November 24, 2025

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

RE: Docket No. FDA-2025-D-3049: Postapproval Methods to Capture Safety and Efficacy Data for Cell and Gene Therapy Products; Draft Guidance for Industry

Dear Sir or Madam,

On behalf of the Pediatric Inclusion Alliance (Alliance), we are pleased to submit comments on FDA's "Postapproval Methods to Capture Safety and Efficacy Data for Cell and Gene Therapy Products," Draft Guidance for Industry. We appreciate FDA's attention to the need for robust long-term monitoring for transformative cell and gene therapy products. Of specific importance for the Pediatric Inclusion Alliance are efforts that ensure children are included in clinical trials at the outset and are subsequently monitored for as long as possible to determine the impact of treatments.

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 cellular and gene therapy clinical trials.

Alliance Recommendations

The Alliance appreciates and agrees with the additional considerations discussed in the background section on page 2 relating to pediatric patients and the need for long-term, possibly lifetime, monitoring for outcomes. We also appreciate that FDA has flagged the need for sponsors to consider transition from child to adult care when determining approaches to long-term follow-up.

We appreciate the flexibility to utilize several methods and approaches to data collection. Having a range of options is useful in rare pediatric diseases where there is great need for well-developed data sources. Our Alliance wishes to emphasize the critical role of prospective and retrospective natural history studies and registries in patients who have never been treated with CGT, as these studies are essential for defining appropriate long-term outcomes for post-approval monitoring. Natural history studies also can provide comparator data to understand what is changing because of the disease vs. the treatment vs. normal development. Natural history studies are particularly important for slowly progressive, pediatric-onset diseases in which reliably measurable phenotypes may take many years to emerge. The real-world data (RWD) generated through these studies can provide the real-world evidence (RWE) needed to establish valid outcome measures tailored to each participant's age and disease stage at the time of treatment. Accordingly, we recommend encouraging study sponsors to incorporate data from natural history studies into their post-approval monitoring strategies for CGT. We also encourage FDA to cross reference the 2019 Draft Guidance: "Rare Diseases: Natural History Studies for Drug Development," in which FDA states that data from natural history studies can be used to provide information during the postmarketing period.[1]

[1] FDA. Rare Diseases: Natural History Studies for Drug Development. Draft Guidance for Industry, (see p. 3 lines 70-72). March 2019. https://www.fda.gov/media/122425/download

In November 2025, FDA announced a *plausible mechanism pathway*, which discusses the importance of having a well-characterized natural history study as one of the five key elements of being able to utilize this pathway, as well as how sponsors will have a postmarketing commitment which will include collecting RWE.[2] The timing of this newly announced pathway is apropos to the solicitation of input into this guidance. Therefore, we encourage FDA to use the opportunity of this guidance to provide additional details on how natural history studies and postmarketing commitments requiring RWE collection can be maximized for sponsors to take advantage of the *plausible mechanism pathway*.

We also request that FDA clarify that they are open to longer-term data collection for programs, especially for younger pediatric populations, seeking accelerated approval based on biomarkers, surrogate endpoints, or intermediate clinical endpoints as discussed in both FDA guidances: Accelerated Approval – Expedited Program for Serious Conditions and Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies.[3,4]

Within section C. *Use of Registries*, beginning on page 4, we encourage FDA to clarify the type of registries to which it is referencing. For example, are you referring to disease state registries, medical product specific registries, or both? The guidance provides an example of the Coordinated Registry Network (CRN) which appears to include device-specific registries. Drug-specific registries have a number of challenges and are limited in scope, whereas disease state registries contain more information specific to the patient population and disease, and thus are more useful for capturing information. If FDA is referring to disease state registries in this guidance, also consider referencing the Rare Disease Cures Accelerator Data and Analytics Platform (RDCA-DAP) alongside the discussion of the CRN. We believe a mention of the RDCA-DAP would be appropriate since it is an FDA-sponsored initiative to standardize, and share data on rare diseases with the goal of accelerating treatments.[5] FDA also should consider noting that uncurated patient

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[2] V. Prasad, M.A. Makary. FDA's New Plausible Mechanism Pathway. The New England Journal of Medicine. Nov 12, 2025. https://www.nejm.org/doi/abs/10.1056/NEJMsb2512695

[3] Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies. Guidance for Industry. March 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/slowly-progressive-low-prevalence-rare-diseases-substrate-deposition-results-single-enzyme-defects

[4] Accelerated Approval – Expedited Program for Serious Conditions. Draft Guidance for Industry. Dec. 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/accelerated-approval-expedited-program-serious-conditions

[5] Critical Path Institute. Rare Disease Cures Accelerator-Data and Analytics Platform. https://c-path.org/program/rare-disease-cures-accelerators-data-and-analytics-platform/ Accessed on October 29, 2025.

reported data will be less valuable in establishing safety and efficacy than data entered in a rigorous natural history registry with defined data elements.

Conclusion

Children with rare diseases, particularly those with early onset and rapid progression, deserve timely access to evidence-based therapies that are scientifically developed and tailored to pediatric patients. Given the transformative potential for cell and gene therapy products, we support FDA's recommendations that children should be included in trials and therefore also in post approval monitoring efforts that may necessitate monitoring and collection of long-term outcomes.

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 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,

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