American Society of Hematology
Helping hematologists conquer blood diseases worldwide

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Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: General Considerations for the Use of New Approach Methodologies in Drug Development; Draft Guidance FDA-2025-D-6131

Dear Dr. Makary:

The American Society of Hematology (ASH) appreciates this comment opportunity on the U.S. Food and Drug Administration's (FDA) draft guidance for *General Considerations for the Use of New Approach Methodologies in Drug Development*, *FDA-2025-D-6131*.

ASH represents more than 18,000 clinicians and scientists committed to studying and treating blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as classical hematology (non-malignant) conditions like sickle cell disease. In addition, hematologists are pioneers and innovators in the fields of stem cell biology, transfusion medicine, and gene and cell therapies. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients.

The Society appreciates the opportunity to comment on this important and timely draft guidance. Animal models are essential for understanding disease pathophysiology and for assessing potential therapeutic options for the treatment of human diseases. However, in situations where animal models fail to adequately reflect human disease biology or drug behavior assessing the validity of emerging new tools for drug development, is important. It aligns with broader efforts to modernize research approaches and enable more predictive, human-relevant methods. We support the draft guidance overall and provide the following comments to strengthen its applicability to the development and innovation of treatments for hematology diseases and conditions.

Role of New Approach Methodologies (NAMs) in Hematology: Beyond Toxicity, Including Efficacy

While the draft guidance appropriately emphasizes safety, NAMs can also provide important efficacy-related insights. Organoid models in other therapeutic areas (e.g., lung organoids that correlate in vitro responses with clinical responses to COVID-19 therapies) illustrate how human-derived systems can predict treatment effect and inform patient selection or regimen optimization. In hematology specifically, bone marrow organoids and "marrow-on-a-chip" could be valuable in helping the field understand disease development, and could inform the design on new therapies, as well as help to predict response to said therapies. We encourage the agency to ensure that guidance considers these types of models.

We recommend that the final guidance explicitly recognize NAMs' dual role in supporting both toxicity and efficacy assessment and provide at least a few brief examples to illustrate how the FDA would view NAMs' efficacy data being integrated in the drug development process.

Validation, Current Limitations, and Avoiding Unintended Barriers

ASH agrees that rigorous evaluation and validation of NAMs are essential. However, in practice, few NAM assays are yet fully validated, and it is often unclear what the appropriate benchmark should be. ASH recommends that FDA clearly state in the final guidance that there are currently no robust tests or assays available to validate existing NAMs, and the Agency should explicitly underscore this point in the guidance to avoid unintended barriers.

Without this clarity, there is a risk that the guidance, while supportive in principle, could impede rather than accelerate innovation if sponsors are unsure how to design clinical trial programs that will meet FDA regulatory expectations.

Where NAMs Already Add Clinically Meaningful Safety Insight

Several NAM approaches already contribute meaningfully to safety assessment in ways that are complementary, and sometimes superior to traditional animal studies. We highlight two broad categories:

1. **Advanced in vitro systems**
   Three-dimensional organoids and functional in vitro models preserve aspects of tissue architecture, cell to cell interaction, and physiologic function. They can move beyond simple measures of cell death to capture clinically relevant endpoints such as barrier integrity, con tractility, cytokine production, and lineage-specific differentiation. In hematology, bone marrow organoids or marrow-on-chip systems are applicable models.

2. **Computational and in silico models**
   In defined contexts, in silico models already play a significant role in regulatory decisions. Examples include:

   - Cardiac safety modeling for QTc prolongation, a known concern for many targeted oncology agents.
   - Myelosuppression models (e.g., the Friberg model) that predict the depth and duration of neutropenia and inform dose and schedule selection.
   - Integrated PK/PD models that relate exposure to toxicity and can guide safer starting doses and escalation schemes.

   In these settings, NAMs can provide information that is at least comparable to, and sometimes more mechanistically or clinically translatable than conventional animal data. We encourage FDA to include and highlight a few such "mature" use cases as positive exemplars for sponsors in the final guidance.

Recognizing Areas Where NAMs Are Complementary, Not Substitutes

ASH believes it is important to acknowledge that current NAMs are not yet sufficient to replace all aspects of systemic evaluation, particularly for:

- Drug metabolism and pharmacokinetics/pharmacodynamics (DMPK).
- Comprehensive, multi-organ toxicology.
- Complex immune-mediated toxicities (e.g., CAR T–cell–related cytokine release syndrome and neurotoxicity, or transplant-related toxicities), which depend on dynamic, system-level immune interactions.

Experience in drug development has shown that "curing cancer" in preclinical models whether in mice or in vitro does not guarantee clinical success. However, these preclinical animal models have provided the theoretical basis for the generation of a number of therapies. For example, preclinical animal models have provided a fundamental basis for the field of allogeneic hematopoietic cell transplantation and continue to be critical for the development of new

concepts. For the near future, success in NAMs alone should not be considered sufficient evidence of safety or efficacy. NAMs are powerful tools, but they must be interpreted alongside, instead of, essential systemic data obtained in living organisms.

For hematologic malignancies and systemic non-malignant blood disorders, this point is especially salient. These diseases are often diffuse and systemic rather than localized to a discrete tumor mass. As a result, understanding distribution, metabolism, and multi-organ toxicity in a whole organism remains critical. We therefore urge FDA to make clear that, while NAMs may replace some traditional in vitro and selected in vivo studies, they cannot fully supplant in vivo drug metabolism and pharmacokinetics (DMPK) and core systemic toxicology at this time.

Integration of Multiple Data Sources and Impact on Investigational New Drug (IND) Decisions

One of the most constructive themes in the draft guidance is the emphasis on integrating multiple data sources and interpreting results within the broader drug development cycle rather than relying on any single method in isolation. ASH strongly endorses this principle and recommends that it be presented as the central conceptual framework for NAM use.

From the perspective of clinical investigators and sponsors, however, the current draft remains somewhat abstract regarding how NAM data will concretely influence IND decisions. It can be difficult to infer:

- Under what specific circumstances NAM data might substitute for, reduce, or augment certain animal studies.
- How NAM-derived findings will be weighed relative to traditional nonclinical data at key decision points (e.g., first-in-human dose justification, expansion cohort dosing, or risk mitigation strategies).

To address this, the draft guidance would benefit from inclusion in the final guidance and supporting materials, disease and context-specific examples illustrating acceptable uses of NAMs. While we appreciate the Agency's emphasis on flexibility, the current high-level framework may create uncertainty for sponsors regarding evidentiary expectations, particularly for complex or systemic diseases like those within the field of hematology. We encourage FDA to provide illustrative case studies or example data packages demonstrating how NAMs can be appropriately integrated with traditional nonclinical and clinical data, including considerations for validation, reproducibility, and regulatory decision-making. At the same time, we emphasize that NAMs should not be used in isolation, as comprehensive evaluation of pharmacokinetics, toxicity, and systemic effects remains essential. Additional clarity in this area would help reduce ambiguity, support innovation, and promote more efficient and predictable regulatory pathways.

Thank you again for the opportunity to provide these comments. Please consider ASH a resource; we would be pleased to provide additional information or support. If you have any questions, please use ASH Director of Government Relations and Public Health, Stephanie Kaplan (*skaplan@hematology.org*) as your point of contact.

Sincerely,

Robert Negrin, MD
President