Amy Comstock Rick â?? Director of Strategic Coalitions, FDA Rare Disease Innovation Hub

> Regulatory conclusions reached in the past should never be assumed to apply indefinitely

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As rare disease science accelerates, regulators face growing pressure to adapt without compromising rigour. In this interview, Amy Comstock Rick explains how the FDA Rare Disease Innovation Hub is strengthening cross-centre coordination, evolving evidence expectations for ultra-rare conditions, and creating new spaces for dialogue between regulators, developers, and patients. The conversation offers a clear view into how policy, science, and patient experience are being brought together to move rare disease development forward.

What prompted the creation of the FDA Rare Disease Innovation Hub, and how does it fit within the Agencyâ??s structure?

Drug development for rare diseases presents persistent and well-recognised challenges, including very small patient populations and significant disease heterogeneity. Around thirty million people in the United States live with a rare disease, yet only about five percent of rare diseases currently have an FDA-approved treatment. Within both the rare disease community and the FDA, there was a growing sense that these challenges and opportunities required a more centralised focus and a clearer home within the Agency.

There were also legitimate concerns about consistency and communication across the FDAâ??s medical product centres, particularly between the Centre for Drug Evaluation and Research (CDER)

and the Centre for Biologics Evaluation and Research (CBER), and to a lesser extent the Centre for Devices and Radiological Health (CDRH). Given the very different types of products reviewed by these centres, ensuring alignment and shared understanding was increasingly important. In response, the Directors of CDER and CBER established the Rare Disease Innovation Hub as a cross-centre, policy-focused initiative. The Hub serves as a central point of engagement with external stakeholders, sharing information on FDA initiatives, progress, and innovation in rare disease regulation, while also creating space to listen to patient communities and other stakeholders, separate from individual product reviews or development programmes.

Internally, the Hub enhances coordination across the FDA through a formal steering committee co-chaired by the Directors of CDER and CBER, with senior leadership participation from the Office of Orphan Products Development, CDRH, the Oncology Center of Excellence, and other relevant offices with an interest in the space. This structure allows the Agency to promote consistency, alignment, and shared learning across centres, while remaining clearly distinct from product review and approval decisions.

Over half of the FDAâ??s novel drug approvals in recent years were designated orphan drugs. How is the FDA adapting its regulatory approach to sustain progress in orphan and rare disease drug development as the field continues to grow?

Under US law, a rare disease is defined by the Orphan Drug Act of 1983 as one affecting fewer than 200,000 people in the United States, or, in some cases, a larger population where there is no reasonable expectation that development costs can be recovered. As patient populations become smaller, often numbering in the hundreds or fewer, the challenges of drug development intensify. Many rare diseases are paediatric, clinically heterogeneous, and evolving over time, which makes traditional trial designs and endpoints difficult to apply. While there is broad agreement that these populations cannot be left behind, the scientific, operational, and economic assumptions that underpin development in common diseases do not translate easily to rare and ultra-rare settings.

Over the past decade, one of the most important shifts has been the FDAâ??s move away from automatically applying evidentiary expectations designed for large populations to very small ones. The statutory requirement to demonstrate safety and efficacy has not changed, but the medical product centres have worked to clarify what that standard can reasonably look like when two randomised, placebo-controlled trials are simply not feasible. This has meant greater flexibility in considering a single adequate and well-controlled study, alternative trial designs, and the use of mechanistic and other supportive data, including approaches that move beyond traditional placebo controls.

That evolution has been supported both by formal initiatives and by accumulated regulatory experience. Programmes such as the Rare Disease Endpoint Advancement (RDEA) initiative have helped advance the development of endpoints that better reflect disease biology and patient experience, while continued reviewer training has strengthened the assessment of alternative evidence. More recently, this work was formalised through the Rare Disease Evidence Principles (RDEP), announced in September 2025, which provide clearer guidance on how multiple sources of evidence may be combined to support regulatory decision-making in ultra-rare diseases. At its core, this reflects a recognition that sustained progress in rare disease development depends on adapting regulatory tools to the realities of very small populations.

Rare communities are increasingly involved not only in advocacy, but also in data generation, endpoint relevance, and trial design. How does patient input shape regulatory decision-making in rare disease development, and where does it add the greatest value?

In rare disease development, patient experience should inform decision-making from the earliest stages, particularly where scientific understanding is limited and traditional clinical endpoints may not fully reflect meaningful benefit. The FDA has long recognised this through its Patient-Focused Drug Development programme, which systematically captures patient and caregiver perspectives on symptoms, daily impact, and treatment priorities. This includes FDA-led public meetings, externally led meetings organised by patient groups, and patient listening sessions, with insights documented in publicly available â??Voice of the Patientâ?• reports that can inform both development planning and regulatory evaluation.

Although Patient-Focused Drug Development sits within the medical product centres rather than the Rare Disease Innovation Hub, there is a consistent message across the Agency that patient engagement should begin well before a therapy reaches the regulatory stage. Early involvement helps ensure that trial design and endpoint selection are aligned with what matters most to patients, reducing the risk that potential benefit is missed because the wrong outcomes were measured. In small and heterogeneous populations, that alignment can be critical to giving a therapy a fair and accurate assessment.

The Rare Disease Innovation Hub reinforces this broader approach by convening stakeholders around shared scientific and regulatory challenges. Through the RISE Workshops series, the Hub brings together the FDA, industry, patient communities, and other partners to examine cross-cutting issues such as data sharing and innovative trial designs. These discussions include how certain types of data might be responsibly shared to improve efficiency, as well as how basket, umbrella, and other master protocol trials can make better use of limited patient populations. While these are complex issues with no universal solutions, the objective is to identify where collective action can accelerate progress, recognising that with effective treatments available for only a small fraction of rare diseases, maintaining the status quo is not an option.

How have the RISE Workshops been received, and why is this level of connectivity particularly important in rare disease development?

The response to the RISE Workshops has been highly encouraging and has reinforced the value of creating a dedicated forum for these discussions. The first workshop, held on 3 September 2025 and focused on control options in rare disease clinical trials, was co-convened by the FDA Rare Disease Innovation Hub and the Duke-Margolis Institute for Health Policy and attracted more than 2,000 registrations, with around half coming from industry. That level of engagement reflected a clear need for thoughtful, open discussion around alternatives to traditional control arms in very small and diminishing populations, and created space for regulators, developers, patients, and researchers to examine what approaches may be considered when standard trial designs are not feasible. The second workshop, held on 20 November 2025 focused on individualised therapies, and saw a similarly strong response, with broad participation across industry, patient organisations, clinicians, and FDA staff.

A defining feature of the RISE series is that its agenda is shaped by the community, not by the FDA alone. In 2025, the Agency opened a public Federal Register docket inviting proposals for future workshop topics, and the volume and quality of submissions demonstrated strong stakeholder interest in contributing to that dialogue. This openness is deliberate. Rare disease science is

evolving quickly, particularly in areas such as individualised and highly targeted therapies, and meaningful progress depends on continuous, two-way learning. Bringing stakeholders together in a single forum allows FDA reviewers to hear directly from those developing and using new approaches, to ask questions in real time, and to test assumptions against practical experience.

That level of connectivity is especially important in rare disease development, where no single organisation can advance the field in isolation. Direct engagement between regulators, industry, and patients enables shared understanding, surfaces perspectives that might otherwise be overlooked, and supports more informed decision-making as the science continues to evolve. The RISE Workshops are designed to foster that exchange, recognising that sustained progress in rare diseases depends on ongoing collaboration and open communication.

What stood out to you as the key learnings and milestones from the Rare Disease Innovation Hubâ??s first full year of operation?

Looking back on 2025, it was a strong and constructive first year for the Hub. Despite a transition in administration, including leadership changes at the FDA and the Department of Health and Human Services, the Hubâ??s emphasis on internal coordination and transparency aligned closely with broader agency priorities, which allowed the work to continue with momentum. The level of engagement around the RISE Workshops confirmed that there was a genuine need for a forum focused on complex and unresolved questions in rare disease development. These sessions were deliberately designed as seminar-level discussions rather than introductory overviews, centred on issues where clear answers do not yet exist, and even the internal planning process became a meaningful opportunity for cross-centre learning and exchange.

Another important area of progress has been strengthening communication across the medical product centres. Through the Hub, a standing council was established between the CDER and the CBER, which now meets monthly to discuss complex issues and promote consistency in analysis and decision-making, while allowing for differences where they are scientifically justified. Over time, this has encouraged more regular dialogue across centres and disease areas that have historically operated more independently, helping to embed a culture of shared understanding and coordination.

At the same time, resource constraints have been real, and some longer-term ambitions will take time to realise. Even so, the strategic priorities established for 2025 have proven sound and will carry forward into the 2026 agenda. These priorities remain focused on advancing scientific approaches for rare diseases, strengthening coordination and communication across the FDA, and providing a central forum for higher-level discussion of cross-cutting challenges. While engagement on individual products appropriately remains within the review centres, the Hub has begun to establish itself as a place where industry, patient organisations, and other stakeholders can engage constructively on broader issues that shape rare disease development as a whole.

How do you see the rare disease landscape evolving over the longer term, and what message would you leave with the rare disease community?

Looking further ahead, what stands out most is the pace at which science is advancing and the potential for different developments to converge in meaningful ways. While I am not a scientist, it is clear that improvements in measurement, analytics, and emerging technologies are creating new opportunities to understand treatment effects with greater precision. Over the coming years, a central challenge will be how we define and measure endpoints, particularly those that reflect what

truly matters to patients. Subtle but meaningful changes, such as increased energy, improved sleep, or a childâ??s ability to engage more fully in daily activities, are often evident to families but are not always captured well in traditional clinical assessments. Being able to measure these effects more reliably and in a timely manner would allow the full patient experience to play a more direct role in shaping drug development and evaluation.

There is also reason to be optimistic about deeper integration of patient experience across the development lifecycle and more thoughtful approaches to collaboration and data sharing. In pre-competitive settings, whether through platform technologies, basket trials, or other shared frameworks, there may be opportunities to pool certain types of data in ways that improve efficiency without undermining the fundamentals of the market. That balance is not simple, but the goal is to learn faster, identify sooner when an approach is not working, and allow promising therapies to move forward with greater clarity and confidence.

The message I would leave with the rare disease community is one we emphasise consistently. The FDA, like any scientific organisation, evolves alongside the science, and regulatory conclusions reached in the past should never be assumed to apply indefinitely. If there is an opportunity to advance a potential treatment for patients, the right approach is to engage early and engage often. Assuming you already know the answer limits what is possible. Bringing questions, data, and ideas forward gives innovation its best chance to succeed and ultimately serves the patients we are all trying to help.

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