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

RE: Docket No. FDA-2026-D-1257

Dear Sir or Madam,

On behalf of the Pediatric Inclusion Alliance, we are pleased to submit comments on FDA's Draft Guidance for Industry "Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing."[1]

As discussed during the September 2025 RISE workshop,[2] many rare diseases, particularly those affecting children, involve extremely small patient populations. In these settings, there may be insufficient numbers of patients to support multiple concurrent clinical trials, making efficient and scientifically sound development approaches essential. Leveraging prior knowledge has the potential to reduce unnecessary duplication, improve development efficiency, and accelerate patient access to safe and effective therapies, including for pediatric populations. The Alliance therefore appreciates FDA's efforts to provide greater clarity through this draft guidance and welcomes the opportunity to offer feedback.

About the Pediatric Inclusion Alliance

The Pediatric Inclusion Alliance[3] (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

[1] Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing; Draft Guidance for Industry. https://www.fda.gov/media/192810/download
[2] On the RISE: Controls in Rare Disease Clinical Trials for Small and Diminishing Populations. Sept. 3, 2025. https://healthpolicy.duke.edu/events/rise-controls-rare-disease-clinical-trials-small-and-diminishing-populations
[3] Pediatric Inclusion Alliance. https://leavittpartners.com/pediatric-inclusion-alliance/

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, 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 cell and gene therapy clinical trials.

General Considerations for Early Pediatric Inclusion

Most rare diseases begin in childhood or exclusively affect children.[4] For many of these conditions, delays in treatment can result in irreversible disease progression and lost developmental opportunities. Despite this reality, pediatric patients are often included only after adult development programs are well underway.

The Alliance appreciates that this guidance lays out opportunities for sponsors and stakeholders to consider leveraging prior knowledge in the development of human gene therapy products incorporating genome editing. However, the draft guidance notes that similar approaches may also be applicable to other cell and gene therapy platforms, such as adeno-associated viral (AAV) vector-based therapies, while leaving additional considerations beyond the scope of the document. Given that the PDUFA VII commitment letter references leveraging prior knowledge across cell and gene therapies more broadly,[5] we encourage FDA to expand the guidance or clarify how the principles outlined here may specifically apply to these related product types.

Specific Considerations for Guidance

Nonclinical

From a pediatric perspective, the Alliance is particularly interested in the discussion of how prior knowledge may be used to support dose selection and identification of appropriate patient populations. Notably, this section contains the most direct discussion of pediatric considerations within the draft guidance.

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[4] 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

[5] PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2023 THROUGH 2027. O.4. Leveraging Knowledge. https://www.fda.gov/media/151712/download?attachment (see p. 56)

FDA states that sponsors may, in some circumstances, leverage clinical data from adults in lieu of juvenile animal studies to support pediatric dose selection.[6] While we support efforts to reduce unnecessary studies and leverage existing evidence when scientifically justified, this approach may have limited applicability in many rare pediatric diseases, especially those that lack a relevant adult population or where disease progression differs significantly between children and adults. In these circumstances, the availability of prior knowledge from sources beyond adult clinical data becomes particularly important. We recommend that FDA provide additional examples and clarification regarding acceptable approaches for leveraging prior knowledge in pediatric rare diseases where adult data are unavailable or not readily extrapolatable.

The Alliance is encouraged by the draft guidance's recognition of New Approach Methodologies (NAMs) as a potential source of leveraged evidence. We strongly support FDA's continued efforts to advance NAMs, when appropriate, as a means of improving development efficiency while reducing reliance on traditional animal models. The Pediatric Inclusion Alliance has provided FDA with our views on this topic through a letter dated June 27, 2025, including the recommendation that FDA establish a data infrastructure that would allow for standardization and data sharing across academic and industry partners.[7] We urge FDA to continue considering flexibilities and alternatives in this area when appropriate.

Furthermore, while we were pleased to see FDA recently issue draft guidances addressing the use of NAMs in drug development,[8,9] these guidances do not specifically address cell and gene therapies. We therefore urge FDA to develop guidance describing how NAMs may be applied in the context of cell and gene therapy development, including considerations specific to pediatric populations. Having greater clarity regarding the role of NAMs in cell and gene therapy programs would facilitate broader and more consistent use of prior knowledge while supporting scientifically rigorous development strategies.

Clinical

The Alliance appreciates FDA's acknowledgment of the important role that natural history studies and real-world evidence can play in supporting product development. However, 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

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[6] Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing; Draft Guidance for Industry. https://www.fda.gov/media/192810/download (see p. 15)

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

[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

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.

As we stated in comments to other draft guidances, 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.[10] FDA already provides guidance to sponsors on these topics and parameters when a sponsor is putting together their drug development program. Moreover, the Alliance continues to urge 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. In that regard, the Alliance encourages the FDA to continue its support of the rare disease natural history data platform, the Rare Disease Cures Accelerator -- Data and Analytics Platform, and to urge additional disease groups to participate by submitting their natural history data so that such data sharing can result in significant learning across diseases. If a 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.

Additionally, the guidance would benefit from clarity regarding when clinical experience from other genome-editing or gene therapy products may support the development of a new product. While the draft guidance notes that data may be leveraged based on product- and disease-related similarities, it does not provide examples of the types of data that may be applicable or the factors FDA will consider when assessing similarity. FDA should consider providing examples of the clinical data that may be leveraged, such as safety, dose selection, clinical pharmacology, and immunogenicity data, as well as the degree of similarity expected between products and patient populations. Clarification regarding similarities in editing technologies, delivery platforms, target genes, diseases, and age groups would help sponsors appropriately utilize existing clinical experience and support more efficient platform-based development of future gene therapies.

Finally, while we are encouraged that draft guidance discusses opportunities to leverage prior knowledge when designing long-term follow-up programs, the recommendation that FDA may reconsider the type, frequency, and duration of follow-up based on accumulating safety data would benefit from additional specificity. Greater clarity regarding the circumstances under which long-term monitoring requirements may be modified would improve predictability for sponsors and facilitate more efficient study planning. We also encourage FDA to address pediatric-specific considerations, including situations in which participants enrolled as children transition into adulthood during the follow-up period. Clarification regarding how prior

[10] 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

knowledge may be leveraged in these circumstances could help reduce unnecessary burden while maintaining appropriate long-term safety oversight.

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.[11]

We encourage FDA to strengthen this guidance by incorporating pediatric considerations throughout the document, providing additional clarity regarding acceptable uses of prior knowledge in pediatric drug development programs, and expanding discussion of how these recommendations apply across cell and gene therapies more broadly.

The Alliance appreciates FDA's leadership on this important issue and looks forward to continued engagement as the Agency finalizes this guidance and advances policies that will help ensure children, particularly those with rare diseases, gain earlier access to safe and effective therapies at the point of maximum impact for them.

If you have any questions or would like to discuss this further, please contact Sara Singleton at Sara.Singleton@Leavittpartners.com.

Sincerely,

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Convenor, Pediatric Inclusion Alliance

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[11] 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