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When Mechanism Becomes Evidence: The FDA's Plausible Mechanism Pathway and the Future of Rare Disease Development

For decades, regulatory science has relied on a familiar evidentiary hierarchy. Randomised trials, population-level statistics, and reproducibility across large cohorts have defined what it means to demonstrate safety and effectiveness. This framework has served medicine well. But in rare and ultra-rare diseases, particularly monogenic, rapidly progressive, and paediatric conditions, it increasingly fails the patients it was designed to protect. Small populations, biological heterogeneity, ethical constraints, and the urgency of irreversible disease progression make traditional development paradigms impractical and, in some cases, impossible.

Against this backdrop, the US Food and Drug Administration (FDA) has articulated what may be one of the most consequential regulatory shifts in decades. In a recent New England Journal of Medicine article, FDA leadership described a plausible mechanism pathway for drug and biologic development (1). Rather than abandoning rigour, the pathway reflects a deliberate re-weighting of evidence. It places greater emphasis on biological plausibility, mechanistic sufficiency, and natural history grounded clinical interpretation when conventional trial structures cannot reasonably be executed.

This evolution is particularly relevant for pharmaceutical physicians working in gene therapy, gene editing, and other precision modalities, where the mechanism is not simply supportive of efficacy but foundational to it.
In many rare diseases, especially severe childhood-onset genetic disorders, the evidentiary expectations embedded in conventional drug development are mismatched to clinical reality. Randomised controlled trials may be infeasible due to population size alone. Placebo control may be ethically untenable in conditions with predictable and devastating natural histories or complex routes of administration. Even well-designed single-arm studies can struggle to demonstrate statistical certainty when patient numbers are counted in the single digits.

The absence of traditional trial structures does not imply an absence of knowledge. In monogenic disease, the causal link between genotype, molecular dysfunction, and phenotype is often well established. Natural history, when rigorously characterised, can be remarkably consistent. In such settings, the central question shifts. It is no longer whether a therapy demonstrates population-level statistical significance, but whether intervention at a defined biological node plausibly alters the expected disease trajectory in a clinically meaningful way. This is the core logic of the plausible mechanism pathway (1).

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As articulated by FDA leadership, this pathway is not intended as a relaxation of regulatory standards. It is a reframing of what constitutes persuasive evidence when traditional approaches are impractical. Several principles define this framework. There must be a clearly defined molecular or cellular abnormality that is causally linked to disease. This pathway is not designed for syndromic diagnoses or poorly understood polygenic conditions. It is grounded in diseases where the biological defect is known.

The therapeutic intervention must act proximally on that defect. Treatments that exert broad or downstream effects without a clear mechanistic link to the inciting pathology are unlikely to qualify. The closer the intervention is to the causal mechanism, the stronger the plausibility argument becomes.

A well characterised natural history is essential. The FDA places substantial weight on understanding how disease unfolds in the absence of intervention, allowing treated patients to be interpreted against a credible counterfactual rather than an artificial control arm. Evidence of target engagement or biological activity, when feasible, further strengthens the case. While invasive confirmation such as tissue biopsy may not always be possible, converging data from biomarkers, model systems, or pharmacodynamic signals can support mechanistic claims.

Finally, there must be a clinically meaningful deviation from the expected disease course. Improvement need not be dramatic, but it must be durable, coherent with the proposed mechanism, and sufficient to exclude regression to the mean or spontaneous fluctuation. This framework does not bypass evidence generation. It reallocates evidentiary weight towards biological coherence when statistical certainty is unattainable.

It is worth emphasising that many of these evidentiary elements are not themselves novel. The FDA has long considered biomarkers, mechanistic data, external controls, and natural history in rare disease development, and approvals based on surrogate or intermediate endpoints are well established. What is different here is not the individual tools, but the explicit way in which senior FDA leadership is reframing their collective acceptability. The plausible mechanism pathway represents a shift in emphasis and transparency, elevating biological coherence and mechanistic sufficiency from supportive evidence to a central organising principle for regulatory judgement when traditional trial paradigms are not feasible.

The case of Baby K.J., an infant with carbamoyl phosphate synthetase 1 deficiency treated with a patient-specific in vivo base editing therapy, illustrates the pathway in practice (2). The disease mechanism was unequivocal. The intervention was precisely targeted to the causal mutation. The natural history of untreated disease was well documented. Post-treatment clinical improvement was aligned with biological expectations (2). Importantly, the case also illustrates a broader regulatory insight. Individualised therapies can generate generalisable knowledge. While each intervention may be bespoke, repeated success across patients using a shared technological platform can establish confidence in the process itself.

In this sense, the FDA is signalling openness to approving not only individual products, but platforms, provided that the underlying science, manufacturing controls, and clinical logic are sufficiently robust. This reasoning extends beyond gene editing alone. Antisense oligonucleotides, RNA-based therapies, gene replacement approaches, and other precision modalities may also qualify when they directly address a defined molecular defect.

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Rare diseases, particularly fatal or severely disabling paediatric conditions, are the natural proving ground for this framework. In these settings, the cost of inaction is high, and the limitations of traditional development models are most acute. The FDA has been explicit that it intends to prioritise such conditions, while leaving open the possibility that similar principles could extend to more common diseases with substantial unmet need. At the same time, the pathway is deliberately constrained. Its integrity depends on disciplined application. Broad extrapolation to conditions with ambiguous mechanisms or heterogeneous biology would undermine its credibility and risk patient harm.

The plausible mechanism pathway does not exist in isolation. It sits alongside other recent FDA initiatives aimed at modernising therapeutic development for rare diseases, including the Rare Disease Endpoint Advancement framework (4) and related Rare Disease Evidence Principles or RDEP (3). Rather than functioning as a new endpoint qualification programme or regulatory shortcut, RDEP is best understood as an early alignment mechanism. It provides a structured opportunity for sponsors and the FDA to agree, before pivotal development, on what constitutes sufficient evidence of effectiveness in settings where conventional trial designs are not feasible.

Under RDEP, the statutory standard for safety and effectiveness does not change. What changes is the transparency around how different forms of evidence may be weighed. Mechanistic data, relevant nonclinical models, pharmacodynamic signals, rigorously collected natural history, and external or self-controlled comparators can all contribute to a coherent evidentiary package (3), underpinned by effectiveness established based on one adequate and well-controlled single-arm trial when randomised controls are impractical. In this way, RDEP complements the plausible mechanism pathway by clarifying evidentiary expectations early, reducing downstream uncertainty, and anchoring regulatory judgement in biological coherence rather than trial architecture alone.

Taken together, these initiatives suggest a broader regulatory evolution towards process-based reasoning. Rather than evaluating isolated data points, the FDA is increasingly focused on the coherence, reproducibility, and scientific integrity of an entire development approach.

For pharmaceutical physicians, this shift carries practical implications. Development strategies must increasingly be built around rigorous natural history studies, mechanism- driven endpoint selection, and early integration of biomarker logic. Regulatory engagement becomes less about negotiating trial size and more about aligning on biological narratives, uncertainty, and risk tolerance.

At the same time, the plausible mechanism pathway places significant responsibility on clinicians, sponsors, and regulators to exercise judgement. Overconfidence in mechanism, insufficient post-marketing follow-up, and inequities in access remain real risks. The FDA has emphasised that approvals under this framework will be coupled with ongoing evidence generation and that tolerance for uncertainty will remain proportional to disease severity and therapeutic benefit. What is clear, however, is that the agency is signalling a willingness to evolve.

By formalising a path for individualised and mechanism-defined therapies, the FDA is not only addressing an immediate need in rare disease but also establishing a regulatory foundation that could enable personalised therapeutic development more broadly. Other regulators are already watching closely. The United Kingdom, for example, has announced plans to explore a dedicated pathway for individualised genetic therapies (5), reflecting growing international recognition that traditional development paradigms are poorly suited to this class of medicines.

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For patients with rare and devastating diseases, and for the physicians who care for them, this shift offers a pragmatic and scientifically grounded path forward. In certain contexts, mechanism is no longer simply supportive of evidence. It becomes evidence itself.

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