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‘The Correct Clinical Study’ for Ultra-Rare Diseases Involving Genetic Defects: FDA’s Rare Disease Evidence Principles Process Provides Guidance for Applications Supported by a Single Pivotal Trial

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On September 3, 2025, the US Food and Drug Administration (FDA) announced a new process to support the development of drugs intended to treat rare genetic diseases. The Rare Disease Evidence Principles (RDEP) process offers drug sponsors increased clarity on what constitutes “substantial evidence” of effectiveness for certain rare disease drug treatments, recognizing the unique challenges facing rare disease drug development, i.e., difficulties in enrolling large and randomized clinical trials.

Because the challenges in developing treatments for rare diseases are well established, Congress recognized the need for certain flexibilities that it granted to FDA under the Federal Food, Drug, and Cosmetic Act (FDCA). While the FDCA intimates that “substantial evidence” of effectiveness requires more than one adequate, well-controlled clinical investigation “each convincing on its own, to establish effectiveness,”[1] the FDCA also specifically allows FDA to approve an application based on one adequate and well-controlled investigation that demonstrates effectiveness, supported by confirmatory evidence that reinforces that the results of the single trial are not a fluke or the result of chance, but rather a drug’s efficacy.[2]

Types of data FDA may accept as confirmatory evidence

While FDA has long had this flexibility under the FDCA, the RDEP announcement adds important detail on the types of data that may be considered “substantial evidence” of effectiveness. For drugs eligible for RDEP, FDA states that it “expects that substantial evidence of effectiveness may generally be established based on one adequate and well-controlled study,” which may be “a single-arm trial,” supported by “robust data that provides strong confirmatory evidence of the drug’s treatment effect.” [3,4] FDA further explains that confirmatory evidence may include:

- Evidence of the drug’s treatment effect on the direct pathophysiology of the disease.
- Evidence from a relevant nonclinical model.
- Therapeutically relevant clinical pharmacodynamic data.
- Other clinical data, including case reports and expanded access data.

These appear to be similar to examples offered in FDA’s 2019 draft guidance, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products.

This announcement aligns with Dr. Vinay Prasad’s recent remarks announcing the approval of the first immunotherapy for recurrent respiratory papillomatosis. In an August 14, 2025, release, Prasad explained that, “[r]andomized trials are not always needed to approve medical products,” but “[t]he FDA will always demand the correct clinical study for the specific medical product and disease.” Forecasting the RDEP program, Prasad further explained that FDA’s “requirements for products given to tens of millions of healthy people will be different than products given to at most hundreds or thousands of patients with unique diseases.”

RDEP eligibility criteria

Drug sponsors may apply for the RDEP process at any time prior to the launch of a pivotal trial if the investigational therapy is specific to the correction of the genetic defect in question. Other eligibility criteria include:

- The drug is for a very small, rare disease population or subpopulation (e.g., generally less than 1,000 persons in the US).
- The drug is intended to treat a known, in-born genetic defect that is the major driver of the pathophysiology.
- The clinical course of the disease is progressive deterioration in function leading to rapid and/or significant disability or death in a relatively short period of time.
- There are no adequate alternative therapies that alter the course of the disease.

Notably, the limit of 1,000 persons is much lower than the 200,000-person ceiling used for orphan drug designation. Additionally, RDEP-eligible rare diseases are only those driven by a known genetic defect. While many rare diseases meet this criterion, some, like certain rare cancers without a clear genetic cause, may not qualify under this framework.

The decision to accept a drug into the RDEP process is made by the relevant FDA review team, in consultation with the Center for Drug Evaluation and Research/Center for Biologics Evaluation and Research (CDER/CBER) Rare Disease Policy and Portfolio Council (RDPPC). Launched in 2024 as part of FDA's Rare Disease Innovation Hub, the RDPPC is a senior staff-level forum that promotes cross-center dialogue on complex rare disease drug development issues. The hub serves as a single point of engagement with outside parties for drug and biological product development and facilitates collaboration between CBER and CDER on rare disease-related issues.

Building on what FDA already does – and what's new

Because the FDCA already provides FDA with the authority to approve a drug based on a single pivotal trial supported by confirmatory evidence, the RDEP is not a game-changer in the rare disease space.[5] FDA had already adopted a more flexible approach to evaluating effectiveness in rare disease drug development, which it explained in its 2019 draft guidance.[6] Yet, RDEP formalizes this approach and provides greater certainty for sponsors seeking to align with FDA expectations, and potentially suggests even greater flexibility for therapies aimed at ultra-rare diseases based on genetic defects.

In addition to enhanced predictability, the RDEP process sets parameters around when and how sponsors can request participation and gain agency insight on whether a single pivotal trial will be sufficient to support approval earlier in the review process, as RDEP requests must be submitted before the launch of a pivotal trial. Now, sponsors can submit RDEP requests in their formal meeting requests to discuss their pivotal trial with the agency, which will enable sponsors to secure agency buy in on their substantial evidence package even before a sponsor conducts its pivotal trial. This earlier alignment with FDA has the potential to increase trial efficiency, as sponsors will know before they dose patients with an investigational drug whether the single trial plus confirmatory evidence pathway is viable.

Potential impact on investment

From an investment perspective, these new RDEP guidelines may provide fresh encouragement to investors in the genetic rare disease space, as regulatory clarity is a key investment consideration, alongside cost and capital efficiency, commercial potential and viable exit opportunities – all areas these guidelines may support.

Greater clarity around trial processes and evidence requirements and improved communication pathways with the regulators may translate into saved time, resources and spend, with the potential to both streamline trials and free up capital or require less capital commitment. Thus, if companies can position the new RDEP framework to investors as a way to reduce traditional costs and time to commercialization, appetite for rare genetic disease investment may increase. In particular, by signaling when and how FDA will apply its flexibility, RDEP could help unlock innovation and encourage earlier investment, which is vital in the rare disease space.

Investors may also interpret the updated guidelines as a sign of renewed FDA commitment to advancing rare disease treatments, which enhances confidence in program viability. In addition, the perception of stronger regulatory support may encourage strategic or larger pharmaceutical and biotech companies to pursue partnerships or joint ventures with rare disease players, which may result in better exit opportunities. That, in

turn, may attract additional outside investment and further strengthen the ecosystem.

Notes

1. US Food and Drug Administration, Draft Guidance: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, December 2019, page 4.
2. See 21 USC 355(d).
3. US Food and Drug Administration, CDER/CBER Rare Disease Evidence Principles (RDEP).
4. FDA's 2023 draft guidance, Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence, describes factors to consider when assessing whether a single adequate and well-controlled clinical investigation and confirmatory evidence are sufficient to demonstrate substantial evidence of effectiveness.
5. 21 USC 355(d).
6. US Food and Drug Administration, Draft Guidance: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, December 2019, page 4.

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