September 1, 2026

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing; Draft Guidance for Industry [Docket No. FDA-2026-D-1257]**

Dear Sir/Madam:

The Personalized Medicine Coalition (PMC), a multi-stakeholder group comprising more than 150 institutions from across the health care spectrum, appreciates the opportunity to comment on the U.S. Food and Drug Administration's draft guidance, Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing.[i] PMC and the FDA share the goal of ensuring greater access to safe and effective therapies for a broader scope of diseases. Allowing developers to utilize chemistry, manufacturing and controls (CMC) data, as well as nonclinical and clinical information from gene edited or other relevant products represents an important step forward. We applaud FDA's efforts through the draft guidance to further streamline development of treatments for patients with genetic conditions that until now have been beyond the reach of drug development. PMC's comments highlight the meaningful impact the draft guidance may have by alleviating the need to generate new information or data where it already exists and they identify areas for further refinement in the final 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 FDA's draft guidance, Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing, 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 draft guidance.

**Importance of Gene Therapies to Personalized Medicine**

Since 2020, personalized medicines have accounted for at least a quarter of newly FDA-approved therapies each year, with a growing number of approvals for rare diseases.[ii] 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.[iii] Cell and gene therapies (CGT) 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 CGT includes more than 4,100 therapies ranging from pre-clinical through pre-registration stages.[iv] As of 2025, more than 30 cell and gene therapies are now available for patients in the United States, including the first gene-edited therapy for patients with sickle cell disease, an individualized gene-edited therapy for severe carbamoyl phosphate synthetase 1 deficiency, and CGT for idiopathic macular telangiectasia type 2, recessive dystrophic epidermolysis bullosa, spinal muscular atrophy (SMA), and Wiskott-Aldrich syndrome.[v] Many of the other approved therapies and those in the pipeline target rare, inherited disorders in small patient populations with few or no alternatives.[vi]

Technological advancement has and continues to open new routes for treating rare conditions.[vii] Advances in genomics and platform technologies make it possible to shorten the timeline from diagnosis, target identification, and genetic therapy design from years to months.[viii] 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.[ix] Recent success in the design and clinical use of a personalized gene editor demonstrates a potential new pathway for treating disease, offering hope to millions of patients and families worldwide.[x] 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 was pleased with the release of FDA's proposed Plausible Mechanism Framework earlier this year, and we provided feedback focused on improving that draft so the FDA could meet its goal of advancing personalized genetic therapies more efficiently from laboratory to market. [xi] Many of PMC's recommendations for refining the Plausible Mechanism Framework centered around the need for greater detail on how far the agency would be prepared to extrapolate from data beyond what is submitted for approval of a specific product. We also called for the final guidance on the Plausible Mechanism Framework to include a clear and well-defined set of quality standards for efficiently manufacturing personalized therapies.

**Impact of the Proposed Prior Knowledge Draft Guidance and Suggested Refinement**

Successes in pioneering CGT programs demonstrate their transformative potential – curing certain malignancies, saving lives of children with spinal muscular atrophy, and changing the trajectory for some patients with sickle cell diseases using CRISPR-based gene editing. However, experiences in these early programs also surfaced potential challenges such as the manufacturing costs, innate and adaptive immune responses to viral vectors in some patients, and difficulties with efficient biodistribution in tissue beyond the liver.[xii] Science has evolved rapidly. Uncertainties in regulatory flexibility and manufacturing requirements continue to create hurdles for sustainable development and limit commercial interest in CGT. With the field still in its nascency, there is a need to establish more structured approaches that balance regulatory oversight with operational feasibility alongside patient needs.

Recognizing that CGTs have the potential to yield unprecedented improvements in clinical outcomes for some disease areas, and that they continue to be an important area for personalized medicine, PMC supported PDUFA VII resources devoted to developing appropriate regulatory frameworks for assessing the safety and effectiveness of these life-changing therapies and to increasing FDA's capacity for assessing manufacturing and other processes.[xiii] **We appreciate that this draft guidance, made possible through PDUFA VII commitments, focuses on addressing some uncertainty in regulatory flexibility and manufacturing of gene-edited products and that FDA intends for some of its recommendations to apply to other CGT that do not incorporate gene editing, such as adeno-associated viral vectors (AAV), lipid nanoparticle-based (LNP) gene therapy products, and ex vivo-modified cell-based gene therapies.**

Current examples in the draft guidance focus primarily on hematologic and cell-based applications. Fortunately, CGT is now becoming a reality for therapy development outside of hematological diseases. With respect to applicability of the draft guidance to other CGT products, we encourage FDA to further emphasize the unique circumstances of rapidly progressive diseases where preserving function is often as important as achieving improvement. In these instances, development delays themselves pose significant risk to patients. **FDA should expand examples in the final guidance relevant to targeted genome editing programs, including systemic AAV and LNP delivery approaches, among other strategies for preserving a patient's functional capacity.**

CGT development increasingly depends on longitudinal data and standardized analytical approaches. These resources can provide critical context for understanding disease progression, interpreting therapeutic effects, and informing efficient development programs in populations where conventional clinical trial approaches may be impractical. PMC strongly supports FDA's discussion in the draft guidance of real-world evidence, consortium-generated knowledge, collaborative data-sharing initiatives, and natural history studies. Leveraging data from real world clinical practice can be a critical tool for longitudinal monitoring that can help verify outcomes. A framework for prioritizing, collecting, and analyzing real-world data can support approvals and the assessment of long-term benefit. Specifically, rare disease development frequently depends on external controls and longitudinal disease registries, as well as robust natural history and other systematically collected real-world data for contextualizing observed treatment effects. **We recommend that the FDA add language in the final guidance recognizing that validated natural history datasets and disease registries may support efficient development programs for rare diseases by supporting regulatory decision-making and reducing reliance on concurrent control groups in appropriate circumstances**.

Furthermore, **PMC emphasizes the importance of this draft guidance continuing to enable collaboration between clinicians, academic researchers, industry, regulators, and patients.** In a recent forum one of the

team members who contributed to the successful treatment of KJ Muldoon, an infant born with a rare and often fatal metabolic disorder, highlighted the "ingredients" that allowed them to shorten the time and cost to creating his individualized therapy.[xiv] His reflections focused on the collaboration between organizations with complementary but non-overlapping "superpowers." The organizations referenced were a tertiary care hospital with experience managing the needs of complex pediatric patients, two major research universities with experience in CRISPR technology, a private sector manufacturing partner with the capabilities to produce a customized gene editor in real time, and FDA's expertise. Multi-stakeholder collaboration made this fundamentally new path to treatment possible, but many innovators are struggling to make this a sustainable reality. Data-sharing initiatives, precompetitive consortia, and efforts to harmonize datasets collaboration will remain critical as CGT development and genome editing technologies continue to advance**.** This draft guidance represents an important step forward. **FDA should encourage publication of future case studies and examples illustrating successful leveraging strategies made possible through this draft guidance and how these strategies impacted regulatory decision-making.** FDA sharing learnings with stakeholders is important to academics and other innovators who are attempting to shorten the time and cost of on-demand individualized therapy development.

Prior knowledge can not only support the development of new products, but also lifecycle management of approved products. Accumulated manufacturing, analytical, clinical, and real-world experience can provide important evidence to support process improvements, manufacturing scale-up, comparability assessments, and refinement of product specifications. Recognizing the role of prior knowledge in lifecycle management would further support science- and risk-based decision making while reducing unnecessary development burden. **In the final guidance FDA should clarify that prior knowledge may be leveraged throughout the lifecycle of approved products rather than solely across related, but distinct products.**

In our prior comments on FDA's draft Plausible Mechanism Framework, PMC sought additional clarity on the scope of permissible personalization once the foundational construct for an individualized therapy is established, limits of safety and efficacy data extrapolation, criteria for post market follow-up across related therapies, and manufacturing requirements.[xv] PMC understands that this draft guidance on leveraging prior knowledge is intended to complement the Plausible Mechanism Framework. With that context, we offer the following recommendations:

**Leveraging clinical data.** 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 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. The FDA has shown a willingness to leverage information from one circumstance to another, but extrapolation becomes critical because clinical data may encompass one patient or a small group of patients. The final guidance should clarify that prior clinical safety, pharmacology, and biodistribution data may support streamlined development where diseases and biological mechanisms are sufficiently similar. For pediatric diseases, consideration of adult clinical experience may be scientifically justified. Additional discussion of pediatric extrapolation, modeling approaches, and use of adult safety and biodistribution data for pediatric dose justification would be helpful in the final guidance.

**Criteria for follow up.** FDA expresses a willingness in the draft guidance to consider risk-adapted approaches for long-term follow-up, biodistribution, nonclinical testing, and off-target assessment where cumulative

platform knowledge exists. We appreciate that as experience accumulates, FDA may reconsider monitoring expectations. The final guidance should clarify that long-term follow-up expectations remain proportionate to platform-specific risks and cumulative post-market safety experience. Regarding off-target assessment, FDA should encourage harmonized analytical standards across programs using similar editing technologies and articulate clearer expectations regarding confirmatory off-target testing strategies.

**Chemistry, manufacturing, and controls (CMC)**. CMC can be standardized in a risk-proportionate and scientifically grounded manner. PMC supports platform-based CMC development but believes the final guidance would benefit from examples of large-scale systemic manufacturing for non-hematologic diseases. Additionally, to encourage platform-based validation approaches for biomarkers and potency assays that may be used repeatedly across related development programs, the final guidance should clarify that platform validation strategies may be appropriate.

**Conclusion**

Thank you for the opportunity to comment on the draft guidance and your commitment to ensuring that patients can access safe and effective therapies for a broad scope of diseases. As FDA gains additional experience reviewing programs with shared scientific characteristics, continued consistency, predictability and transparency will foster trust in the regulatory process. We look forward to working with you and your colleagues at FDA to facilitate timelier availability of genome-editing treatments and other CGT 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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