April 27, 2026

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

RE: Docket No. FDA- FDA-2026-D-1256: 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Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause; Draft Guidance for Industry

Dear Sir or Madam,

On behalf of the Pediatric Inclusion Alliance, we are pleased to submit comments on FDA's ***Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause***, Draft Guidance for Industry. The Alliance appreciates FDA following up from last year's NEJM article on the *FDA's New Plausible Mechanism Pathway* with issuing this draft guidance to provide greater clarity and to allow for public comment. Of specific importance for the Pediatric Inclusion Alliance is the early inclusion of children in individualized therapy development programs for early onset diseases and conditions.

About the Pediatric Inclusion Alliance

The Pediatric Inclusion Alliance (Alliance) is devoted to full, active collaboration among all stakeholders committed to achieving earlier inclusion of children in clinical trials across all diseases and conditions without compromising safety. For far too long, children have had to wait years for access to safe, effective therapies, often already approved for adult populations. These

therapies might well have been even more effective for younger patients if administered at the best time for them.

By combining a deep understanding of the needs of pediatric patients and their families, technical expertise, and real-world experience in medical research and therapy development, knowledge of regulatory guidance and processes, public policy, regulatory knowledge, and public policy understanding, the Alliance is a united collaborative of stakeholder groups committed to ensuring that children have the earliest opportunity to access safe and effective therapies when those therapies are most likely to have maximum benefit to them. This is especially true for early onset genetic disorders, the affected populations for which could benefit from earlier inclusion of children in CGT clinical trials.

General Considerations for Early Pediatric Inclusion

Scope of the Plausible Mechanism Framework

The Alliance appreciates that this guidance lays out an initial framework for obtaining FDA review of individualized treatments using genome editing and antisense oligonucleotides. To be eligible for consideration under this framework, a treatment program must have the following five criteria:

- An identified genetic, cellular, or molecular abnormality with a clear connection to the disease;
- A therapy that targets the underlying biological alteration;
- Have a well-characterized natural history of the disease;
- Obtain confirmation that the target was successfully drugged or edited; and
- Demonstrate improvement in clinical outcomes.

We believe the draft guidance provides a helpful start into FDA's thinking about which products would be eligible under this pathway. However, the application of the five criteria outlined in the framework remains highly subjective to the interpretation of individual FDA review divisions. To avoid divergent and inconsistent advice from different centers and review divisions, we urge FDA to provide additional details and clarification on the Agency's perspectives, recommendations, and how it will approach the following topics:

- **Scope of "individualized"**: The draft guidance states that "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." While this discussion of how FDA views individualized therapies is helpful, the Alliance recommends providing additional clarification around the term "individualized." For example, how rare must a disease be to qualify for application within the Plausible Mechanism Framework? Additional explanation in this regard would be helpful especially since FDA's perspectives regarding "rare" or "ultra-rare" diseases may differ from patient and industry stakeholders' interpretations. Another point for clarification is whether the Plausible Mechanism Framework is intended to apply to the entire rare disease or only to sub-populations within a rare disease.

- **Meaning of well characterized**: Throughout the guidance, FDA provides that various requirements must be "well-characterized" (e.g. a well-characterized disease, well-characterized natural history, a well-characterized mechanism of action, a well-characterized chemical class, and well-characterized ASOs). However, the guidance does not provide a definition of "well-characterized." Therefore, the Alliance urges FDA to provide additional insight into what the Agency considers the definition of and criteria for the term "well-characterized."

- **Engagement opportunities:** We also encourage FDA to explain what mechanisms are available for early engagement with FDA, especially when INTERACT meetings are not appropriate. For example, the draft guidance recommends sponsors come in early to discuss nonclinical and clinical development programs with FDA and cites the 2023 draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*. However, given this is a new framework with unique criteria, it would be helpful for FDA to further clarify which meetings are appropriate at which point in the framework process. Clarification in this regard would not only be beneficial to sponsors, but also to FDA staff scheduling and conducting these meetings.

Greater Emphasis and Discussion on Pediatric Inclusion

Most rare diseases begin in childhood or exclusively affect children.[1] In many rare pediatric diseases, time is of the essence and delays in treatment result in irreversible disease progression. Yet pediatric patients are often excluded initially from drug development programs.

[1] C. E. Lee, et al. Rare Genetic Diseases: Nature's Experiments on Human Development. iScience, vol. 23. May 22, 2020. https://www.sciencedirect.com/science/article/pii/S2589004220303084

While the draft guidance does not specifically mention the case of "Baby KJ,"[2] during the unveiling of the draft guidance both FDA and HHS gave significant mention to him. Given that the case highlighted in the rollout of this draft guidance specifically involved an infant and that it is likely most treatments that will fall under the plausible mechanism framework will be developed for infants and children to achieve clinical results at the point of maximal impact, we urge FDA to emphasize early inclusion of children in individualized therapy development programs for early onset diseases and conditions. FDA can achieve this by adding substantially more discussion and detail about the application of this framework to the pediatric population, along with any unique considerations that developers will need to account for when designing a program intended under this framework. As it stands, the draft guidance only contains two mentions of pediatrics, and both are to remind sponsors to follow part 50, which is already required by law.

To further clarify FDA's intent, the Agency could consider providing specific examples in the pediatric context to articulate how the five criteria and requirements laid out in the draft guidance could be applied in pediatric diseases. Examples provided in other FDA guidances have provided useful context into FDA's thinking. FDA also could reference other guidances of relevance to pediatric populations to indicate that the thinking in these documents continues to apply (see appendix A below for suggested guidances for consideration).

Specific Considerations for Guidance

The Alliance offers the following comments on specific aspects of the draft guidance:

A. Regulatory Pathway

FDA notes that a traditional approval pathway or accelerated approval pathway may be used depending on the endpoints. FDA further notes that if accelerated approval is used, the Agency intends to require a confirmatory study is underway prior to accelerated approval action. FDA also notes that substantial evidence of effectiveness may be provided through a single adequate and well-controlled clinical investigation and that confirmatory evidence could come from clinical or non-clinical data sources.

[2] " Infant with rare, incurable disease is first to successfully receive personalized gene therapy treatment" NIH news release May 15, 2025. https://www.nih.gov/news-events/news-releases/infant-rare-incurable-disease-first-successfully-receive-personalized-gene-therapy-treatment

The Alliance is supportive of the long-established and statutorily created accelerated approval pathway[3] and that FDA continues to exercise regulatory flexibility for review within the accelerated approval pathway of treatments based on surrogate endpoints. Flexibility is critical for drug development programs involving pediatric populations, particularly in rare pediatric diseases, and the accelerated approval pathway is especially important for pediatric populations where endpoints may not demonstrate immediate clinical benefit. We appreciate FDA's specific recognition that accelerated approval is an option for drug programs under the Plausible Mechanism Framework. We also appreciate FDA stating that it will consider the level of unmet need and small sample sizes for treatments being developed by sponsors seeking to use the Plausible Mechanism Framework.

However, the Alliance urges FDA to consider greater flexibility and to provide greater clarity in outlining the criteria for "substantial evidence of effectiveness." For example, it is worth clarifying the extent to which FDA will rely on previous guidances that reference demonstrating substantial evidence of effectiveness, which is somewhat confusing in the draft guidance. Specifically, there is discussion on p. 3 lines 87-92 that states "it may be challenging to apply these approaches in the context of individualized therapies…" This is followed by discussion on p. 5 lines 163-166 that states "approval of an individualized therapy …require substantial evidence of the drug's effectiveness for use under the conditions prescribed, recommended, or suggested in the proposed labeling" and then references the statute and the draft guidance on *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*. Therefore, it is not clear if FDA will be relying on previous guidances or not, and subsequently what will be the Agency's expectations on sponsors in adhering to these guidances.

Generating a sizable treatment effect is very challenging in many rare disease drug development programs due to small and heterogeneous populations, age related variation, differences in disease progression, and limited disease characterization. It is seldom that there is such a significant physiological change, especially in rare pediatric diseases where children may still be asymptomatic or the disease has not yet progressed to profound damage. At the same time, it is essential that children be included early in clinical trials to proactively determine safety and dosing, and it is precisely at this stage when we can maximize the impact of the treatment in children to change the course of their disease. Several examples of treatments that have been

[3] 21 U.S.C. 356(c): Accelerated approval of a drug for a serious or life-threatening disease or condition, including a fast track product. https://uscode.house.gov/view.xhtml?req=(title:21%20section:356c%20edition:prelim)

administered before disease progression that have been life-changing are for infants and children for spinal muscular atrophy, type 1 diabetes, and cystic fibrosis.[4]

It is also important to consider patient and caregiver preferences for treatments and composite endpoints to better capture the clinical benefit of a treatment. For example, a treatment that has a marginal evidence of effectiveness but allows a child to attend school or improves the quality of life for the entire family, might be preferable to waiting for a cure, especially if no other treatments are available for that disease.[5] If the bar is too high to be achievable, the benefits of this new framework will not materialize, at the expense of hopeful patients. Therefore, the Alliance urges the Agency to encourage developers of individualized therapies to take a patient-centric approach and employ greater flexibility in determining what constitutes substantial evidence of effectiveness in line with the flexibilities already afforded the Agency in the statutory definition of substantial evidence in 21 U.S.C. 505(d).[6]

B. Nonclinical

FDA says the objectives for nonclinical programs are to demonstrate proof of concept and safety to support initiation of a first-in-human study. To do this, a non-clinical program should establish the feasibility of the proposed clinical route of administration, support the scientific rationale for product administration, and identify potential risks.

The Alliance appreciates the overall objective of the nonclinical section and the specific mention that nonclinical data may be supplied to demonstrate the prospect of direct benefit (PDB) for pediatric participation in first-in-human investigations in accordance with 21 CFR 50.[7] However, we encourage FDA to provide two or three examples of nonclinical data that could be used to support the determination of PDB. FDA could also consider discussing how the recommendations on PDB outlined in the 2022 draft guidance, *Ethical Considerations for Clinical Investigations of Medical Products Involving Children*, still apply to the Plausible Mechanism Framework and discuss any unique considerations for PDB, especially to identify the

[4] M. Summar, et al. Including children early in clinical trials: a scientific imperative. Pp. 4-7, 9-10. [In press, 2026.] Clinical Translational Science.

[5] M. Summar, et al. Including children early in clinical trials: a scientific imperative. P. 9. [In press, 2026.] Clinical Translational Science.

[6] 21 U.S.C. 505(d): (d) Grounds for refusing application; approval of application; "substantial evidence" defined. https://uscode.house.gov/view.xhtml?req=(title:21%20section:355%20edition:prelim)

[7] Part 50—Protection of Human Subjects. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50

appropriate treatment dosing and formulation, particularly with gene therapies that can only be administered once.

FDA also encourages the use of new approach methodologies (NAMs) whenever appropriate for nonclinical data. The Alliance is excited about the possibility for NAMs to bring more efficiencies and timeliness to drug development programs. We are encouraged by recent indications from the Commissioner that this is a priority for him. We're also happy to see the release of two recent guidances on NAMs [8,9]. However, we note that these guidances do not apply to cell and gene therapies. We urge FDA to publish guidance on NAMs for cell and gene therapy trials, and to consider specifically how NAMs for pediatric studies can be most effective. The Pediatric Inclusion Alliance has provided FDA with our views on this topic through a letter dated June 27, 2025.[10] We also note there needs to be greater flexibility in general for phase 1 clinical trials. Many phase 1 trials are conducted outside the U.S. because of the FDA's rigid requirements. We urge FDA to continue considering flexibilities and alternatives in this area.

C. Clinical

FDA indicates that a small number of patients are expected to be treated so early planning is critical to identify potential sources of safety and efficacy data, clinical outcomes, and biomarkers relevant to the disease. FDA also reiterates in this section that if children are involved in a study, the sponsor must comply with part 50.

As discussed above, the Alliance urges FDA to provide additional clarity on its standard for meeting "substantial evidence of effectiveness," including its statistical expectations in the context of small populations and single arm trials.

One of the criteria for utilizing the Plausible Mechanism Framework is "relying on a well-characterized natural history of the disease" and robust natural history data. Although natural history studies have the potential to provide an incredible amount of data and information on the progression and impact of diseases, there are lots of challenges with natural history studies,

[8] Monoclonal Antibodies: Streamlined Nonclinical Safety Studies. Draft Guidance for Industry. December 2025. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/monoclonal-antibodies-streamlined-nonclinical-safety-studies

[9] General Considerations for the Use of New Approach Methodologies in Drug Development. Draft Guidance for Industry. March 2026. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-considerations-use-new-approach-methodologies-drug-development

[10] Letter available at: https://leavittpartners.com/wp-content/uploads/2025/09/FINAL-PIA-Preclinical-WG_Animal-Letter.pdf

particularly for rare diseases. Not every rare disease is well-established. There are over 10,000 rare diseases,[11] some with very small populations or a subset of populations, and more rare diseases are being identified as science and knowledge evolve. For newer, less understood, or very rare diseases, it may not be possible to have a well-characterized natural history study. Consequently, making a well-characterized natural history a requisite will potentially make many drug development programs, especially those for ultra rare diseases, ineligible for the framework.

To avoid this, FDA should consider clarifying its expectations on the evidentiary bar for understanding disease progression and the Agency should show flexibility in how natural history studies capture data on the impact and trajectory of a disease. Given that FDA has issued draft guidance in 2019 on *Rare Diseases: Natural History Studies for Drug Development*, FDA should consider outlining in this guidance where the recommendations in the Natural History Studies guidance align with the expectations under the Plausible Mechanism Framework and where they differ. If they differ, FDA should explain why and clarify the new expectation being cognizant of the challenges and showing receptivity to flexibility.

Another topic that FDA should consider clarifying is the Agency's expectations on the use of well-characterized natural history studies while at the same time demonstrating substantial evidence of effectiveness, particularly as these requirements will be applied to pediatric populations. On p. 14 lines 488-490 FDA states, "When the effects of the drug on clinical outcomes are not obvious (e.g., because functional losses are more slowly progressive), robust natural history data will likely be necessary to serve as an external control." However, even with robust natural history data, it will be challenging to demonstrate substantial evidence of effectiveness if the natural history study is not contemporary. In other words, if the treatment is targeted to a young population but the disease progression is slow, the substantial evidence of effectiveness will not be seen until the child is older. For example, in Duchene Muscular Dystrophy (DMD), it could be several years after the treatment is administered before we see a change based on the impact of the therapy. Similarly, it could take years to see the impact of a treatment for limb girdle muscular dystrophy which is slowly progressive. We urge FDA to clarify these seemingly at odds recommendations and explicitly allow for generation of substantial evidence of effectiveness over time and supported with real world data, for slowly progressing diseases.

On p. 17 lines 608-609, FDA mentions that long-term follow up studies will be required for genetic editing products. However, there is no mention of what FDA's follow up requirements are

[11] Rare Diseases at FDA. https://www.fda.gov/patients/rare-diseases-fda#:~:text=on%20rare%20diseases?-,What%20is%20a%20rare%20disease?,a%20rare%20disease%20or%20condition. Accessed on April 5, 2026.

for antisense oligonucleotides (ASOs). FDA should consider including its requirements for follow up for ASOs to allow drug program sponsors to plan and assess resources accordingly.

FDA also should include information on any special or unique post-marketing follow-up requirements for pediatric populations, particularly if there are expectations that the pediatric population would transition to adults during the follow-up phase. FDA also should provide clarification on its receptivity and expectations for post-approval safety studies requirements using real world data.

E. Other Considerations

The Alliance is pleased that FDA talks about the importance of data sharing, encouraging shared learning through appropriate data sharing and incorporating language into informed consent documents to allow participants to share data for future research. We also are pleased this was the subject of the March 30, 2026 RISE workshop.[12] As we heard during the RISE workshop, with small patient populations, there may not be enough people to participate in several clinical trials, especially at the same time. Thus, it is imperative to collaborate and share data.

Yet, the collective experiences of several Pediatric Inclusion Alliance members have been that natural history data remains siloed, there is a reluctance among data holders to share information, and it is difficult and sometimes costly to access data across registries. There also are ethical concerns related to natural history data collection, ownership, and sharing.

To overcome some of these barriers, one suggestion is for FDA to incentivize sponsors to share data. FDA also could consider providing additional guidance to overcome some of the known challenges, such as standardization of data, privacy concerns, and informed consent.[13] FDA already provides guidance to sponsors on these topics and parameters when a sponsor is putting together their drug development program.

We recognize that some of these challenges are outside of FDA's purview. However, the Alliance urges FDA to consider providing additional guidance on appropriate data collection strategies, especially for rare disease populations, and any other aspects of data sharing that could help build capacity to develop the well-characterized natural history studies that FDA envisions. If a

[12] RISE Together: Data Sharing Across the Rare Disease Ecosystem. Duke Margolis Institute for Health Policy. March 30, 2026. https://healthpolicy.duke.edu/events/rise-together-data-sharing-across-rare-disease-ecosystem

[13] N. Pagliarulo. RISE workshop sees agreement on data sharing's benefits, but hurdles remain. AgencyIQ. April 2, 2026. https://home.agencyiq.com/article/0000019d-4f51-db6a-a3df-df53412d0001?subType=analysis&articleSource=aiq-analysis

legislative change is needed for FDA to obtain additional authorities to take a more proactive approach, we encourage FDA to work with Congress to request this. Patients are the source of this invaluable information, and we must maintain a collaborative community approach with the ultimate goal of benefiting patients.

Conclusion

Children deserve timely access to evidence-based therapies that are scientifically developed and tailored to pediatric patients. The Alliance believes that pediatric inclusion at the outset of a drug development program is the most effective way to achieve this goal and we appreciate the continued progress in FDA's thinking about pediatric inclusion.[14] Incorporating considerations and recommendations for pediatric inclusion throughout this guidance, offering greater clarity on FDA's recommendations, and allowing for flexibility where appropriate will further demonstrate FDA's recognition of the urgent need for safe and effective products to treat serious and severely debilitating diseases in small populations, including children.

The Alliance appreciates FDA's work on this important guidance. We look forward to future discussions with you as you finalize this and other guidance documents that will help ensure children, especially those with rare diseases, are included as early as possible in clinical trials. If you have any questions or would like to discuss this further, please contact Sara Singleton at Sara.Singleton@Leavittpartners.com.

Sincerely,

Ron Bartek
Co-Founder, President, Friedreich's Ataxia Research Alliance
Convenor, Pediatric Inclusion Alliance

Sara Singleton
Principal, Leavitt Partners
Co-Convenor, Pediatric Inclusion Alliance

[14] S. Usdin. How FDA plans to make room for kids. Biocentury. July 17, 2024. https://www.biocentury.com/article/652989/how-fda-plans-to-make-room-for-kids

APPENDIX A. FDA GUIDANCES RELATED TO PEDIATRIC POPULATIONS

1. Benefit-Risk Assessment for New Drug and Biological Products. Guidance for Industry. Oct. 2023.

2. Ethical Considerations for Clinical Investigations of Medical Products Involving Children. Draft Guidance for Industry, Sponsors, and IRBs. Sept. 2022.

3. FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making. https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

4. General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products. Draft Guidance for Industry. Sept. 2022.

5. Pediatric Drug Development: Regulatory Considerations – Complying with PREA and Qualifying for Pediatric Exclusivity Under the BPCA. Draft Guidance for Industry. May 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-drug-development-regulatory-considerations-complying-pediatric-research-equity-act-and

6. Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations. Draft Guidance for Industry. May 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-drug-development-under-pediatric-research-equity-act-and-best-pharmaceuticals-children-act

7. Pediatric Rare Diseases--A Collaborative Approach for Drug Development Using Gaucher Disease as a Model. Draft Guidance for Industry. December 2017. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-rare-diseases-collaborative-approach-drug-development-using-gaucher-disease-model-draft