

REAGAN-UDALL FOUNDATION FOR THE FDA

Rare Disease Framework Initiative Public Meeting

Public Meeting Summary | November 2026

ABOUT THE REAGAN-UDALL FOUNDATION FOR THE FDA

The Reagan-Udall Foundation for the FDA (Foundation) is an independent nonprofit created by Congress to advance regulatory science to help the U.S. Food and Drug Administration accomplish its mission. The Foundation manages a suite of programs that assist the FDA in engaging with external stakeholders and that facilitate evidence generation, improve public understanding of the FDA, and deliver more accessible health information to the public.

Funder

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Introduction and Background

On October 28, 2026, the U.S. Food and Drug Administration (FDA), in partnership with the Reagan-Udall Foundation for the FDA, convened a hybrid public meeting to seek input on the FDA's recently announced Rare Disease Framework Initiative[1] to reimagine the Agency's approach to rare disease drug development. The intent of this new initiative is to develop a fit-for-purpose framework that reflects the realities of rare disease drug development by considering the nuances of each disease, patient needs, product type, and the evidence that realistically can be generated in small patient populations.

1 U.S. Food and Drug Administration. (2026). A new framework for rare disease review. https://www.fda.gov/media/195694/download?attachment

Framework Initiative Discussion & Remarks from the Acting Commissioner

FDA leaders Michael Davis, Director, Center for Drug Evaluation and Research; Karim Mikhail, Director, Center for Biologics Evaluation and Research; and Amy Comstock Rick, Director, Rare Disease Innovation Hub, presented the Rare Disease Framework Initiative. They described the initiative as a fresh look at how the Agency handles rare disease drug development and review, with the vision of moving from incremental to transformational change. The framework initiative will lay the groundwork for a durable, fit-for-purpose system for rare-disease drug development that aims to align regulatory pathways with each disease, patient population, and product while improving consistency and predictability. The intent is to focus on what is possible in the rare disease context rather than start what is expected for traditional approaches built around large trials.

FDA's Outcome Commitments outline the key principles supporting the successful implementation of the Rare Disease Framework Initiative:

1. **Providing greater clarity, consistency, and predictability in regulatory decision-making through tailored guidance and transparent communication.**

   This means moving away from "flexibility," which can produce inconsistent expectations and late-in-the-process disagreements and move toward predictability. Predictability is proactive and structured, allowing for customization within a transparent framework. FDA and sponsors would identify acceptable, fit-for-purpose pathways at the outset, align on evidence and endpoints, and reconfirm decisions at key milestones. Different diseases may require different routes, but stakeholders should know the available routes, governing standards, responsibilities, and evidence expectations.

2. **Embedding patient's voices both early and at clearly defined milestones in the drug development and review process.**

   Sponsors will be expected to build in the patient perspective. Patient perspectives on disease burden and risk tolerance need to be brought into development and reviewed early enough to influence decisions in the drug development and review process.

3. **Further leveraging external expertise to support customization of regulatory review.**

   FDA, developers, clinicians, and patients should agree on evidence, endpoints, and key milestones early and revisit them throughout product development.

4. **Building shared resources, robust training, and institutional knowledge on rare disease drug development and review.**

   The goal is to share insights into rare disease product development across FDA review teams, so innovations and expertise gained in one program benefit others.

5. **Applying risk-based approaches to chemistry, manufacturing, and controls (CMC) review and pre-approval inspections.**

   Current CMC costs are often a barrier for drug development in rare and ultra-rare diseases. Manufacturing requirements should reflect the product, development stage, risk, and extremely small patient populations while maintaining safety and current good manufacturing practice (CGMP) standards.

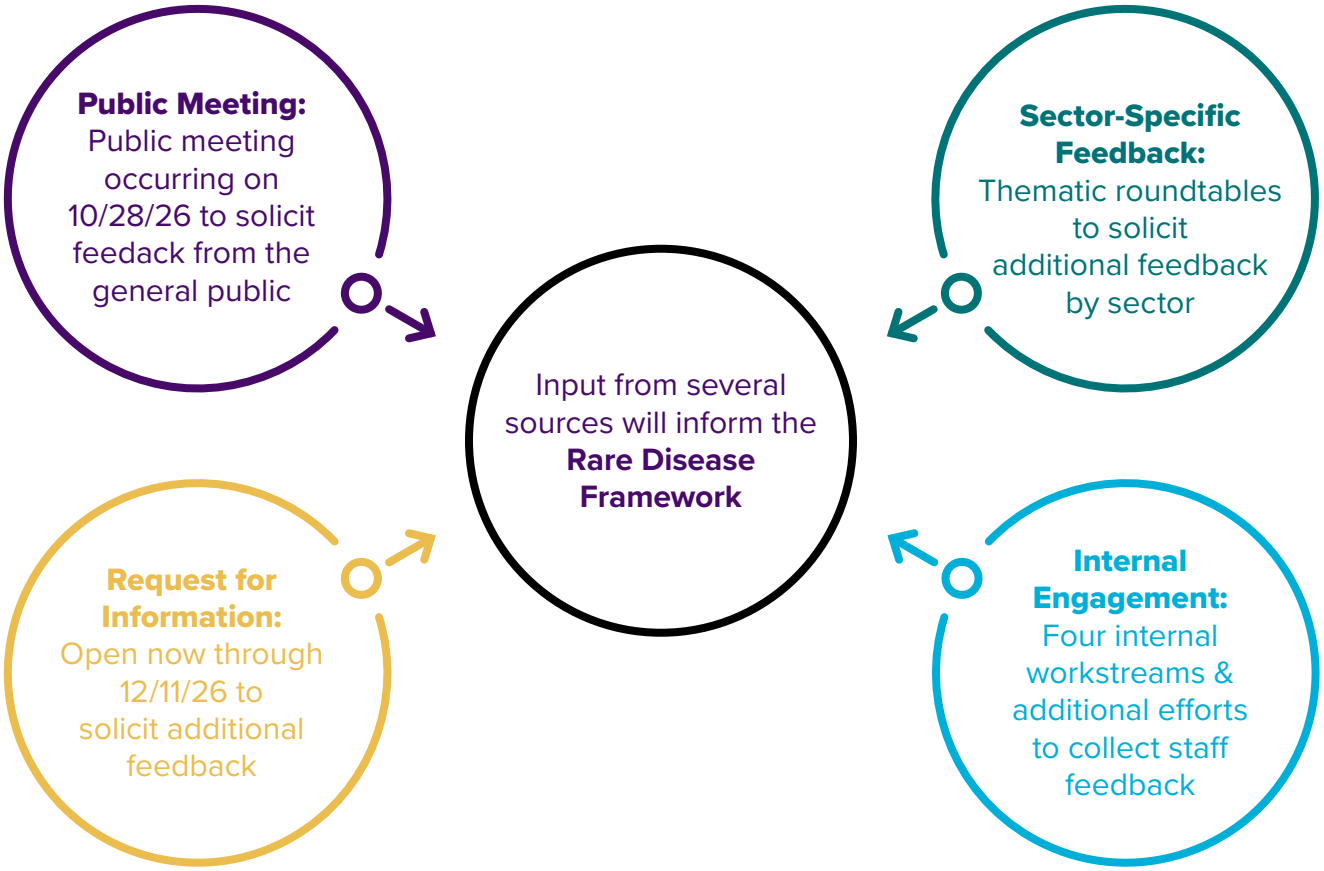
6. **Championing the use of cutting-edge science, novel methods, and innovative statistical approaches in rare disease drug development.**

   Large randomized controlled trials (RCTs) often don't fit rare diseases, and an underpowered RCT doesn't count as an "adequate and well-controlled" study. FDA wants to consider alternatives when conventional large, randomized trials are infeasible, including natural-history data, external controls, and novel statistical methods.

Input from multiple sources will inform the framework (Figure 1). FDA is drawing on its own expertise and insights from the broader ecosystem to identify improvements and foster innovation in rare disease product development.

> *"I feel strongly that sustained stakeholder engagement is the best way to ensure this Agency is responsive to the needs of the entire rare disease community."*
>
> — Kyle Diamantas, FDA

FIGURE 1. ENGAGEMENT FRAMEWORK INITIATIVE



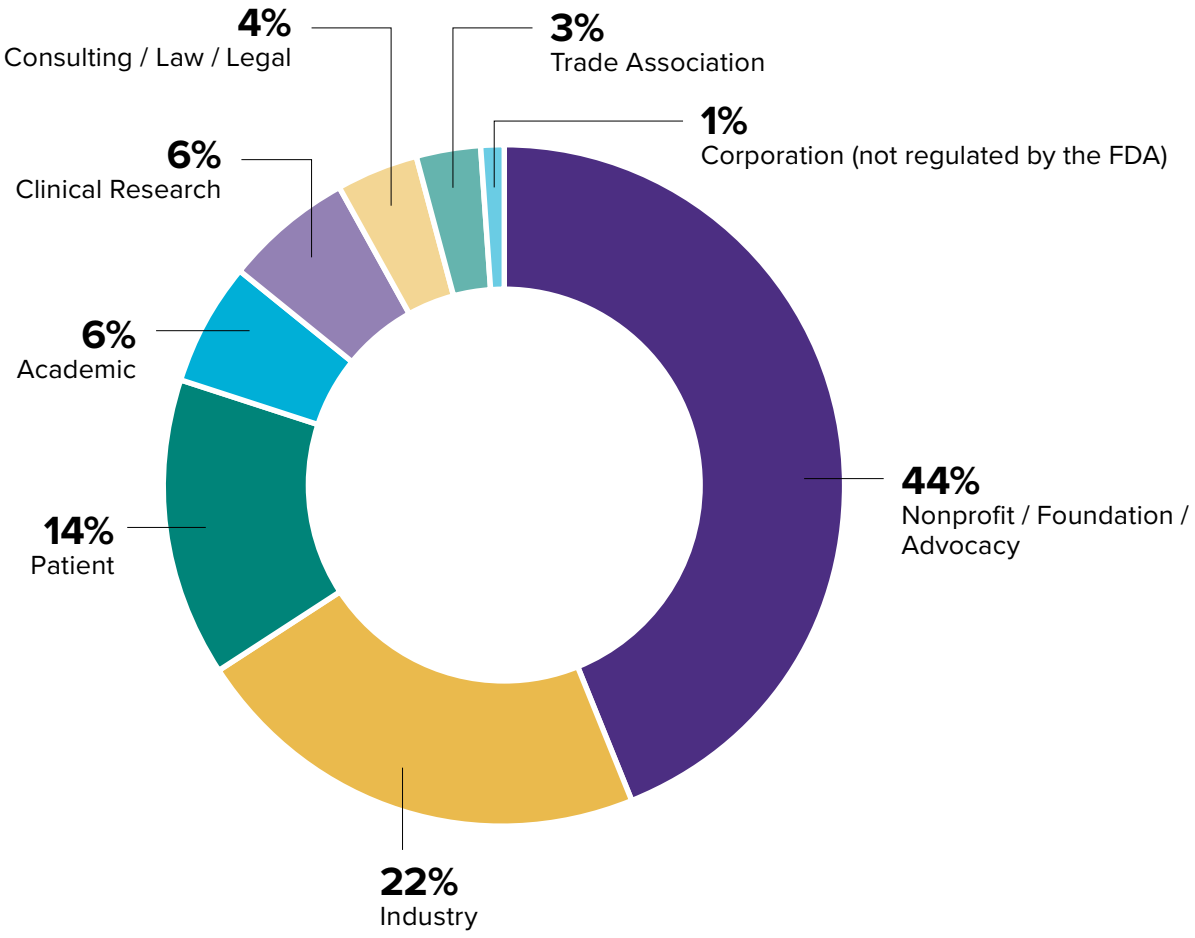
Stakeholder Input

The Foundation received 260 requests for public comment, offered 85 opportunities to present, and scheduled 74 people to provide remarks. Seventy-one stakeholders, representing a wide range of backgrounds, provided up to 2.5 minutes each for public comment. Twenty-five public commenters participated virtually and 46 presented in-person. Stakeholders provided personal perspectives or represented nonprofit organizations, patient advocates, academia, industry, legal practices, technology companies, and trade associations (Figure 2).

Stakeholders provided public comments related to the Framework Initiative, and in particular, the following topic areas:

- Fit-for-purpose review of rare disease therapies based on attainable evidence, particular disease state, and population
- FDA consistency and predictability of drug development and review regulatory requirements
- FDA engagements with external parties — including patients, clinical experts, and researchers — to inform review decision-making
- Considerations for CMC requirements specific to rare disease therapies

FIGURE 2. PUBLIC COMMENTER REPRESENTATION



The comments showed broad support for FDA's framework, but support was conditional on implementation. Stakeholders want rigorous standards adapted to rare-disease realities that are applied consistently, informed by patients, and judged by whether therapies reach people sooner.

This summary is an analysis of comments delivered during the public meeting. The dataset consists solely of information submitted by the public and was not independently evaluated for factual accuracy.

Key Themes from Public Commenters

1. COMMENTERS WANT CONSISTENT, PREDICTABLE DECISIONS ACROSS FDA DIVISIONS AND REVIEW TEAMS

The strongest cross-cutting message was that commenters want consistent, predictable decisions across FDA. Commenters urge FDA to apply rare disease regulatory approaches consistently and predictably across centers, divisions, and individual review teams, including the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Oncology Center of Excellence. They call for clear evidentiary standards, early written agreements on evidence requirements, continuity of advice when personnel change, transparent documentation and explanations of changing expectations, and stronger reviewer training and oversight. They emphasize that success should be measured by consistent protocol reviews and decisions that maintain scientific rigor while reducing avoidable delays.

> *"The challenge is to make scientifically appropriate approaches predictable rather than exceptional."* — Nonprofit/Foundation/Advocacy

> *"Regulatory flexibility cannot simply exist on paper. It must be consistently applied in practice."* — Patient

> *"Rare disease sponsors make consequential development decisions years before an application reaches FDA, relying on regulatory advice about endpoints, trial design, evidence generation and other issues, yet sponsors can later encounter regulatory skepticism and some variation of, 'We recognize the principle, but it does not apply in this case.' When those differences are difficult to anticipate, regulatory adaptability becomes difficult to rely upon."* — Industry

2. INVOLVE PATIENTS EARLY AND THROUGHOUT DEVELOPMENT AND REVIEW; TREAT PATIENTS AS SCIENTIFIC PARTNERS

Commenters call for patients and caregivers to be treated as scientific partners throughout product development. They want patient involvement formalized at defined times during the drug development process, from disease understanding and pre-investigational new drug application (IND) discussions through trial design, review, and post-approval. Patient input should shape meaningful endpoints, acceptable risk, trial feasibility and burden, eligibility, and benefit-risk assessments. Commenters also urge FDA to define engagement milestones, include underrepresented patients, document how input changes decisions, and provide written feedback. The goal is more relevant evidence, feasible trials, greater trust and participation, and fewer avoidable delays.

> *"Move from listening to patients to learning from them."* — Nonprofit Organization

> *"Without clear structures…the framework could risk institutionalizing performative patient engagement."* — Patient

> *"Reviewers must document in the legal record what they learned from patients and experts and how it informed endpoints and study design."* — Nonprofit Organization

3. USE FIT-FOR-PURPOSE EVIDENCE WITHOUT LOWERING SCIENTIFIC STANDARDS

Commenters strongly support fit-for-purpose evidence to maintain scientific rigor while matching requirements to the realities of each rare disease. They emphasize using the totality of evidence, including natural history data, registries, external controls, biomarkers, real-world evidence, patient-generated data, mechanistic evidence, innovative statistical methods, and single patient experience.

Commenters call for reduced reliance on placebo and sham controls (e.g., inactive procedures or simulated interventions). Many urged greater use of natural history data and external controls when randomization is infeasible, unethical, or overburdens scarce patients. They also call for carrying safety, manufacturing, and nonclinical knowledge across related gene therapies, gene-editing products, antisense oligonucleotides (ASOs), and genetic subtypes.

They also call for:

- Evidence expectations scaled to population size, disease severity, progression, heterogeneity, and unmet need.
- Meaningful, stage-appropriate endpoints focused on preserving function and quality of life.
- Alternatives to randomized or placebo-controlled trials when infeasible or unethical.
- Patient and disease-expert input on attainable evidence, acceptable risk, and clinically meaningful benefit.
- Clear standards governing registries, medical records, real-world evidence, external controls, Bayesian methods, single-arm studies, and patient-as-own-control designs.
- For individualized and N-of-few therapies, avoid treating each mutation or patient as a new program.

The consistent message is that fit-for-purpose evidence should not lower standards; it should generate the strongest credible evidence realistically attainable for each disease while reducing unnecessary burden and delay.

> *"Fit-for-purpose evidence must reflect what is at stake…the evidence bar should account for the cost of having no new option at all."* — Patient Advocacy

> *"It's critical that the framework allows for evidence generation scaled by rare disease prevalence. What you can collect in 5 or 10 patients…is very different than what you can collect in 200 patients."* — Academia

> *"It is demoralizing to join a study where the definition of success is half of you get demonstrably and permanently sicker."* — Patient

4. CHOOSE OUTCOMES THAT REFLECT MEANINGFUL DAILY BENEFIT

Commenters urge FDA to choose outcomes that capture benefits patients experience in daily life, not just changes in symptoms, biomarkers, or broad functional scales. Meaningful benefit may include preserving the ability to breathe, swallow, communicate, steer a wheelchair, attend school, work, care for family, or remain independent. For progressive diseases, stabilization or slowing decline can itself be clinically important. They also wanted biomarkers or mechanism-based endpoints accepted when a therapy corrects the root cause.

Commenters recommend involving patients and caregivers early to identify what matters, using stage-appropriate and multidomain endpoints, and supplementing traditional measures with patient- and caregiver-reported outcomes. The consistent message was that treatment success should reflect maintained function and quality of life, even when conventional measures fail to show dramatic improvement.

> *"Ensure that outcomes include real life improvements as well as symptom management. Patients need to know that treatments will help them learn, work, care for their families, and participate in their lives."* — Nonprofit Organization

> *"Treatment success isn't necessarily walking unassisted; it's stabilization and preservation of what she has now. It's keeping that upper limb strength to steer her chair, protect her breathing, having the stamina for a full day of school."* — Patient

> *"The impact on daily functioning, independence, symptom burden, and quality of life may represent the most meaningful benefit and are often not fully captured by traditional clinical measures alone."* — Industry

5. ACT URGENTLY AND MEASURE SUCCESS BY PATIENT ACCESS

Commenters stress that urgency must be treated as a core regulatory consideration because rare diseases are often progressive, irreversible, or fatal, and delay can mean lost function, missed treatment windows, disability, or death. They urge FDA to implement available changes immediately rather than wait for the full framework, streamline development and access pathways, and consider the risks of waiting alongside the risks of treatment.

They also argue that success should not be measured by policies, guidance, or review activity alone. The meaningful test is whether barriers are removed, development time is reduced, and safe and effective therapies actually reach patients. A scientifically rigorous review that does not result in timely patient access was repeatedly characterized as incomplete success.

> *"Progressive diseases require progressive thinking, so please move quickly to turn your policies into practice and to make those practices standard."* — Foundation

> *"Please measure success not only by rigorous review, but also by whether patients can receive safe and effective therapies…A therapy that cannot reach patients is an incomplete success."* — Foundation

> *"We must always be asking, what are the consequences for patients if a treatment is not approved and how can we identify pathways that enable approval while appropriately managing risk?"* — Foundation

6. RIGHT-SIZE CMC, MANUFACTURING, AND PRECLINICAL REQUIREMENTS

Commenters identify CMC, manufacturing, and preclinical requirements as major barriers for ultra-rare, individualized, nonprofit, and academic programs. They call for risk-based requirements proportionate to patient numbers and product characteristics, with early FDA alignment and greater use of prior knowledge, platform data, patient-derived models, and existing safety evidence. They also urge FDA to support small-batch production, avoid unnecessary repetition across related therapies, and permit post-approval commitments where appropriate. The goal is to maintain rigorous quality and safety standards while preventing one-size-fits-all requirements from making promising therapies too costly or slow to reach patients.

> *"Set practical manufacturing requirements for ultra-rare therapies that are proportionate to their scale…We need a framework that still demonstrates quality and consistency but fits the patient numbers and financial realities."* — Foundation

> *"What is the minimum in vivo package needed for biodistribution and immunogenicity where a near identical construct has already been cleared, and can its preclinical package be referenced rather than repeated?"* — Patient Advocacy

> *"Rare disease also presents unique chemistry, manufacturing and controls challenges, particularly for cell and gene therapies with limited patient samples. Fit-for-purpose, risk-based CMC expectations will be critical."* — Patient Advocacy

> *"Developing each of these as a separate small molecule style program would mean repeating the same non-clinical and manufacturing work that takes a very, very long time—a time that these patients do not have."* — Industry

7. BUILD PATHWAYS FOR NONPROFIT, ACADEMIC, AND PATIENT-LED SPONSORS

Numerous therapies are being advanced by families, foundations, and academic institutions. Commenters urge FDA to create explicit, navigable pathways for nonprofit, academic, and patient-led sponsors to advance therapies for diseases lacking commercial investment. These sponsors face distinct constraints, including limited funding, regulatory expertise, manufacturing capacity, and access to timely FDA advice, that conventional industry-oriented processes do not adequately address.

Commenters call for funding incentives, small-scale manufacturing support, shared infrastructure, and mechanisms for patient organizations to obtain scientific feedback independently. The goal is not to lower standards, but to make rigorous development feasible for sponsors pursuing treatments that might otherwise never be developed.

> *"We don't have a pharmaceutical partner. We're just parents desperate to get our kids treatment as soon as possible."* — Nonprofit Organization

> *"Please permit academic nonprofit sponsors, clinical syndrome INDs inclusive of multiple genes with common clinical endpoints."* — Academia

> *"Ongoing dialogue regarding the regulatory expectations for ultra-rare diseases… individualized and gene-targeted therapies and scalable approaches for both academic and non-commercial developers would be particularly valuable."* — Clinical Research

8. ADDRESS OVERLOOKED POPULATIONS

Commenters also identified populations at risk of being left out. These include:

- Children — update the ethics guidance on pediatric trials and include more pediatric and pregnancy data
- Adults with childhood-onset disease
- Rare cancers — enroll by mutation rather than where the tumor started
- "Middle" diseases that are too big for ultra-rare evidence principles, but too small for conventional trials
- Highly variable diseases, those where several ultra-rare subtypes exist within a single disease
- Patients outside organized advocacy groups

Additional themes from the comments:

- **Expand and streamline access pathways:** Commenters discussed expanded access, provisional or conditional approval, rolling review, intermediate clinical endpoints, and feasible post-approval evidence plans.
- **Improve diagnosis and trial eligibility:** Commenters advocate earlier genetic identification, broader eligibility, basket trials, mutation-based enrollment, and avoiding permanent exclusion after prior therapies.
- **Make post-approval obligations feasible:** Confirmatory studies and evidence plans should be agreed early, achievable in small populations, and not become barriers to access.
- **Support funding and commercial viability:** Suggestions included incentives, National Institutes of Health (NIH) coordination, cost-sharing, small-scale manufacturing support, and pathways for diseases with little or no financial upside.
- **Strengthen reviewer expertise and external input:** Commenters seek disease experts, rare-disease and real-world-evidence specialists on review teams, reviewer training, and better use of advisory committees.
- **Preserve and share regulatory learning:** Proposals include case-study libraries, standardized templates, documented scientific reasoning, clarify which approaches may or may not be applicable to different diseases, and broader dissemination of what evidence succeeded or failed.
- **Accountability for framework implementation:** Commenters request leadership oversight, public reporting, measurable benchmarks, and evidence that guidance is being applied in actual protocol reviews.
- **Recognize innovative methods and data sources:** These included Bayesian methods, digital health technologies, patient-derived induced pluripotent stem cell (iPSC) models, new approach methodologies (NAMs), patient-generated evidence, and single-patient IND data.
- **Coordinate beyond FDA:** Commenters call for collaboration with NIH, Centers for Medicare & Medicaid Services (CMS), institutional review boards (IRBs), international partners, manufacturers, academia, industry, and patient organizations.
- **Plan for combination therapies:** Commenters noted the need for guidance on studying, sequencing, and monitoring multiple approved treatments used together.

Overall, there is strong overlap between the themes identified from public comments and FDA (Table 1). The most noticeable differences are in how public commenters view implementation processes. They want patient input documented, consistency enforced at the level of individual reviews, and training commitments made concrete.

TABLE 1. FDA OUTCOME COMMITMENT ALIGNMENT WITH KEY THEMES

COMMITMENT	CLOSELY-MATCHED PUBLIC COMMENT THEMES
1. Clarity, consistency, and predictability in regulatory decision-making; tailored guidance, transparent communication	• Consistency and predictability across FDA • Fit-for-purpose evidence • Pathways for nonprofit, academic, and patient-led sponsors • Act urgently and measure success by patient access • Expanded/streamlined access pathways • Feasible post-approval obligations • Regulatory knowledge-sharing • Framework implementation accountability • Combination therapy guidance
2. Patient voice both early and at clearly defined milestones	• Involve patients early and throughout development • Outcomes that reflect meaningful benefit • Fit-for-purpose evidence • Act urgently and measure success by patient access • Inclusion of overlooked populations • Earlier diagnosis and broader trial eligibility • Framework implementation accountability
3. Leveraging external expertise	• Involve patients early and throughout development • Fit-for-purpose evidence • Pathways for nonprofit, academic, and patient-led sponsors • Reviewer expertise and external input • Cross-agency coordination
4. Shared resources, training, and institutional knowledge	• Consistency and predictability across FDA • Fit-for-purpose evidence • Pathways for nonprofit, academic, and patient-led sponsors • Reviewer expertise and external input • Regulatory knowledge sharing • Framework implementation accountability
5. Risk-based approaches to CMC and pre-approval inspections	• Right-size CMC, manufacturing, and preclinical requirements • Pathways for nonprofit, academic, and patient-led sponsors • Act urgently and measure success by patient access • Platform approaches and reuse of prior evidence • Feasible post-approval obligations • Funding and commercial viability
6. Cutting-edge science, novel methods, and innovative statistical approaches	• Fit-for-purpose evidence • Outcomes that reflect meaningful benefit • Platform approaches and reuse of prior evidence • Inclusion of overlooked populations • Earlier diagnosis and broader trial eligibility • Feasible post-approval obligations



Summary

The report summarizes FDA's Rare Disease Framework Initiative and stakeholder feedback calling for predictable reviews, meaningful patient involvement, fit-for-purpose evidence, risk-based requirements, and faster access to safe, effective therapies.

The FDA has opened a public docket for comments related to the Rare Disease Framework Initiative.

Comments can be submitted electronically through Regulations.gov or as written/paper submissions and are due December 11, 2026. Commenters should reference Docket No. FDA-2026-N-12214. To submit a written comment, click here.

Appendix

REAGAN-UDALL FOUNDATION FOR THE FDA

Rare Disease Framework Initiative Public Meeting

OCTOBER 28, 2026 | 1–5 pm ET

1 pm	**Welcome** **Susan C. Winckler, RPh, Esq.** *CEO, Reagan-Udall Foundation for the FDA*
1:05 pm	**Framework Initiative Discussion** **Speakers** • **Michael Davis, MD, PhD**, Director, Center for Drug Evaluation and Research, FDA • **Karim Mikhail, BPharm, MSc**, Director, Center for Biologics Evaluation and Research, FDA • **Amy Comstock Rick, JD**, Director, Rare Disease Innovation Hub, FDA
1:45 pm	**Break**
1:55 pm	**Remarks from the Acting Commissioner** **Speaker** • **Kyle Diamantas, JD**, Acting Commissioner of Food and Drugs, FDA
2 pm	**Public Comment**
5 pm	**Adjourn**

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