if they are established to predict clinical benefit.

The guidance calls for the careful evaluation of the results of nonclinical and clinical data, and chemistry, manufacturing and controls (CMC) data necessary to support product quality. To determine effectiveness of a drug, FDA will consider the specific disease, the strength of the evidence and the challenges of conducting clinical investigations for individualized therapies.

FDA is providing a 60-day comment period.

Categories

Policy & Regulation

Food and Drug Administration (FDA)

Life Sciences

Biologics

[Subscribe to the Eye on FDA Blog Series >](#)

© 2026 Akin Gump Strauss Hauer & Feld LLP. All rights reserved. Attorney advertising. This document is distributed for informational use only; it does not constitute legal advice and should not be used as such. Prior results do not guarantee a similar outcome. Akin is the practicing name of Akin Gump LLP, a New York limited liability partnership authorized and regulated by the Solicitors Regulation Authority under number 267321. A list of the partners is available for inspection at Eighth Floor, Ten Bishops Square, London E1 6EG. For more information about Akin Gump LLP, Akin Gump Strauss Hauer & Feld LLP and

other associated entities under which the Akin Gump network operates worldwide, please see our Legal Notices page.