Via Electronic Submission

June 27, 2025

Food and Drug Administration Leadership
10903 New Hampshire Avenue
Silver Spring, MD 20993

National Institutes of Health Leadership
1 Center Drive
Bethesda, Maryland 20892

RE: FDA and NIH Announcements to Phase Out Animal Studies in Preclinical Development

Dear Dr. Prasad,

On behalf of the Pediatric Inclusion Alliance[i] (Alliance), we are writing in response to the recent announcements by the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) prioritizing the accelerated development and use of human-based technologies to replace animal testing in preclinical medical research. The Alliance seeks to continue working closely with FDA, NIH, and all stakeholders in medical product development to maximize the ability of preclinical testing platforms to provide the data necessary to enable the early inclusion of pediatric subjects in clinical trials. This letter outlines the unique considerations for the pediatric population that the Alliance encourages FDA and NIH to consider as they work to prioritize human-based technologies in preclinical development.

Background on Recent Policy Announcements

On April 10, 2025, FDA announced its "Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs."[ii] The associated "Roadmap to Reducing Animal Testing in Preclinical Safety Studies"[iii] (Roadmap) proposes to replace animal testing with new approach methodologies (NAMs), to include organ-on-a-chip systems, computational modeling, and advanced in vitro assays. The goal of the Roadmap is to advance the use of NAMs to evaluate safety in humans, including immunogenicity, toxicity, and pharmacodynamics studies, and increase the predictive relevance of preclinical drug testing.

Additionally, on April 29, 2025, NIH released a statement closely aligned with FDA's, announcing adoption of a new initiative to prioritize expansion of innovative, human-based technologies for preclinical testing while reducing the use of animals in medical research. NIH Director Dr. Jay Bhattacharya stated, "For decades, our biomedical research systems have relied heavily on animal models. With this initiative, NIH is ushering in a new era of innovation." He continued, "By integrating advances in data science and technology with our growing understanding of human biology, we can fundamentally reimagine the way research is conducted—from clinical development to real-world application. This human-based approach will accelerate innovation, improve healthcare outcomes, and deliver life-changing treatments. It marks a critical leap forward for science, public trust, and patient care."

About the Pediatric Inclusion Alliance

The Alliance is a multistakeholder group comprised of more than 25 organizations representing industry, patient and disease organizations, academic medical centers, clinical trial designers, bioethicists, regulatory consultants, and IRBs. The 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. The Alliance is committed to ensuring that children have the earliest opportunity to access safe and effective therapies, at the time when those therapies are most likely to have the maximum benefit to them. Of pertinence here, one of the Alliance's initial priorities—being handled by the Preclinical Data and Endpoints Workgroup—is furthering conversations about the preclinical studies, data, and evaluations needed to advance earlier pediatric inclusion in clinical trials. The workgroup is comprised of experts in preclinical requirements, data, and endpoints for pediatric product development.

With this focus in mind, the Alliance urges careful consideration of the importance of the earliest possible inclusion of children in clinical trials as the NIH and FDA move forward in phasing out animal testing in preclinical safety studies in favor of human-based platforms. Accordingly, the Alliance invites your attention to the following background and policy considerations pertaining to preclinical testing data needed to enable early pediatric inclusion.

Background on Pediatric Clinical Development

Traditionally, animal models have been a prerequisite in most drug development processes for the sponsor to advance to first-in-human trials, and this has generally also been true for pediatric trials. However, studies in juvenile animals or other systems that predict effects in pediatric populations—and so could inform early studies in pediatric populations and/or de-risk initiation of such studies—are frequently de-prioritized given costs and perceived risks.

This historical prioritization of adult populations has left pediatric patients with few therapeutic options other than relying on off-label medications untested in their age groups. These therapies, if studied and administered earlier, might well have been even more effective for younger children. Additionally, for many conditions, the point of maximal benefit for a pediatric therapy is much earlier than the ages traditionally studied in clinical trials for regulatory approval.

Moreover, in many cases, conducting lengthy studies in adults prior to enrolling pediatric subjects runs a serious double risk. First, there is a likelihood that the adult—who may be in the later stages of disease—will not manifest the benefits that would be potentially demonstrated at the point of maximal benefit in children. Second, the safety signals obtained in adult data are not necessarily predictive of those observed in children. These scenarios highlight the distinct set of issues that pediatrics face and the unique environment for both drug development generally and preclinical studies more specifically.

Policy Considerations

It is essential that we develop safe and effective therapies for children in order to treat them at the best time for them, which requires improved preclinical testing platforms that enable the inclusion of children earlier in clinical trials. As FDA and NIH implement their recent initiatives and increasingly consider NAMs in preclinical studies, the Alliance encourages these agencies to take into account special considerations and implications for the pediatric population:

- **Include Pediatrics at the Forefront of Alternative Model Design Development:** As FDA bolsters NAMs, these alternative models should be explicitly and intentionally designed to incorporate pediatrics from the start, including those focused on safety, as the FDA and NIH announcements plan, as well as NAMs focused on pediatric efficacy as advancements in the field allow. While it is unlikely that an effective transition from animal studies to NAMs in children can be as expeditious as the transition in some drug classes for adults, NAMs offer more predictive and human-relevant ways to conduct preclinical studies that have the potential to be leveraged in children. Given the other considerations noted below, this transition should not be made prematurely, and animal studies should be continued as necessary until pediatric data for NAMs is sufficiently robust to make the transition. However, given the potential, the Alliance recommends FDA create a plan *now* to ensure the future and effective use of NAMs in children once appropriate.
- **Address the Issue of Limited Existing Data in Pediatric Drug Development:** Given the limitations in pediatric drug development and heightened off-label use of products, existing data on pediatric subjects is limited. Because AI requires large datasets to accurately predict and generalize to the pediatric population, the near-term use of AI as a NAM will present challenges. We therefore urge FDA and NIH to:
    - Press for rapid development of NAMs that provide the information necessary to conduct clinical trials in pediatric patients;
    - Establish a data infrastructure that would allow for standardization and data sharing across academic and industry partners; and
    - Not require reliance on NAMs alone where they are not suited to provide the preclinical information necessary to conduct clinical trials in pediatric patients.
- **Encourage Collaboration with Global Regulatory Agencies:** Collaboration with global regulatory agencies could help expedite the use of NAMs in trial development. For example, global databases would make a greater amount of information available to FDA, NIH, and industry and academic partners, and could encourage industry partners to provide a wide array of data when making a submission. This information could then be leveraged to bolster the datasets needed to validate submissions using a NAM.
- **Take Into Account Pediatric Ethics:** Children are often granted greater protections in drug development given their vulnerability and inability to fully consent to research, especially under the ethics principal of "do no harm" and how that has been interpreted in

children.[iv] Given this higher bar, it is vital that appropriate data is available and suited to reducing risks to children participating in clinical trials. Further, robust data—whether from animal models or other preliminary data sources—to bolster NAM databases is a requirement to ensuring the appropriate risk tolerance between protecting children and leveraging new technologies, keeping in mind that the objective is to include children in clinical trials as early as possible so as to provide them with safe, effective therapies at the best time for them.

- **Recognize that Animal Models are Not Always the Best Predictor of Efficacy in Pediatrics:** As FDA's plan indicates, it is true that animal models have inherent limitations around reliably predicting the toxicology and pharmacology of a drug in humans; often, different species experience drug effects differently. For example, in a study assessing the relationship between preclinical animal models and Phase 1 toxicology studies in more than 100 oncology trials, researchers found that "animal toxicity did not show strong correlation with human toxicity."[v] A 2021 paper detailed the limitations in animal models, highlighting, "many nonclinical models have limitations and are not reliable surrogates of the complex human condition, so the ultimate value of the model is grounded in its relevance to the question(s) the study is designed to address."[vi] Therefore, addressing the policy considerations listed in this letter are important to expedite the ability to leverage NAMs in place of certain preclinical animal studies in pediatric clinical trial development.
- **Assess How NAMs May Support the Prospect of Direct Benefit:** In pediatric research, the prospect of direct benefit is an integral ethical and regulatory threshold for advancing new therapies when there is more than minimal risk involved in a study.[vii] Preclinical data is important to support the prospect of direct benefit before beginning in-human studies, though, as discussed in this letter, establishing these data through existing methods can be challenging. Therefore, NAMs have the potential to bolster the preclinical data needed to meet the prospect of direct benefit threshold since they offer more human-relevant and predictive data at the preclinical stage. As FDA and NIH expand NAMs, they should consider the connection between NAMs, pediatric preclinical studies, and the prospect of direct benefit.
- **Expand Platform Approaches for Conditions with Early Childhood Onset:** For rare disease therapies, including gene therapies, patients, industry, and FDA have recognized that platform approaches will be necessary to effectively streamline the development of treatments for small disease populations.[viii] Platform technologies are an important advancement to increase efficiency of clinical development through reproducibility and adaptability, with specific opportunity in gene therapy, in addition to drugs. Further, many of the conditions that could benefit from platform approaches and NAMs are conditions with early childhood onset. Therefore, FDA and NIH should incentivize research into and expand platform approaches for conditions impacting pediatrics.
- **Ensure FDA and NIH Collaboration With Each Other and the Community:** As FDA and NIH expound on their proposed methods to embrace NAMs, the agencies should collaborate with each other and the community to define where there are opportunities and technologies that exist to embrace earlier pediatric inclusion.[ix] Additionally, through

early and extensive collaboration between FDA and sponsors—especially during the period of transition from animal to NAM preclinical testing—an understanding should be achieved as to what level of NAM and/or animal testing will be required to enable clinical research with the maximum prospect of safe, effective therapies for adults and children. A lack of effective communication channels can unnecessarily lead to greater generation of data than FDA would otherwise require from a sponsor. Through communication from and collaboration with FDA, sponsors can better curate preclinical studies to only use animal testing to fill identified gaps in data.

We welcome the opportunity to discuss these issues further with NIH and FDA leadership.

Sincerely,

The Pediatric Inclusion Alliance*

*For a list of our members and additional information, please visit our website: https://leavittpartners.com/pediatric-inclusion-alliance/

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[i] https://leavittpartners.com/pediatric-inclusion-alliance/
[ii] https://www.fda.gov/news-events/press-announcements/fda-announces-plan-phase-out-animal-testing-requirement-monoclonal-antibodies-and-other-drugs
[iii] https://www.fda.gov/media/186092/download?attachment
[iv] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ethical-considerations-clinical-investigations-medical-products-involving-children
[v] https://www.nature.com/articles/s41416-020-01033-x
[vi] https://pmc.ncbi.nlm.nih.gov/articles/PMC8262097/
[vii] https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50/subpart-D
[viii] https://www.genengnews.com/topics/genome-editing/peter-marks-outlines-fdas-commitment-to-advancing-gene-therapies/
[ix] https://www.statnews.com/2025/05/19/animal-models-testing-nih-fda-pharma-drug-discovery-fda-nih-congress/