American Association for Cancer Research®
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615 Chestnut Street | 17th Floor
Philadelphia, PA 19106-4404
215-440-9300 | 215-440-9313 Fax
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Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2025-D-6131, "General Considerations for the Use of New Approach Methodologies in Drug Development; Draft Guidance for Industry"

To Whom It May Concern:

On behalf of the American Association for Cancer Research (AACR), the world's oldest and largest scientific organization dedicated to cancer research, education, and collaboration, we appreciate the opportunity to provide comments on FDA's draft guidance entitled "General Considerations for the Use of New Approach Methodologies in Drug Development." We commend the Agency for issuing this important guidance, which represents a meaningful step toward advancing the integration of human-relevant, nonanimal methods into drug development.

New Approach Methodologies (NAMs) are increasingly important across oncology drug development, including applications in predictive toxicology, mechanism-of-action studies, dose selection, and evaluation of complex or novel therapeutic modalities. The AACR supports FDA's efforts to provide a structured framework that promotes scientific rigor while maintaining the flexibility necessary to foster innovation and improve patient-centered drug development.

As a consortium of academic investigators, industry professionals, and patient advocates committed to advancing cancer research, we respectfully offer the following comments and recommendations to strengthen the draft guidance:

1. Reinforcing a Risk-Based, Fit-for-Purpose Framework
The AACR appreciates the guidance's recognition that NAMs do not require full validation for all regulatory applications and may be used within a fit-for-purpose framework. However, additional clarification would help ensure that the validation considerations outlined in Section III are interpreted as guiding principles rather than a prescriptive checklist. We recommend reinforcing throughout the guidance that validation should be context-dependent and risk-based, and that "fit-for-purpose" represents the conclusion derived from context of use, human biological relevance, and technical characterization, rather than an independent requirement.

2. Definition and Scope of NAMs
The AACR appreciates the inclusion of a working definition of NAMs. However, the definition provided in the draft guidance is narrower than those used in prior FDA and international discussions, which may create challenges for consistency and global harmonization. We recommend that FDA provide a clear, finalized Agency definition of NAMs, clarify the scope of methods included in this guidance, and consider focusing the document primarily on in vitro NAMs, given that in silico approaches are addressed in other regulatory frameworks.

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3. Context of Use (CoU) Considerations
The AACR agrees that CoU is foundational to the evaluation of NAMs. Additional clarity regarding how CoU should be defined in practice would enhance regulatory predictability. We recommend providing more specific, decision-oriented examples of CoU, greater alignment with structured regulatory programs such as ISTAND, and clearer expectations regarding how CoU informs evidentiary standards.

4. Role of Comparators and Human Biological Relevance
The AACR appreciates the discussion of comparative performance with traditional methods. However, direct comparison with animal models may not always be appropriate, particularly where such models are known to have limited predictive value for human outcomes. We recommend that the guidance emphasize human biological relevance and predictive performance as primary considerations, encourage the use of well-characterized reference compound sets to evaluate model performance as described in ICCVAM guidance, and avoid default reliance on comparison to traditional animal models when those models may not be informative.

5. Weight-of-Evidence (WoE) Framework
The AACR strongly supports the placement of NAMs within a WoE framework, recognizing that their value lies in how they contribute to the overall understanding of a drug's safety profile. We recommend reinforcing that NAMs should be evaluated in the context of the full evidentiary package and that their contribution should be assessed based on how they inform regulatory decision-making alongside other data sources.

6. Clarification of Submission Expectations
To facilitate consistent implementation, additional clarity regarding submission expectations would be valuable. We recommend that FDA clarify the appropriate format and location of NAM data within regulatory submissions, expectations for study documentation and reporting, and how NAM data should be presented to support regulatory review.

7. Applicability Beyond Technology
While the guidance appropriately focuses on toxicology, the AACR notes that NAMs have broader applicability across drug development, including in pharmacology, efficacy, and product quality. We recommend that FDA consider clarifying that these principles may be adaptable to other domains, with appropriate risk-based considerations

8. Cross-Center Alignment
We appreciate that this guidance is issued by CDER and recognize the thoughtful work that has gone into its development. Given the growing importance of NAMs in areas such as cell and gene therapy, we believe there may be opportunities for alignment across FDA Centers that could benefit the broader community. We would welcome continued dialogue between CDER and CBER on these approaches and would appreciate any clarification on applicability across

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different product types where it might be helpful.

9. Specific Technical Clarifications

The AACR offers the following targeted recommendations to improve clarity and flexibility within the guidance:

- **Lines 73–74:** We recommend considering the removal of language that implies NAMs must "improve" predictivity to be acceptable.
- **Line 77:** We suggest explicitly referencing INTERACT and pre-IND meetings as engagement pathways.
- **Lines 108–109:** These lines would benefit from clarification regarding expectations for review of ISTAND-qualified NAMs.
- **Lines 153, 160, and 179:** We recommend broadening the terminology from "toxicities" to "drug responses."
- **Lines 204–207:** These lines could be improved by replacing "dose" with "concentration" for in vitro methods.
- **Lines 212–213:** We suggest adding flexibility for predictive performance metrics "if possible."
- **Lines 224–225:** These lines would benefit from qualifying expectations regarding biological variability with "if known."
- **Lines 239–242:** We recommend allowing grouping of technical factors rather than requiring individual assessment.
- **Line 265:** We propose reinforcing integration within the overall WoE framework.

Conclusion

The AACR appreciates FDA's forward-looking approach to this important guidance. NAMs are central to advancing more predictive, human-relevant, and efficient drug development. We support the Agency's efforts to clarify regulatory expectations while maintaining the flexibility necessary to foster innovation. We thank FDA for its continued leadership in regulatory science and look forward to ongoing collaboration.

Sincerely,

Kenneth Anderson, MD
Chair, Regulatory Science and Policy Subcommittee
The American Association for Cancer Research