FDA's Plausible Mechanism Pathway for Personalized Therapies to Treat Rare Diseases

The clock was ticking as soon as baby KJ was born in the summer of 2024. Within two days of his birth, he was lethargic and struggled to breathe. His blood test results showed elevated ammonia levels, leading to a diagnosis of carbamoyl-phosphate synthetase 1 (CPS1) deficiency. This ultra-rare disease affects around 1 in 1,300,000 individuals, and only half of those born with the disorder will make it beyond early infancy.

As soon as KJ was diagnosed, a team of researchers began developing a bespoke gene editor for him. Within six months, the baby had received two doses of his individualized therapy, and his parents say that every day, he's showing signs of growing and thriving.

Time was of the essence in creating KJ's treatment — at five months old, his condition had worsened to the point he was on a list for liver transplantation. Due to this urgency, the Food and Drug Administration (FDA) approved his experimental treatment plan after only one week of review following submission of the Investigational New Drug application.

Now, top officials from the FDA want to make it easier to help future baby KJs. Published in the New England Journal of Medicine, Marty Makary and Vinay Prasad explain a Plausible Mechanism Pathway for approving future personalized gene-editing treatments (1).

Shortly after the NEJM article was published, the FDA released a Draft Guidance Document titled "Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause."

The draft guidance provides greater detail and addresses some concerns raised after the release of the NEJM article.

Five aspects of KJ's therapy: how the Plausible Mechanism Pathway works

Traditional FDA drug approvals emphasize proven safety and efficacy through phased clinical trials with multiple participants. However, for patients with rare diseases that have a bespoke therapy targeting their unique genetic mutation, assembling enough participants for a randomized controlled trial is unfeasible due to small patient pools.

The new pathway outlined in the NEJM article addresses this limitation by allowing approval based on a plausible-mechanism framework that includes mechanistic evidence plus clinical-course interpretation. Makary and Prasad state that Baby KJ's story highlights several aspects that define the FDA's plausible mechanism category. First, there was a specific molecular or cellular abnormality, not a broad diagnostic spectrum. Makary and Prasad state that the FDA will reserve the Plausible Mechanism Pathway for diseases like this, for which the biological cause is known, to "safeguard against misapplication to disparate conditions with similar phenotypes" (1).

Secondly, the NEJM paper states that KJ's therapy was developed to target the underlying biological alterations, and thirdly, that his care team relied on a well-characterized natural history of the disease, both of which support a reliable interpretation of clinical changes.

In mouse models of Baby KJ's disease, results showed successful editing in 42% of liver cells. This evidence of target editing, demonstrated in cell or animal models, is listed as the fourth eligibility criterion for a therapy to be included in the Plausible Mechanism Pathway (1).

Finally, they state that the patient must show improvement in clinical outcomes or course. Makary and Prasad clarify that for conditions with progressive deterioration, consistent improvements will be viewed positively by the FDA. For conditions characterized by episodic waxing and waning, the FDA will look for prolonged periods of disease remission (1).

"The FDA will consider previous clinical course and, in some cases, will view patients as their own control," the authors state in the NEJM article. "Clinical data must be strong enough to exclude regression to the mean" (1).

FDA Draft Guidance: Further Developing the Plausible Mechanism Pathway Framework

Following the NEJM article, the FDA released the much more comprehensive Draft Guidance, which "outlines a set of recommendations to help developers of individualized therapies generate sufficient clinical safety and efficacy data to demonstrate that a drug or biological product is safe and effective for the intended use, and that the product can be manufactured to regulatory quality standards." The data generated under this framework is then used to support approval or licensure of the therapy for a specific indication.

While the NEJM article uses five aspects from the development of Baby KJ's therapy to show how the framework would be developed, the Guidance Document provides far greater detail in outlining recommendations. In some recommendations, the FDA Guidance departs from the NEJM article.

Notably, the Guidance explains that approval occurs within existing regulatory approval pathways. Highlighting this, the Guidance references many prior guidance documents to point to existing recommendations, such as those providing recommendations for design of nonclinical POC and safety studies for genome editing (GE) and antisense oligonucleotide (ASO) products, nonclinical recommendations to assess safety of ASOs, ethical considerations for individualized therapies, development of drugs for rare diseases, IND submissions for individualized RNA-targeted therapies, and potency assays for GE products.

The five aspects mentioned in the NEJM article are clearly provided in the FDA Guidance:

"Application of the plausible mechanism framework involves:

- Identifying a specific genetic, cellular, or molecular abnormality with a clear connection between specific alteration and disease indication
- Developing a therapy that targets the underlying or proximate pathogenic biological alterations
- Relying on a well-characterized natural history of the disease in an untreated population
- Confirming that the target was successfully drugged or edited or both
- Demonstrating improvement in clinical outcomes or course."

The Guidance specifically discusses genetically targeted therapies, including both GE technologies and RNA-targeted therapies, such as ASOs and small interfering RNAs. However, it also allows that the general concepts may apply to other types of individualized therapies.

It outlines the regulatory pathway, goals of nonclinical programs, and opportunities for data leveraging. Then, it separately outlines study and safety assessment recommendations for the FIH trial for Gene Editing products and ASOs, followed by guidance on studies to support approval for each type of therapy.

Under the Clinical section, the Guidance emphasizes safety, planning, and data quality, requiring substantial evidence of effectiveness. "Given the very small number of patients expected to be treated, early planning is critical to identify the potential sources of efficacy and safety data for the product to support a future marketing application. FDA anticipates that the first-in-human clinical investigation that will open an IND will also be the primary source of evidence to support approval; therefore, protocols should be designed to be adequate and well-controlled."

Timely and urgently needed: potential benefits of the Plausible Mechanism Pathway

The Plausible Mechanism Pathway is mainly for cases like Baby KJ's, where quick, targeted therapies can be lifesaving. For patients with rare diseases, this path could potentially mean no longer having to wait years for treatment, but only months.

Currently, single patients can receive treatment from investigational therapies in clinical trials under the expanded access, without an expectation that the data be used. In contrast, therapies developed under the plausible mechanism pathway could be used to generate critical clinical

safety and efficacy data to be used in developing products that can be modified to address other genetic mutations (1).

Additionally, according to the NEJM article “sponsor will be tasked, as a postmarketing commitment, with collecting real-world evidence to confirm continued preservation of efficacy and to show that there were no off-target edits… as well as to study the effect of early treatment on childhood growth and developmental milestones and to detect unexpected safety signals” (1).

The FDA Guidance clarifies that, “FDA may require that data on safety continue to be collected in the post-marketing setting. This may also include collection of efficacy outcomes if there is evidence of a potential for loss of efficacy over time… FDA also intends to closely monitor reports of adverse events from the trial and any signals of unexpected or delayed adverse events in the post-market setting. If a safety signal emerges, FDA will investigate the signal to determine if any action is warranted.” Further recommendations are also found in existing FDA Guidance documents mentioned previously.

While rare diseases, especially those that are fatal or linked to severe childhood disability, will be prioritized under this pathway, Makary and Prasad say a Plausible Mechanism Pathway will also be available for common diseases, specifically conditions that lack proven alternative treatments or have a large unmet need after trying available therapy (1). “For instance, a single disease with 150 different genetic mutations with the same functional implication may require 150 different therapies, and the Plausible Mechanism Pathway would be ideally suited to such therapies,” they state (1).

In this, the two documents differ. The FDA Guidance narrows the scope to only encompass individualized therapies, going on to definine them as “For the purposes of this guidance, individualized therapies are considered therapies that target a specific pathophysiologic abnormality serving as the root cause of a disease, for example, specific pathogenic genetic variant(s) causing a severely debilitating or life-threatening disease or condition in a small number of patients where a randomized controlled trial typically is not feasible.”

An editorial response to the NEJM article that was published in Molecular Therapy characterizes the pathway as important, timely, and urgently needed (2). Timothy Yu, one of the lead authors of the article, writes that reserving the pathway for interventions grounded in compelling genetic evidence of a correctable mechanism will ensure its integrity. For example, it could apply to “strategies that directly address the primary molecular defect in well-characterized monogenic disorders, such as restoring functional gene expression in a loss-of-function condition, specifically knocking down the expression of a nonessential but toxic gene product, or precisely correcting disease-causing mutations back to wild-type sequences” (2).

Additionally, Yu proposes that sponsors using this pathway should be required to submit data about the manufacturing processes and outcomes to a centralized evidence base, allowing the industry to learn from each treated patient. “Analysis of pooled preclinical, clinical, and post-marketing data will be required to assess overall outcomes, refine regulatory requirements and best practices, assess safety signals, and accelerate collective learning for this new pathway in a responsible manner” (2). Products approved under this framework would have met the same safety and efficacy standards as other FDA-approved therapeutics (2).

The FDA Guidance also emphasizes this, with an entire section on the importance of data sharing, which states, “Shared learning through appropriate data sharing is one opportunity to facilitate continued research.”

“A final imperative is timely development of consistent reimbursement models by payors to ensure equitable patient access and continued investment,” Yu notes. “Fatal or very serious disorders of children are prime candidates for these therapies, and time is of the essence if intervention is to be successful.”

Yu views this new pathway not just as a niche fix, but as a way to advance individualized genetic medicines into routine clinical practice for patients and families affected by these rare conditions worldwide (2).

Unclear criteria and risk of becoming the norm: potential risks and criticisms of the NEJM Article

Enthusiasm for the new pathway is high, and some concerns are not about the plausible mechanism idea but about the approach and how it could be extended beyond narrowly defined cases. While there’s consensus that a new pathway is needed for individualized therapies, some regulatory experts and bioethicists caution that the pathway could be used to push forward treatments with less certain efficacy or those with enough patients for which a rigorous, controlled trial should take place, for the benefit of patients.

Holly Fernandez Lynch, a bioethicist at the University of Pennsylvania and the lead author of an editorial published in Health Affairs Forefront, which responded to Makary and Prasad’s article, explains that the concern is not about the plausible mechanism idea. Instead, one of the bigger concerns is that the fuzzy legal process initially used to announce the pathway may leave it open to legal disagreements with companies that believe they should be eligible for the Plausible Mechanism Pathway.

Additionally, Lynch says, “the concern is that they’ve done it out of compliance with the good guidance practice regulations, which specifically say that if you’re making a substantial change to FDA policy, you cannot announce that to the public for the first time through media interviews and through journal articles, which is exactly what they did here.” Instead, Lynch says a guidance document that would have provided more detail on the pathway’s legal authority should have been created first. Lynch explains that this type of document would’ve informed the regulated community of precise details and given people an opportunity to weigh in.

Lynch also says the criteria of the Plausible Mechanism Pathway are unclear, explaining that Makary and Prasad list out the five characteristics of Baby KJ’s case but do not specify if all five need to be present to meet the requirements.

And then there are the scope concerns, and the risk of approving therapies that seem promising in theory but fail in practice. She explains that the drug Sarepta — approved for treating Duchenne muscular dystrophy — is one such example. Despite Sarepta having four drugs approved for the disease, all with a plausible mechanism, none have shown any clinical benefit in clinical trials, and one recent trial testing two of the drugs demonstrated little difference between placebo and treatment.

“We know that when the FDA opens the door to these things, there’s a lot of pressure … to then open the door a little wider and then a little wider and then a little wider until you have an exceptional program becoming the norm,” says Lynch. “These are desperate disease areas, and so sponsors and patient groups are going to be grasping at anything that could be beneficial to them here.”

This has happened before: in 1992, the FDA dismissed concerns that a new accelerated approval pathway designed for getting drugs to dying AIDS patients more quickly would become the norm for drug approval. Now, nearly a third of oncology drugs are approved this way, many of which have not demonstrated an improved survival rate.

Additionally, Makary and Prasad write about expanding the pathway beyond cases like Baby KJ, and Lynch questions what the limits would then be. She argues that it should apply only when a traditional randomized trial is not feasible, keeping it as close as possible to an n-of-1 or n-of-a-few design. “The concern is: How strictly are those characteristics or requirements going to be interpreted once FDA rolls this out? How strict are they going to be about confirming that the target was successfully drugged, or improvement in clinical outcomes?”

Yet others see it as being clearly “designed to evaluate personalized, N=1 therapies—treatments so individualized that traditional randomized controlled trials are impossible.” This editorial goes on to state that “the PMP is intentionally narrow and relies on biological clarity… is not intended for common or biologically complex diseases.”

The FDA Guidance document addresses many of these concerns, and the FDA is accepting comments on the Draft Guidance through April 27, 2026, allowing stakeholders to provide the necessary input.

Future of the Plausible Mechanism Pathway

The fast approval of Baby KJ’s therapy likely saved the infant’s life. While researchers are still in the early stages of understanding the extent to which his bespoke therapy has benefited him, he will likely live with a milder form of his disease. The Plausible Mechanism Pathway aims to drastically shorten development timelines for future individualized medicines, providing hope for patient populations that typically have no treatment options.

However, Prasad and Makary caution that disciplined implementation will be imperative to the pathway’s success. By prioritizing mechanisms over outcomes, there is a risk of approving therapies that seem promising in theory but fail in practice. Additionally, without data from randomized control trials, it’s harder to assess the true benefits versus placebo effects or natural disease progression. As Lynch noted, there is potential for companies to pressure the FDA to accept drugs that don’t necessarily fit the pathway’s mould, and for that to become the norm.

This tension over evidentiary standards and regulatory flexibility has come into sharper focus amid recent leadership changes at the agency: on March 6, it was announced that Prasad would be stepping down as director of the FDA's Center for Biologics Evaluation and Research. Prasad’s departure follows criticism from the biotech and pharmaceutical industries, which have accused the FDA of reversing previous guidance on the evidence they can use to support their applications. In the past year, the agency has rejected or deferred approval for at least eight drugs for rare diseases, citing issues with the data companies provided to support their

applications. However, this has raised questions about how consistently the FDA applies the regulatory flexibility it promotes.

As for the plausible mechanism pathway, the Prasad and Makary article states that the FDA is always open to additional feedback and suggestions regarding it. “Meanwhile,” they state, “for patients and families, there is no time to wait.”

The swift release of the FDA Draft Guidance and commentary in its press release supports this view. “We anticipate our Plausible Mechanism draft guidance will inspire industry to place increased focus on individualized therapies, thereby driving innovation, improving safety, lowering costs and offering more patients with ultra-rare diseases a unique shot at a life-saving treatment.”

References:

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