CAPITOL STREET

September 3, 2025

FDA's New Ultra Rare Review Pathway

One Single Arm Trial Allowed; Multiple Modalities for Rare Diseases Eligible

Relevant Companies

Our Take & Next Up

The FDA plans to create a new review pathway that has significant flexibility on efficacy data for approval for ultra rare, genetic disease products. Today, the FDA's CDER & CBER proposed a new program, Rare Disease Evidence Principles (RDEP), that allows nontraditional efficacy data to be relied on for approval for ultra rare diseases therapeutics (drugs, biologics, gene therapies) here. The new pathway allows product reviews to rely on one adequate and well-controlled study that may be a single arm trial, along with other data that shows confirmatory evidence. We expect the FDA to solicit additional feedback on the program and for companies to begin applying shortly after. As a reminder, this is the pathway that was floated by Commissioner Makary in April which allows drug review "based on a plausible mechanism." See our April 20 analysis here.

Key Points

The FDA will allow one adequate and well-controlled study that may be a single arm trial for efficacy data. The FDA will meet with sponsors to determine what data will be used to substantiate safety and effectiveness. In addition to the one single-arm study, the FDA will accept: (a) data on treatment effect on the direct pathophysiology of the disease, (b) evidence from a relevant non-clinical model, (c) therapeutically relevant clinical pharmacodynamic data, or (d) other clinical data. Then, (e) therapeutics approved after participation in this process may be subject to additional post marketing requirements.

The pathway can apply to multiple medicines -- not just gene therapies -- that treat ultra rare genetic conditions. The Rare Disease Evidence Principles (RDEP) would apply to both CBER and CDER products. A qualifying product may either correct the gene (gene therapies) or be a replacement of an essential physiological protein that is otherwise deficient (mRNA, monoclonal antibodies, etc.).

- The pathway is intended for products that treat a very small, rare disease population or subpopulation (less than 1,000 persons in the US) that is the result of a known, in-born genetic defect.
- Sponsors may apply for the RDEP process at any time prior to the launch of a pivotal trial. The drug review teams will consult with the Rare Disease Policy and Portfolio Council (RDPPC) prior to accepting a drug for this new program.

This is likely the ultra-rare pathway that Commissioner Makary announced in April of 2025. See our analysis here. On April 18, the FDA Commissioner announced his intention to create an ultra-rare disease pathway on the Megyn Kelly show. We had said that the FDA can likely approve ultra-rare therapies without a new legislative pathway.

The FDA continues the work at the Rare Disease Hub. The Rare Disease Innovation Hub (started in 2024) is an FDA cross-center program focused on collaboration for rare disease product reviews. Today, the Rare Disease Innovation Science and Exploration (RISE) meeting held its first workshop to discuss the choice of control arms for studies in small populations.

Post-marketing requirements could be more burdensome under this pathway to address safety concerns. Due to recent adverse events and deaths from controversial FDA approvals (SRPT), products approved under this pathway may face significant post marketing data and reporting requirements. The FDA is also focusing more on data transparency for consumers and patients, particularly for adverse events. In late August, the FDA began daily publication of adverse event data from the FDA Adverse Event Reporting System (FAERS).

Ipsita Smolinski
Managing Director I Capitol Street
ipsita@capitol-street.com

202.250.3741 I www.capitol-street.com

900 19th St NW 6th Fl
Washington, D.C. 20006

CAPITOL STREET
