



U.S. FOOD & DRUG
ADMINISTRATION

A New Framework for Rare Disease Review

October 2026

A New Framework for Rare Disease Review

October 2026

Table of Contents

Executive Summary.....	3
The Scale of the Rare Disease Crisis	4
Who Is Affected	4
The Economic Burden of Untreated Rare Disease.....	4
The Scientific and Operational Challenges of Rare Disease Drug Development	5
Current Rare Disease Initiatives	5
The Framework Initiative: Purpose and Approach	7
Statement of Purpose	7
Scope	7
Guiding Principles	7
Stakeholder Engagement.....	8
Expected Outcomes	9
Leadership and Governance	9
The Path Forward.....	9

Executive Summary

Thirty million Americans, or approximately one in ten, live with a rare disease. Globally, the affected population reaches an estimated 300 million people across 7,000 to 10,000 distinct conditions. Collectively, they represent one of the most significant unmet medical needs in the United States and the world.

As of 2025, only approximately 5% of recognized rare diseases have an approved treatment by the United States Food and Drug Administration.

The Food and Drug Administration is making progress to address the rare disease community's unmet need; in recent years, about half of the Center for Biologics's Evaluation and Research and Center for Drug Evaluation and Research's novel approvals have been for rare diseases. Center-specific efforts, including both rare disease-focused initiatives and programs designed to engage patients and external experts, have made huge progress in advancing rare disease regulatory science. But the pace of progress has not matched the scale of the need.

The FDA needs a clear, consistent regulatory approach tailored to the specific challenges of rare disease drug development, addressing small patient populations, disease heterogeneity, and natural history that may be incomplete or poorly understood. While flexibility is built into the regulatory framework for drug development and approval of therapies addressing unmet medical need, the FDA needs to leverage recent technologies and scientific understanding of the biologic basis for any particular rare disease coupled with the perspectives of the patient to maximize the use of current authorities that can ensure scientific rigor without unnecessary demands that are infeasible for diseases that affect small patient populations. The Rare Disease Framework Initiative is the FDA's commitment to a fresh approach to reviewing rare disease therapies, utilizing all the review criteria outlined in FDA regulations, guidances, and related documents. The goal is a regulatory framework where fit-for-purpose evidentiary expectations are the norm for all rare disease applications; the FDA will work closely with sponsors and patients to support innovative approaches to generating evidence that will meet the FDA's rigorous statutory standard of safety and effectiveness.

The Scale of the Rare Disease Crisis

Who Is Affected

The term “rare disease” encompasses a wide variety of conditions. The Federal Food, Drug, and Cosmetic Act classifies a disease as rare if it affects fewer than 200,000 people, but many rare diseases have even smaller patient populations. Rare conditions range from relatively well-characterized genetic disorders affecting tens of thousands of patients to global patient populations numbering in the low hundreds, or fewer. In addition, many rare diseases are serious or life-threatening and disproportionately affect children.¹ Many also have limited natural history data with poorly characterized disease progression and lack reliable, fit-for-purpose biomarkers or clinical outcome assessments.² This scientific uncertainty represents a significant challenge for developing treatments, which leads many patients with rare diseases to use treatments approved for other indications in lieu of treatments that have been demonstrated to be safe and effective for their specific disease.

Patients living with rare diseases represent one of the most significant areas of unmet medical need in our country.

The Economic Burden of Untreated Rare Disease

The economic consequences of undertreated rare disease are substantial and well-documented. Rare disease care costs approximately ten times more per patient than care for common diseases, reflecting the complexity of diagnosis, the intensity of management, and the frequent lack of effective treatment.

A 2019 economic analysis of 379 rare diseases estimated the total annual burden on the U.S. economy at \$997 billion: \$449 billion in direct medical costs, \$437 billion in indirect costs including lost productivity, and \$73 billion in non-medical costs.³ Critically, the absence of an approved therapy is not a neutral baseline: research has found that the lack of an approved treatment is independently associated with a 21.2% annual increase in total per-patient costs.¹ Not moving as efficiently as possible through research, development, and review processes has a real, measurable cost that is borne directly by patients and families.

¹ Stern S, Zhang Y, Pressly M, et al. Evolving landscape of drug development for pediatric rare diseases-from successes to strategies for addressing unmet needs. *J Pharm Sci.* 2026;115(9):104401. doi:10.1016/j.xphs.2026.104401

² Beckman, R.A., Antonijevic, Z., Ghadessi, M. et al. Innovations in Clinical Development in Rare Diseases of Children and Adults: Small Populations and/or Small Patients. *Pediatr Drugs* **24**, 657–669 (2022). <https://doi.org/10.1007/s40272-022-00538-7>

³ Yang G, Cintina I, Pariser A, Oehrlein E, Sullivan J, Kennedy A. The national economic burden of rare disease in the United States in 2019. *Orphanet J Rare Dis.* 2022;17(1):163. Published 2022 Apr 12. doi:10.1186/s13023-022-02299-5

The Scientific and Operational Challenges of Rare Disease Drug Development

Developing therapies for rare diseases presents challenges that are qualitatively different from those in common disease drug development. Patient populations are small, sometimes numbering in the hundreds globally, and are often geographically dispersed, making clinical trial enrollment difficult and slow. Natural history data, which forms the evidentiary foundation for trial design and endpoint selection in common disease drug development, is frequently sparse or nonexistent for rare diseases. Biomarkers that could serve as surrogate endpoints may be non-validated or entirely absent. Disease heterogeneity — genetic, phenotypic, or both — can make it difficult to define a homogeneous study population or to interpret results across subgroups.

These constraints have direct implications for trial design. The evidentiary tools that are routine in common disease drug development (e.g., placebo-controlled trials, primary endpoints with validated surrogate measures or meaningful clinical endpoints) may simply not be available. Rare diseases require a regulatory approach based on attainable evidence, product type, and the needs of the patient population. While this approach is certainly utilized at the FDA on many occasions, it is important that all review divisions use this approach as a matter of course and communicate it transparently with sponsors.

Rare diseases demand a regulatory framework that accounts for the nuances of each particular disease and product application, takes patients' needs into account, and makes the best use of both internal and external expertise in regulatory decision-making.

Current Rare Disease Initiatives

Over the past decade, the FDA has demonstrated its commitment to accelerating access to rare disease medical products via numerous programs and initiatives aimed at advancing the science of rare disease product development and promoting outreach and education for the rare disease community. A [2024 GAO report](#) cites 18 rare disease programs at the FDA, most launched since 2019, and that number has grown since the report's publication. In addition to rare disease-specific programs and initiatives, the FDA's efforts in the rare disease space benefit tremendously from its patient and external expert engagement programs. The FDA's review teams further benefit from programs designed to bolster their knowledge of specific diseases by engaging with patients living with those diseases and external experts in those diseases. The FDA's programs and initiatives focused on rare diseases, patient engagement, and external expert engagement include:

- [FDA's Rare Disease Innovation Hub](#)

- Critical Path partnerships on specific diseases
- CDER's [Accelerating Rare disease Cures \(ARC\)](#) program⁴
- CDER's [Patient-Focused Drug Development \(PFDD\)](#) public meetings
- FDA's Patient Listening Sessions
- CDER's and CDRH's Network of Experts Program
- CDER's [Learning and Education to ADvance and Empower Rare Disease Drug Developers \(LEADER 3D\)](#) educational initiative
- [CBER's Regenerative Medicine Advanced Therapy \(RMAT\)](#) designation (not exclusive to, although often used for, rare disease products)
- the [Support for clinical Trials Advancing Rare disease Therapeutics \(START\)](#) pilot program
- CBER and CDER's [Rare Disease Endpoint Advancement \(RDEA\)](#) pilot program⁵
- [Rare disease Innovation, Science, and Exploration \(RISE\) Workshop](#) series

The FDA's individual programs, coupled with efforts to promote best practices within CBER and CDER, have translated into real progress for the rare disease community. These successes and more will be outlined in the upcoming report to Congress required under Food and Drug Omnibus Reform Act of 2022 (FDORA), which covers the FDA's rare disease drug development and approval activities for fiscal years 2023 through 2025, including select regulatory statuses of drug applications with orphan-drug designation, trends in novel drug approvals, use of expedited programs, patient and stakeholder engagement, and efforts to promote best practices in the development and review of novel therapies for rare diseases or conditions. Yet despite these impactful programs, 95% of patients with a rare disease still lack an FDA-approved treatment.⁶ The Rare Disease Framework will both build on these prior efforts and take a fresh look at areas where we can do more. We need to build on, systematize, and operationalize these individual efforts into a consistently utilized, cross-center approach that champions the use of cutting-edge science, novel methodologies, and innovative statistical approaches.

⁴ CDER ARC released a five-year [Strategic Plan for 2025-2030](#).

⁵ A report to Congress on the RDEA pilot program is due to publish in fall of 2026.

⁶ Fermaglich LJ, Miller KL. A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. *Orphanet J Rare Dis.* 2023;18(1):163. Published 2023 Jun 23. doi:10.1186/s13023-023-02790-7

The Framework Initiative: Purpose and Approach

Statement of Purpose

The FDA will build an improved framework for rare disease drug development and regulatory review where advice and decision-making are consistently tailored to what evidence is reasonably attainable given the nature of the disease, its onset and progression, target population, patient needs, and the characterizations of the product under investigation, and clearly communicated throughout the development and review process. The FDA intends to implement and communicate these improvements as appropriate, including potentially via changes to regulations, guidance documents, and internal processes and resources, which in turn will increase efficiency and enhance consistency and predictability.

Scope

The Framework Initiative will review existing policies, procedures, programs, guidances, and regulations addressing rare disease drug development, with an emphasis on coordination of rare disease drug reviewers' subject matter expertise within FDA to build greater institutional knowledge, integration of the patient voice in the development and review process as early as possible, and greater reliance on external disease experts. The scope extends from pre-IND engagement through post-approval obligations and chemistry, manufacturing, and controls requirements, and encompasses CDER and CBER institutional knowledge. Where relevant activities overlap with Center for Devices and Radiological Health, Oncology Center of Excellence, or Office of Orphan Product Development initiatives, those organizations will be engaged. The Framework continues to adhere fully to the statutory requirements of safety and effectiveness.

Guiding Principles

The outcome of this Framework Initiative will be a rare disease drug development process that:

- **Provides greater clarity, consistency, and predictability for drug developers, patients, disease advocates, and researchers regarding rare disease regulatory decision-making** through tailored guidance and transparent communication based on the latest science.
- **Embeds the patient voice both early and at clearly defined milestones in the development and review process for rare disease therapies** such that both sponsors and reviewers can benefit from patient perspectives on disease burden, benefit-risk priorities, and meaningful measures of progress.
- **Further leverages external expertise to support a tailored approach in regulatory review**, especially for rare conditions with very small patient populations and limited

understanding of natural history, as a structural feature to direct FDA reviewers in customizing their decision-making to each specific development program, product, and disease state.

- **Builds shared resources, robust training, and institutional knowledge on rare disease drug development and review** to ensure consistency in drug development and review.
- **Applies risk-based approaches, particularly to chemistry, manufacturing, and controls review and pre-approval inspections**, to support earlier patient access without compromising rigorous quality, safety, and effectiveness standards.
- **Champions the use of cutting-edge science, novel methods and clinical trial designs, and innovative statistical approaches in the development of rare disease therapies** via guidance, transparent communication, and programming that reflects FDA's commitment to partnering with rare disease innovators to accelerate patient access to rare disease therapies.

Stakeholder Engagement

The FDA will solicit extensive feedback from patients and disease advocates, industry, and government regulators on persistent challenges for rare disease regulatory review. Planned opportunities to provide input include:

- **Public meeting.** A public meeting to provide an opportunity for all interested parties to engage with the Framework's goals and assessment process, and to submit comments on the record.
- **Federal Register Request for Information (RFI).** A Federal Register Request for Information inviting written input from patients, caregivers, developers, researchers, clinicians, and other members of the public.
- **Sector-specific roundtables.** Targeted roundtables with drug developers, patient and disease advocacy organizations, academic researchers, and practicing clinicians — enabling sector-specific dialogue on issues most relevant to each community.
- **FDA-internal feedback sessions.** Internal feedback sessions with CDER and CBER review teams and other relevant FDA staff, ensuring that the perspectives of those who implement the framework are incorporated into its design.

Expected Outcomes

Both internal and external feedback will inform the Framework Initiative's review of rules, guidances, institutions, and organizational norms, ultimately resulting in the development of the Rare Disease Framework. Expected deliverables may include:

- **Regulatory revisions.** FDA may consider revisions to existing regulations or, where appropriate, new regulatory provisions, to embed fit-for-purpose evidentiary standards into the legal foundation of the rare disease review process.
- **Guidance review and revision.** Systematic review of existing guidance documents and potentially issuance of new or revised guidance to provide clearer, more predictable direction on endpoints, statistical approaches, trial design, patient engagement, external expert consultation, and post-approval obligations in the rare disease context.
- **Alignment within CDER and CBER** to improve consistency across review divisions and consolidate rare disease review expertise.
- **Training plan.** A plan for training on non-regulatory changes, and post-revision training to ensure that reviewers and leadership fully understand and can consistently apply the new Framework.

Leadership and Governance

The Initiative is led by the FDA's Rare Disease Innovation Hub, partnering with the Office of the Commissioner, the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research, with engagement from the Office of Orphan Products Development (OOPD), the Office of Oncology Excellence (OCE), CDRH, the Office of Public Affairs, and other relevant FDA programs and offices.

The Path Forward

Rare diseases are individually rare. Collectively, they represent one of the most pressing unmet medical needs in the country and are a clear signal that the FDA's regulatory framework must evolve to address patient needs and innovative scientific approaches.

The science of rare disease drug development has advanced considerably. Genomic characterization, platform trial designs, real-world evidence methodologies, and Bayesian statistical approaches have expanded what is scientifically achievable in small-population settings. The Framework Initiative is designed to build a regulatory

structure that is as robust as the science it governs and as responsive to patients as the mission of the agency demands.

The FDA will take the time required to build an improved framework that is scientifically sound, legally durable, operationally consistent, and calibrated to the rare disease context. It will do so transparently, with robust public engagement, and with the sustained commitment of the agency's leadership.

The scale of the unmet need demands nothing less.

The FDA invites patients, caregivers, drug developers, clinicians, researchers, and all interested members of the public to participate in the Framework Initiative's stakeholder engagement process. [Details will be available on the FDA's Rare Disease Innovation Hub.](#)