ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

April 27, 2026

Dockets Management Staff (HFA-305)
US Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

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Framework To Develop Individualized Therapies That Target Specific Genetic Conditions With Known Biological Cause; Draft Guidance for Industry (Docket No. FDA–2026–D–1256)

Dear Commissioner Makary:

The American College of Medical Genetics and Genomics (ACMG)[1] appreciates the opportunity to review and provide feedback on the FDA's draft guidance concerning the plausible mechanisms framework. Due to advances in genetic therapies, combined with genomic sequencing and diagnostic tools, it is increasingly feasible to explore potential curative therapies for rare genetic conditions once considered uncurable. Further, high-throughput methods now enable more rapid functional characterization in rare or newly described disorders. Current efforts on genomic newborn screening will add to our ability to diagnose early, ideally pre-symptomatically, and understand the longitudinal history of a disorder from an early age. We commend the FDA for acknowledging that there are circumstances in which evidence of effectiveness for individualized therapies can be appropriately established based on a single well-controlled clinical investigation with confirmatory evidence.

[1] Founded in 1991, the American College of Medical Genetics and Genomics (ACMG) is a prominent authority in the field of medical genetics and genomics and the only nationally recognized medical professional organization solely dedicated to improving health through the practice of medical genetics and genomics. The only medical specialty society in the US that represents the full spectrum of medical genetics disciplines in a single organization, the ACMG provides education, resources, and a voice for more than 2,500 clinical and laboratory geneticists, genetic counselors, and other healthcare professionals. ACMG's mission is to improve health through the clinical and laboratory practice of medical genetics as well as through advocacy, education and clinical research, and to guide the safe and effective integration of genetics and genomics into all of medicine and healthcare, resulting in improved personal and public health.

7101 Wisconsin Avenue, Suite 990
Bethesda, MD 20814
Telephone: 301-718-9603
Fax: 301-381-9379

acmg.net

We offer the following comments for consideration when finalizing the guidance on *Plausible Mechanism Framework To Develop Individualized Therapies That Target Specific Genetic Conditions With Known Biological Cause*.

Establishing a diagnosis

In Section III.D., the Agency provides guidance for establishing a "genetic mutation/diagnosis". Specifically, the guidance states that *sponsors should confirm the patient's diagnosis using appropriate laboratory testing (e.g., sequencing, biochemical or enzymatic tests, imaging) and should validate assays for their intended use and include all results in the NDA/BLA submission*. The ACMG agrees with the importance of diagnostic rigor and recommends that the guidance more explicitly acknowledge the importance of a multidisciplinary clinical genetics framework for establishing a patient diagnosis and identifying the genetic basis of disease, including incorporation of the laboratory interpretation from a CLIA regulated clinical laboratory and clinical correlation by certified genetics healthcare professionals and disease specialists. Confirmation of the diagnosis by the clinical genetics experts is particularly critical when the diagnosis from the DNA finding is not definitive, for example, in cases involving variants of unknown significance (VUSs), or autosomal recessive cases that fit the clinical or biochemical picture but lacking a second variant. This will be particularly important as we shift to genomic newborn screening, enabling earlier disease identification but also raising additional uncertainties as new data are obtained.

The guidance also states that *sponsors should demonstrate that the targeted genetic variant(s) are unique to the patient(s), including prevalence estimates in the disease population and projected incidence in new cases based on molecular genetic characteristics*. Interpretation may be complicated by variant penetrance, which may require additional clarification. This is particularly relevant for autosomal recessive conditions, where variants are not necessarily unique to affected individuals and may be present in healthy populations. In such cases, disease association is typically observed only when a second disease-causing variant is also present, unless the condition follows an X-linked or autosomal dominant inheritance pattern. As currently written, it is not

7101 Wisconsin Avenue, Suite 990
Bethesda, MD 20814
Telephone: 301-718-9603
Fax: 301-381-9379

acmg.net

clear if this point is geared towards demonstrating evidence of pathogenicity for the targeted variant or about the potential scale of therapeutic impact on the affected population.

Study Design

When designing a clinical investigation protocol, consideration may be needed for the potential scope of individuals who could benefit from treatment which may span adult and pediatric patients, presymptomatic individuals, and even fetuses. Early and ongoing coordinated involvement of geneticists and disease experts is strongly encouraged to minimize misunderstanding of the diagnosis, genetic contributions, interpretation of VUSs, incomplete penetrance and phenotypic heterogeneity, etc.

Additionally, the draft guidance appears to be largely focused on products for different variants within a specific gene, giving flexibility to the variables needed to target different variants within the same gene. However, in section III.C., under *Design of the clinical investigation*, the Agency acknowledges that they are open to the use of master protocols for the evaluation of therapies that target different genetic changes for the same disease and refers stakeholders to *Draft Guidance for Industry: Master Protocols for Drug and Biological Product Development (December 2023)*. The current Master Protocol guidance, which is notably still in draft form, describes three types of trials that could be used.

- Umbrella trial: a trial designed to evaluate multiple medical products concurrently for a single disease or condition.
- Platform trial: a trial designed to evaluate multiple medical products for a disease or condition in an ongoing manner, with medical products entering or leaving the platform.
- Basket trial: a trial designed to evaluate a medical product for multiple diseases, conditions, or disease subtypes.

In the context of ultra-rare genetic diseases, umbrella trials and basket trials are likely the most significant. Basket trials may be particularly significant given the mechanistic and phenotypic similarities among a family of conditions with different underlying affected genes. In such cases, the plausible mechanisms frameworks could be extrapolated to

7101 Wisconsin Avenue, Suite 990
Bethesda, MD 20814
Telephone: 301-718-9603
Fax: 301-381-9379

acmg.net

study a specific gene editor system with different gRNAs to target different genes within the same cell population to correct a single pathway implicated in a family of ultra-rare diseases. Another example is an antisense oligonucleotide targeting the same nucleotide expansion studied in multiple diseases sharing the nucleotide repeat mechanism. However, while a basket trial is defined in the draft guidance, the document only provides guidance specific to umbrella and platform trials. Additional guidance about approaches for basket trials should be included in the final guidance.

Similarly, an "umbrella of umbrella trials" approach is already being pursued by investigators looking to streamline trials for a urea cycle disorders[2]. Similar to the logic behind basket trials, this approach is likely significant for subsets of ultra-rare diseases caused by disruptions in the same molecular pathways. Additional guidance on an "umbrella of umbrellas" approach is also needed, including specification of the criteria for other disease groups that would qualify under this model.

Evidence of Safety and Effectiveness

The FDA acknowledges that substantial evidence of effectiveness can be established based on a single adequate and well-controlled clinical investigation with confirmatory evidence. It may be helpful for the Agency to provide further detail on the potential use of safety and efficacy data beyond that generated in the primary investigation and how it may be considered to support product development and regulatory decision-making. Further discussion of when and how data derived from studies using comparable vector components, delivery platforms, or shared molecular mechanisms of action could be leveraged would be valuable. For many investigational products, especially those employing well-characterized viral vectors, regulatory elements, or editing modalities, substantial nonclinical and clinical experience may be extrapolated from other trials and approved products to enhance consistency and

[2] Feierman ER, et al. Implications of the FDA's new plausible mechanism framework for the development of a personalized in vivo prime editing platform. *Am J Hum Genet*. 2026 Mar 31:S0002-9297(26)00148-5. doi: 10.1016/j.ajhg.2026.03.018. Epub ahead of print. PMID: 41923647; PMCID: PMC13058825.

7101 Wisconsin Avenue, Suite 990
Bethesda, MD 20814
Telephone: 301-718-9603
Fax: 301-381-9379

acmg.net

predictability for sponsors. While potentially benefiting participants across the age spectrum, leveraging existing safety data for similar agents could inform and justify recruitment of young patients for first-in-human studies in early-onset disorders.

Additionally, the guidance states that *substantial improvement in symptoms or **change in disease trajectory** that is inconsistent with the natural history of the disease may provide substantial evidence of effectiveness*. Greater emphasis on the change in disease trajectory, including stabilization of symptoms or mitigation of disease progression, is needed. For conditions in which progression of clinical symptoms may be slow, molecular (e.g., RNA expression) and biochemical evidence or incorporation of disease biomarkers can indicate stabilization.

We appreciate the Agency's focus on the use of biomarkers as surrogate endpoints to generate evidence of effectiveness and recognize that such biomarkers must be clearly linked to clinical outcomes and fit-to-purpose. However, given recent Agency actions, there is concern about the consistency with which FDA accepts such biomarkers to support accelerated approval when such biomarkers were agreed upon as part of the trials design. For trials in which extremely low numbers of patients are available to participate, performing a second trial because of a change in decisions about acceptable biomarkers may not be possible. Therefore, providing concrete guidance on criteria that could render a biomarker acceptable would be a welcome resource for investigators.

Natural History Data

The guidance places significant emphasis on the use of well-characterized natural history data as an external control. Much clarification is needed regarding what constitutes adequate natural history data, particularly for patients with extremely rare diseases or genetic variants for which longitudinal natural history studies may not be feasible. It is important to recognize that longitudinal history for many rare disorders starts at the point when the patient becomes symptomatic. Although genomic testing in newborns and presymptomatic diagnoses may certainly impact our understanding of the evolution of a disorder, the reality is that many rare disorders do not have the benefit of a systematic collection of

7101 Wisconsin Avenue, Suite 990
Bethesda, MD 20814
Telephone: 301-718-9603
Fax: 301-381-9379

acmg.net

comprehensive natural history data. Therefore, guidance on the contributions of expert clinician attestation, published case reports, cross-sectional studies, retrospective analyses of disease course, standard-of-care treatment allowed in the natural history data, and patient-led disease registries is needed.

While referenced draft guidance for *Rare Diseases: Natural History Studies for Drug Development* provides some information on studies, it does not address situations, such as ultra-rare diseases and variants, for which such studies may not be feasible. Further, this guidance has been in draft form since 2019 which generates uncertainty regarding its content.

Confirmatory Studies

Given the nature of many ultra-rare diseases for which the plausible mechanisms framework would be needed, it is likely that many would rely on biomarkers as surrogate endpoints and thus require a confirmatory study after approval. However, these trials will likely involve very few or only a single participant. As such, clarification is needed regarding the potential withdrawal of a participant for a post-approval confirmatory study.

Approved Indication

It is currently unclear how clinical trial data will be extrapolated to define an approved target population. Even when a product is designed to target a specific gene, different variants within that gene may be associated with heterogeneous phenotypes, variable ages of onset, or incomplete penetrance. As conditions are added to newborn screening and data are generated for presymptomatic individuals, our understanding of disease penetrance and expressivity often changes, and genotype-based phenotypic prediction does not always apply. An exemplary case is X-linked adrenoleukodystrophy in which the same genotype may or may not lead to the cerebral disease in which gene therapy is conditionally indicated. Moreover, scientific understanding of variant pathogenicity is continually evolving, and reclassification of variants over time is an

7101 Wisconsin Avenue, Suite 990
Bethesda, MD 20814
Telephone: 301-718-9603
Fax: 301-381-9379

acmg.net

expected and well-recognized occurrence. This also raises questions about adding new variants to a product indication after approval.

While flexibility is needed to allow an approved product to address multiple variants, appropriate safeguards are necessary to ensure that treatment is used only in patients for whom it is clinically and molecularly appropriate. Because variant pathogenicity alone does not establish gene-disease validity, consideration should be given to whether an established, definitive gene-disease relationship (e.g., as curated by ClinGen) is relevant to the patient's phenotype and clinical diagnosis. In many cases, application of a multidisciplinary clinical genetics framework, including variant interpretation performed by a CLIA-certified clinical laboratory and clinical correlation by certified genetics professionals trained in variant interpretation, will be critical to ensuring appropriate use of therapy, particularly for less common or less well-characterized variants. This will be particularly important as genomic newborn screening becomes a reality, significantly increasing the genomic data available for individual patients.

Chemistry, Manufacturing, and Controls (CMC)

For products approved under the plausible mechanism framework, some aspects of manufacturing will need to occur at the hospital where the patient is being treated rather than a centralized facility. This raises many concerns and questions regarding the application of CMC requirements. Guidance is needed for de-centralized manufacturing as well as potential models for a shared manufacturing infrastructure and supervision of the quality standards. This includes consideration of the feasibility, including costs, to establish fully compliant manufacturing processes for each single-patient treatment as well as streamlining of manufacturing for rapidly progressing diseases that require treatment soon after diagnosis to avoid irreversible harm or death. Additional clarification is also needed regarding application of CMC requirements such as comparability data and release testing given that each "batch" may correspond to a single patient.

7101 Wisconsin Avenue, Suite 990
Bethesda, MD 20814
Telephone: 301-718-9603
Fax: 301-381-9379

acmg.net

ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

Additional Comments

The ACMG greatly appreciates the FDA's attention to identifying approaches for generating sufficient data from a single study to support drug approval. The plausible mechanisms framework represents an important step toward facilitating innovation for patients with ultra-rare genetic diseases or variants. However, practical limitations and challenges may remain under the existing statutory pathways, and continued dialogue, including consideration of future legislative solutions, may be needed. Consideration should also be given to the potential role of the FDA or other federal agencies in aggregating and sharing data about these therapies to break down data silos and enable informed trial designs, especially for new investigators. In addition, involvement of disease experts and family support groups in feedback regarding study design and endpoints will be crucial to ensure study success and clinically meaningful outcomes.

For questions or additional information, please contact Michelle McClure, PhD, ACMG Director of Public Policy, at mmcclure@acmg.net.

Sincerely,

Mira Irons MD

Mira B. Irons, MD, FACMG
President
American College of Medical Genetics and Genomics

7101 Wisconsin Avenue, Suite 990
Bethesda, MD 20814
Telephone: 301-718-9603
Fax: 301-381-9379

acmg.net