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HHS Kicks Off Rare Disease Week with FDA Release of Draft Guidance on Plausible Mechanism Framework for Individualized Therapies

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On February 23, 2026, the Food and Drug Administration (FDA) released a draft guidance entitled "Considerations for the Use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with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.

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