Insight Guide

FDA's Rare Disease Evidence Principles (RDEP)

Use real world evidence in ultra-rare drug development

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In September 2025, the United States (U.S.) Food and Drug Administration (FDA) announced the Rare Disease Evidence Principles (RDEP),[1] a new review process designed to provide greater clarity and predictability for therapies targeting ultra-rare, genetically defined diseases. For sponsors who are developing therapies for conditions where patient populations number in the dozens rather than thousands, this framework acknowledges a long understood, and grappled with, reality: when randomization is difficult or impossible, a well-defined and innovative evidence strategy becomes central to clinical development. In these settings, high-quality real world evidence (RWE), geared toward understanding the experience of the small number of patients, is not only essential for identifying and characterizing disease, but also for generating robust, decision-grade evidence.

This Insight Guide explores how the RDEP process compares to existing pathways, in what situations it should be considered, and how sponsors can strategically leverage RWE and other evidence sources, as well as artificial intelligence (AI)-driven analytics, to prepare a successful submission.

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RDEP builds on existing FDA guidance

RDEP builds on the precedent established in FDA's 2023 draft guidance on **Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence.**[2] The guidance clarifies that, under certain conditions, a single robust, well-controlled trial supplemented by confirmatory evidence from related indications, real world data (RWD), or a strong mechanistic rationale, can satisfy the statutory requirement for "substantial evidence."

In recent publications, FDA has placed emphasis on the importance of mechanistic rationale in ultra-rare disease settings. Specifically, in November 2025, the Agency announced the "plausible mechanism pathway" for personalized therapies. Under this pathway, therapies may be approved once sponsors show consistent success across multiple patients treated with individualized constructs, supported by convincing mechanistic evidence. Post-marketing RWE collection is then required to confirm real-world safety and effectiveness and identify unanticipated issues in growth, development, or disease trajectory.[3] While distinct, this new pathway reflects principles that align strongly with RDEP objectives.

RDEP explicitly recognizes a broad range of high-quality evidence sources, including mechanistic and biomarker data, relevant non-clinical studies, pharmacodynamic evidence, natural history data, expanded access data, and case reports, offering sponsors assurance that regulators will consider these diverse forms of confirmatory evidence when evaluating therapies for ultra-rare conditions.[4] In doing so, RDEP formalizes the paradigm FDA has used in prior ultra-rare approvals. More recently, on November 24th 2025, FDA approved Itvisma (onasemnogene abeparvovec-brve) for the treatment of spinal muscular atrophy (SMA) in adult and pediatric patients 2 years of age and older with a confirmed mutation in the SMN1 gene.

Itvisma demonstrated substantial evidence of effectiveness based on primary evidence from an adequate and well-controlled Phase III study, supplemented by confirmatory evidence characterizing the product's mechanism of action as well as efficacy findings from Zolgensma (onasemnogene abeparvovec-xioi), which contains the same active ingredient in an intravenous formulation.[5] RDEP formalizes this precedent, signaling FDA's intent to apply a more consistent, transparent framework going forward, accelerating the path for future therapies serving populations with profound unmet need.

RDEP therefore complements existing mechanisms, such as Accelerated Approval, Orphan Drug Designation, and the Rare Disease Endpoint Advancement (RDEA) pilot, by providing clarity on evidentiary expectations rather than offering incentives or a new pathway (Table 1).

When is RDEP the right path?

RDEP is intended for sponsors developing therapies that meet all the following:

- The disease is caused by a **known in-born genetic defect**
- **Fewer than 1,000 patients** are affected in the U.S.
- **The condition is life-threatening**, rapidly progressive, and has no available therapy that alters disease trajectory
- The sponsor can reasonably demonstrate that **one adequate and well-controlled study**, supported by robust confirmatory evidence, **can establish substantial evidence of effectiveness**

Table 1: FDA regulatory pathways, designations, and engagement programs for rare disease

REGULATORY TOOLS	TYPE	PURPOSE	ELIGIBLE POPULATIONS	APPLICABILITY CRITERIA	POST-MARKETING OBLIGATIONS
RDEP	Engagement frameworks /Pilots	Leverage flexible approaches to enable alternative forms of evidence generation for accelerated access	<1,000 patients in the U.S., life-threatening, no adequate therapy	One adequate & well-controlled study + confirmatory evidence	Likely, case dependent (e.g., LTFU for CaGT)
ACCELERATED APPROVAL	Approval pathways	Earlier approval based on surrogate/intermediate endpoints	Serious conditions	Effect on surrogate endpoint + confirmatory trial required	Confirmatory PMRs required
ORPHAN DESIGNATION	Designations	Incentivize development for rare diseases	<200,000 patients in the U.S.	Standard requirements for approval	Incentives: tax credits, fee waivers, exclusivity
RDEA PILOT*	Engagement frameworks /Pilots	Advance novel endpoint development in rare disease	Active Pre-IND or IND for rare disease, novel efficacy endpoint	Endpoint-focused, not approval focused	N/A
PLAUSIBLE MECHANISM	Engagement frameworks /Pilots	Enable approval of bespoke therapies when RCTs are impractical	Primarily rare, severe, early-onset conditions	Clinical benefit in multiple patients + strong mechanistic rationale	Mandatory RWE collection; ongoing safety + efficacy monitoring; additional commitments likely for pediatric growth/ development risks

Notes: Some exceptions may apply. *Pilot slated to end Sept 2027.
Acronyms: CaGT = cell and gene therapy; IND = Investigational New Drug; LTFU = long-term follow-up; PMR = post-marketing requirement; RCT = randomized controlled trial; RDEA = rare disease endpoint advancement; RDEP = rare disease evidence principles; RWE = real world evidence; and, U.S. = United States.

For sponsors targeting ultra-rare conditions, RDEP enhances predictability by formalizing evidentiary expectations already articulated in FDA guidance and reflected in emerging policy, such as the emphasis on a plausible mechanistic rationale and early, iterative engagement with review divisions. The program also provides context for FDA's September 2025 draft guidance on **Innovative Designs for Clinical Trials of Cellular and Gene Therapy in Small Populations**, which describes various innovative approaches (e.g., adaptive and Bayesian designs) to maximize data efficiency while preserving scientific rigor.[6] In addition, RDEP underscores the importance of early investment in registries, biobanks, and RWE infrastructure to support both pre-approval and post-market needs, including the real-world validation FDA anticipates under pathways like the plausible mechanism approach.

Relatedly, sponsors must anticipate payer evidence needs early, as limited pre-approval data may increase reliance on post-market studies for coverage decisions. Because RDEP is a U.S.-only framework, global alignment remains a challenge, and sponsors will need to manage the complexities of aligning this approach with regulatory expectations in other regions.

Where RWE creates advantage — from patient finding to external controls

Before sponsors can qualify for the RDEP process, they must demonstrate that the disease meets the ultra-rare prevalence threshold. Just as RWE has long supported prevalence estimates in orphan drug applications, it can also be used to substantiate eligibility for RDEP. Linking medical claims, electronic health records, genomic databases, and patient registries can yield more precise estimates of disease burden, particularly for conditions that are underdiagnosed, inconsistently coded, or have heterogenous phenotypes.

AI-enabled analytics can further refine these estimates. Natural language processing (NLP) models can surface phenotypic patterns, genetic variants, and diagnostic descriptors from unstructured sources including clinical notes, diagnostic reports, medical literature, or case studies, improving the precision in defining the population and confirming that the disease meets RDEP's prevalence threshold.

Central role for RWE in RDEP

Once a program enters RDEP, RWE continues to play a central role:

- **Natural history studies** establish baseline progression in untreated patients
- **Patient registries** provide longitudinal outcomes, support endpoint selection, and enable patient finding
- **External comparator arms** derived from high-quality RWD can strengthen causal inference when randomization is not feasible
- **Expanded access data and case reports** add another layer of rich contextual information, capturing early safety and effectiveness signals in real-world settings

Sponsors must anticipate payer evidence needs early, as limited pre-approval data may challenge establishing the added value of the therapy and increase reliance on post-market studies for coverage decisions.

Especially in ultra-rare disease, RWE can play a critical role in developing and validating novel endpoints, as well as in supporting innovative or adaptive trial designs that streamline development. Hybrid study designs that integrate prospective and retrospective data can maximize available data, while AI-based approaches can help harmonize heterogeneous datasets, link fragmented records while preserving privacy, and surface clinically meaningful trends.

The challenge is to ensure, to the extent possible, that these diverse, often fragmented data sources are fit-for-purpose for regulatory decision-making. By integrating heterogeneous data sources and applying advanced analytic methods, sponsors can improve prevalence estimation, strengthen causal inference, and support endpoint validation, ensuring that regulatory decisions are grounded in scientifically robust evidence, with the patient front and center.

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Embedding patient-focused drug development and advocacy

Ultra-rare diseases are often poorly characterized, with clinical expertise concentrated in only a few centers worldwide. This makes patient-focused drug development essential, requiring endpoints that are both clinically meaningful and patient-centered. Natural history studies and registries, especially when co-designed with advocacy groups, help identify which functional changes matter most to patients and caregivers.

Patient advocacy organizations also play a critical role in identifying undiagnosed or misdiagnosed individuals, raising clinician awareness through targeted education, and supporting recruitment into both interventional and observational studies. Here, Medical Affairs becomes a strategic enabler: beyond traditional scientific exchange, teams can lead disease education initiatives, develop clinical training programs on endpoint interpretation, and partner on evidence generation through registry design and RWE studies. These activities help to close knowledge gaps and strengthen a sponsor's readiness for the evidentiary standards formalized under RDEP.

Timing Considerations

A request should be submitted to a sponsor's existing investigational new drug (IND) prior to the launch of a pivotal trial for each protocol the sponsor wants reviewed under the RDEP, when early clinical data are available but there is still flexibility to shape trial design, evidence strategy, and potential use of external controls. The request should include reasonable evidence that the eligibility criteria are met and that the safety and efficacy of the drug can be demonstrated by one adequate and well-controlled study with confirmatory evidence.[6] A request for participation in this process should be accompanied by a formal meeting request appropriate for the sponsor's stage in the drug development process, and early dialogue with FDA can clarify whether a program qualifies and what forms of confirmatory evidence will be acceptable. More information on the review process can be found on the FDA website.

If a novel endpoint is being developed, sponsors may wish to engage FDA through the RDEA pilot first to align on endpoint strategy before proceeding under RDEP. Accelerated approval may remain an option later in development if a validated surrogate endpoint emerges, but RDEP provides a tailored path for programs unlikely to meet traditional requirements.

FDA has indicated that drug review teams in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) will consult the Rare Disease Policy and Portfolio Council (RDPPC), and route to the Oncology Center of Excellence (OCE) as appropriate. Given the novelty of this framework, early conversations are essential to avoid missteps and ensure alignment with FDA on evidence expectations.

Conclusion

The RDEP process represents an incremental but meaningful evolution in FDA's approach to ultra-rare disease drug development. It reinforces the Agency's commitment to scientific flexibility and innovation while maintaining rigorous evidentiary standards.

For sponsors in the ultra-rare disease space, the need for a clear and innovative evidence strategy has never been greater. Success under RDEP will hinge on strategic integration of RWD, strong confirmatory evidence, and thoughtful engagement with regulators. At IQVIA, we combine deep therapeutic expertise, advanced RWE infrastructure, AI-driven analytics, regulatory strategy, and medical affairs leadership to help sponsors design, generate, and defend evidence packages aligned with FDA's expectations. As this framework evolves, collaboration will be key to accelerating therapies for patients who need them most.

References

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