April 27, 2026

Martin A Makary M.D., M.P.H.
Commissioner
U.S. Food & Drug Administration
Department of Health and Human Services
10903 New Hampshire Ave
Silver Spring, MD 20993

Re: Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause; Draft Guidance for Industry [Docket No. FDA-2026-D-1256-0002]

Dear Commissioner Makary:

The Personalized Medicine Coalition (PMC), a multi-stakeholder group comprising nearly 200 institutions from across the health care spectrum, appreciates the opportunity to comment on the U.S. Food and Drug Administration's (FDA) draft guidance for industry on considerations for the use of the Plausible Mechanism Framework to develop individualized therapies that target specific genetic conditions with known biological cause.[i] We applaud the FDA's efforts through the draft guidance to clear a path for the treatment of patients, many of whom are children, with genetic conditions that have been beyond the reach of conventional drug development. PMC and FDA share the goal of ensuring greater access to safe and effective individualized therapies for a broader scope of rare diseases and encouraging further scientific advances that lead to the development of treatments. Recognizing the meaningful impact the Plausible Mechanism Framework could have on treatments designed, developed, and tested for a single patient or small groups of patients, PMC's comments recommend further refinement to the Plausible Mechanism Framework as the Agency moves to finalize the draft guidance.

PMC defines personalized medicine as an evolving field in which physicians use diagnostic tests and individual details about a person's health to determine which medical treatments will work best for each patient or use medical interventions to alter molecular mechanisms that impact health. By combining data from diagnostic tests with an individual's medical history, circumstances, and values, health care providers can develop targeted treatment and prevention plans with their patients.

Personalized medicine is helping to shift patient and provider experiences away from trial-and-error toward a more streamlined process for making clinical decisions, which leads to improved patient outcomes, a reduction in unnecessary treatment costs, and better patient and provider satisfaction. PMC and its members are leading the way in personalized medicine and in developing evidence showing how patients and the health care system can benefit from appropriate testing and tailored treatment as soon as possible during their clinical experiences.

Statement of Neutrality

Many of PMC's members will present their own responses to the recent FDA proposed Plausible Mechanism Framework to develop individualized therapies that target specific genetic conditions with known biological causes and will actively advocate for those positions. PMC's comments are designed to provide feedback so that the general concept of personalized medicine can advance, and are not intended to adversely impact the ability of individual PMC members, alone or in combination, to pursue separate comments with respect to the proposal.

Importance of Individualized and Genetic Therapies to Personalized Medicine for Rare Diseases

Half of patients with rare conditions are children, and approximately 70 to 80 percent of rare diseases are due to genetic causes.[ii] [iii] Since 2020, personalized medicines have accounted for at least a third of newly FDA-approved therapies each year, with a growing number of approvals for rare diseases.[iv] The transformation of health care from one-size-fits-all, trial-and-error medicine to targeted treatment utilizing each patient's molecular information is progressing, however, 95 percent of rare diseases still have no FDA-approved treatments.[v]

The availability of highly personalized cell and gene therapies that often function more like individualized medical procedures than conventional therapies manufactured for larger patient populations is increasing. Cell and gene therapies represent one of the most significant advances in modern medicine, addressing the root causes of disease by modifying gene expression or repairing abnormal genes. The development pipeline for cell and gene therapies includes over 4,100 therapies ranging from pre-clinical through pre-registration stages.[vi] As of 2025, more than thirty cell and gene therapies are now available for patients in the United States. Many of these therapies target rare, inherited disorders in small patient populations with few or no alternatives.[vii]

Since 2017, the FDA has also approved small-interfering RNA drugs and antisense oligonucleotide (ASO) drugs to treat various diseases, with most targeting rare genetic disorders.[viii] This new class of oligonucleotides has become a powerful tool for gene silencing messenger RNA that carries instructions for disease-causing proteins. Instead of replacing a faulty gene, scientists dampen its output. These technologies have opened new routes for treating rare, inherited conditions.[ix] According to one estimate, 45 percent of the total global burden of disease could be treated with existing biotechnologies – but they require ongoing development support.[x]

Impact of the Proposed Plausible Mechanism Framework and Suggested Refinement

One recent breakthrough made possible by advances in personalized medicine is the treatment of Baby KJ Muldoon. KJ was the first patient to receive a personalized CRISPR gene editing therapy.[xi] Diagnosed with severe carbamoyl phosphate synthetase 1 deficiency, a rare, life-threatening genetic condition shortly after birth, KJ was treated with a custom therapy gene-editing therapy intended to correct the underlying genetic defect.[xii] Advances in genomics and platform technologies made it possible to shorten the timeline from diagnosis, target identification, and genetic therapy design from years to months. KJ celebrated his first birthday in August 2025. While this treatment was developed for a single child, its implications extend far beyond one case. FDA displayed regulatory flexibility in the effort to treat KJ, and this experience led the FDA to develop the draft guidance on considerations for the Plausible Mechanism Framework.

The successful design and clinical use of a personalized gene editor demonstrates a potential new pathway for treating rare disease, offering hope to millions of patients and families worldwide. As the application of personalized therapeutic development and clinical care increases, regulatory actions must keep pace with that opportunity, especially given the rapid progression of many genetic disorders. PMC supports the aim of the FDA's draft guidance in that it leverages a pathway for personalized genetic therapies to advance more efficiently from the laboratory to market. However, in the final guidance we urge FDA to broaden the established scope of permissible personalization and provide further clarification for sponsors on limits of safety and efficacy data extrapolation, criteria for post market follow up across related therapies, and manufacturing requirements.

PMC understands that under the Plausible Mechanism Framework contemplated in the draft guidance, a sponsor may seek approval for a core genetic therapeutic platform. Once the foundational construct is established in the form of a specific treatment for a particular genotype, sponsors can then modify certain aspects of the genetic construct to target a different variant of the gene. The resulting therapies can be customized for each patient without starting from scratch for each patient.[xiii] The draft guidance, however, does not define all the regulatory boundaries for grouping multiple genetic variants under a single approval. Although the FDA acknowledges that individualized therapies may be modular, it stops short of explaining how that variation can be aggregated within one product approval rather than treated as a succession of separate, independent therapies. Greater clarity, especially about limits on variables like sequence length, structural configuration, and other design features, would more clearly define the development pathway for these therapies and show sponsors where adaptation is permitted and where it begins to alter the identity of the product. [xiv]

To further encourage development in this space, the FDA should provide greater detail on how far the agency is prepared to extrapolate safety and efficacy beyond the data submitted for approval. We note, however, that feasibility alone does not fully capture whether a given study design will generate interpretable and scientifically reliable evidence in the context of a specific disease and treatment. There is strong interest across the rare disease community in ensuring that development approaches are evaluated based on their ability to generate meaningful and scientifically grounded conclusions, given the biological and clinical context of the disease, rather than on a threshold determination of randomized controlled trial feasibility alone.
The FDA has shown a willingness to leverage information from one circumstance to another but as part of the proposed framework extrapolation becomes more critical because clinical data may encompass one patient or a small group of patients. The final guidance should specify evidentiary criteria for the shared molecular mechanism, comparable vector biology, or overlapping patient phenotype that a sponsor must satisfy to justify extrapolating safety and efficacy data from one variant to another.[xv] PMC strongly supports FDA's emphasis on well-characterized natural history data, including those informed by systematically collected real-world data where appropriate, as well as externally controlled or within-patient study designs in settings where they are scientifically justified. In many rare diseases, robust natural history data, including registry-based and other systematically collected real-world sources, are essential to contextualizing observed treatment effects. Such data can also help mitigate ceiling and floor effects that might otherwise obscure clinically meaningful benefit. These principles are strengthened by fit-for-purpose data sources, including systematically collected real-world data and registry-based natural history information, where appropriate. Such data help contextualize disease progression, inform endpoint selection, and support interpretation of treatment effects, particularly in heterogeneous or slowly progressive conditions. Greater predictability in how

evidentiary determinations are made would therefore have meaningful implications for patient access while preserving scientific rigor.

The final guidance should also include a clear and well-defined set of quality standards for efficiently manufacturing personalized therapies under the Plausible Mechanism Framework. Chemistry, manufacturing, and controls can be standardized even when the genetic payload varies within preapproved bounds. Applying CMC expectations in a risk-proportionate and scientifically grounded manner is therefore essential to the overall evaluability of individualized therapies. The draft guidance leaves open questions about how much process validation, comparability data, and release testing will be required when each batch may correspond to a single patient.[xvi] Because the clinical data for these treatments may be derived from one or a small group of patients, the final guidance should establish criteria for how post approval data, including real world data, can be pooled to inform modifications to therapies developed under the Plausible Mechanism Framework.

Conclusion

Thank you for your commitment to ensuring that patients can access safe and effective individualized therapies for a broader scope of rare diseases. As FDA gains additional experience reviewing programs with shared scientific characteristics, continued transparency around how risk-based and proportionate expectations are applied—particularly with respect to post-approval evidence generation—will support consistency, predictability, and patient trust in the regulatory process. With further refinement the draft guidance can make personalized gene editing a reality for patients no matter how rare the disease or how rare the variant. We look forward to working with you and your colleagues at FDA to facilitate timelier availability of these and other advances in personalized medicine. If you have any questions about the content of this letter, please contact me at 202-499-0986 or cbens@personalizedmedicinecoalition.org.

Sincerely,

Cynthia A. Bens
Senior Vice President, Public Policy

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