PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

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Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

RE: Draft Guidance for Industry; "Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause" FDA-2026-D-1256

To Members of the FDA:

Public Responsibility in Medicine and Research (PRIM&R), which has more than 3,500 active members throughout the research enterprise, appreciates the opportunity to respond to the FDA's Draft Guidance regarding the Plausible Mechanism Framework (FDA-2026-D-1256).

PRIM&R is a nonprofit organization dedicated to advancing the highest ethical standards in the conduct of research. Since 1974, PRIM&R has served as a professional home and trusted thought leader for the research protections community. PRIM&R seeks to ensure that all stakeholders in the research enterprise appreciate the central importance of ethics to the advancement of science.

As stated in the RFI, "FDA is announcing the availability of a draft document entitled 'Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause.' The draft guidance describes considerations for generating substantial evidence of effectiveness and evidence of safety of individualized therapies based on a plausible mechanism framework. The guidance specifically discusses genome editing and RNA-based therapies; however, the general concepts may apply to other types of individualized therapies. Specifically, the draft guidance applies when clinical evidence from a limited number of patients will be available to support the individualized product's safety or efficacy in the intended patient population."

We would like to highlight some areas and aspects that we feel could be strengthened in the FDA's Draft Guidance.

The guidance should define clear eligibility thresholds for when the framework applies. Without explicit limits on patient population size, the use of plausible mechanism framework risks

extending to situations where randomized controlled trials remain feasible, weakening existing standards in ways that could be detrimental.

PRIM&R's members, many of whom serve on IRBs throughout the United States, need clear standards to fulfill their oversight responsibilities. This guidance presents an opportunity for the FDA to clarify whether all criteria must be met and what is required before proceeding with the plausible mechanism framework.

The Draft Guidance states the following in lines 449-452:

> *In accordance with 21 CFR 50.20, the sponsor must obtain legally effective informed consent that includes all the required basic elements under 21 CFR 451 50.25(a) from the trial participant, or the participant's legally authorized representative, before administration of the investigational product.*

Notably, the draft guidance's discussion of informed consent, above, does not address assent for pediatric patients, which is required under Subpart D when an IRB determines it is appropriate. This omission should be corrected in the final guidance.

Additionally, this section of the draft guidance, beginning at line 439, "Ethical and Human Subject Protection Considerations," is relatively limited because it cites only regulatory requirements while not acknowledging that studies involving rare, genetically linked diseases often raise complex ethical issues. In such cases, consultation with clinicians, patients, parents and families, as well as ethicists may be beneficial.

In addition to definitional clarity, PRIM&R would like to note, when a Randomized Controlled Trial (RCT) is not possible, sponsors typically rely on natural history studies as a comparator for the therapy being tested. As the U.S. Department of Health and Human Services, explain, "a natural history study is a preplanned observational study intended to track the course of the disease. Its purpose is to identify demographic, genetic, environmental, and other variables (e.g., treatment modalities, concomitant medications) that correlate with the disease's development and outcomes. Natural history studies are likely to include patients receiving the current standard of care and/or emergent care, which may alter some manifestations of the disease."[1]

Many, if not most, rare diseases exhibit substantial variation in natural history. This represents an area in which the FDA has been inconsistent, and the current guidance presents an opportunity to provide clarification. The draft guidance can do more in clarifying what the options are for those cases.

In reading this draft guidance, PRIM&R appreciates that the guidance encourages the following to address key risks of gene editing (GE) therapies: long-term follow-up studies to collect data

[1] U.S. Department of Health and Human Services; National Center for Advancing Translational Sciences (NCATS) https://toolkit.ncats.nih.gov/glossary/natural-history-study/

on delayed adverse reactions; and the use of subject-level stopping rules that allow for clinical judgement.

These provisions reflect the type of careful, participant-centered thinking that should guide the framework as it continues to develop.

We hope our comments are useful to the FDA. PRIM&R stands ready to provide any further assistance or input that might be of use. Thank you for the opportunity to provide feedback on this critical issue and for your commitment to advancing ethical research practices.

Sincerely,

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