18 May 2026

Dockets Management Staff (HFA-305)
Food and Drug Administration
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 Guidance for Industry

To whom it may concern:

The International Society for Stem Cell Research (ISSCR) Consortium on Advanced Stem Cell-Based Models in Drug Discovery and Development appreciates the opportunity to comment on the Food and Drug Administration's (FDA) draft guidance for General Considerations for the Use of New Approach Methodologies in Drug Development Guidance for Industry. The Consortium is a global group of industry and academic scientists working with regulatory experts to establish standards, develop tools, and build the collaborative infrastructure needed to accelerate responsible integration of stem cell-derived models into preclinical stages of drug development. They are convened by the ISSCR, a global, nonprofit, scientific society that promotes excellence in stem cell science and applications to human health.

The ISSCR's Consortium commends the FDA for issuing a draft guidance that provides general recommendations for the validation and regulatory use of NAMs in drug development. Additional guidance from the FDA will help our members, who are at the forefront of research and innovation, in their work. To complement FDA's initiatives and foster progress in this field, we offer the following comments and recommendations:

General Comments

The draft guidance provides a clear and well-structured framework for the evaluation and use of New Approach Methodologies (NAMs) in drug development. The emphasis on context of use (COU), human biological relevance, technical characterization, and fit-for-purpose considerations is appropriate and generally aligns well with current scientific and regulatory approaches to integrating NAMs into decision-making.

Given the broad scope of this document, intended to encompass diverse NAM modalities, including in vitro, in silico, and computational approaches, the high-level, principle-based nature of the guidance is both appropriate and effective. The document successfully

establishes a flexible foundation that can support a wide range of technologies and applications without being overly prescriptive.

The comments below are offered to further enhance clarity and ensure that the guidance remains adaptable to the rapidly evolving landscape of NAMs and ensure that they facilitate the adoption of these transformative approaches:

1. **Flexibility in biological complexity and model design**
   The discussion of human biological relevance (section B, line 149) could be interpreted as favoring increasingly complex systems, rather than a cellular composition and level of complexity that is commensurate for and reflective of fitness-for-purpose. Exceeding the minimally required platform composition for the intended application can lead to challenges in scaling, standardization and reproducibility that could impede NAM adoption. We thus strongly suggest that the guidance explicitly state that the level of biological complexity is aligned with the intended COU, thereby supporting both reductionist and high-throughput models alongside more complex systems.

2. **Fit-for-purpose evaluation beyond comparison to traditional models**
   While comparison to established methods is appropriate where relevant, NAMs should also be evaluated based on their ability to provide human-relevant insights, including in areas where traditional models are limited or not informative.

3. **Clarification of NAMs within a weight-of-evidence (WoE) framework**
   The guidance appropriately references the use of NAMs within a WoE approach. Additional clarification that NAMs may serve as primary, complementary, or mechanistic evidence depending on the COU would improve interpretability.

4. **Broader recognition of in silico, computational modeling and AI-integrated NAMs**
   The role of diverse in silico NAMs including computational modeling, PBPK, QST/QSP and AI-enabled approaches is only partially addressed. Given their increasing integration with experimental NAMs, i.e. hybrid in vitro - in silico modeling, we recommend a more explicit acknowledgement of these methods, particularly when used in combination with human-relevant datasets.

5. **Scaling of technical characterization expectations**
   The technical characterization section is comprehensive but may be interpreted as a fixed checklist. Clarifying that the level of characterization should be commensurate with the intended use and regulatory impact of the NAM would help maintain flexibility.

6. **Recognition of the distinct characterization considerations for stem cell-derived NAMs**
   Stem cells, especially induced pluripotent stem cells (iPSC), are important tools for

the development of human- and disease-relevant models. These widely used cells are a sustainable source of the many cell types in the body and include the genetic background of the donor, thus providing an unmatched ability to model human disease at the cellular, tissue, and potentially organ level. The unique biological features of these cells and their derivatives require specific guidance to ensure they faithfully and reproducibly become the cell(s) of interest, recapitulate the desired cellular functions, maintain the genetic background of the donor, among other aspects. The FDA should consider whether future guidance, qualification pathways, or public workshops for iPSC-derived NAMs would be valuable for disseminating specific recommendations. ISSCR's Standards for Human Stem Cell Use in Research is a useful source of best practices for the characterization of stem cells.

Overall, the guidance represents an important step toward broader integration of NAMs in drug development. The suggestions above aim to ensure that it remains sufficiently flexible to accommodate both current and emerging NAM technologies.

Thank you for considering our views on the draft guidance for General Considerations for the Use of New Approach Methodologies in Drug Development Guidance for Industry. If the Consortium can clarify any of these views or be of additional assistance, please contact Jack Mosher, ISSCR's Scientific Director at jmosher@isscr.org.

Respectfully submitted,

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Specific Comments

Section (Line)	Issue	Proposed Change
160	Doesn't mention molecular characterization such as retention of epigenetic features and profile from human tissue relevant for the phenotype	**molecular** and physiological characteristics involved in toxicology findings may be mimicked in the
170	Include simpler models which represent one cell type	**one or more of** the relevant cell types (e.g., hepatocytes, stellate cells, Kupffer cells) and biological
220	Include purity of cell population and derivation of stem cell of origin	Document and describe the cell type used (e.g., primary, immortalized, stem cell derived), cell/tissue isolation, **stem cell derivation** and/or differentiation methods, cell source (e.g., commercial, patient-derived, catalog and batch number) **including method for derivation of stem cell of origin (if applicable)**, and species. **Document purity of the cell type used, as well as unwanted cell types, and demonstrate reproducibility across cell differentiations.**
Section III.B Human Biological Relevance	Potential implicit bias toward highly complex systems	Add statement that biological complexity should be aligned with COU and does not require full recapitulation of tissue architecture
Section III.C Technical Characterization	May be interpreted as a prescriptive checklist	Clarify that extent of characterization should be commensurate with intended regulatory use
Section III.C Technical Characterization, 220-222	Recommendations around technical characterization should include more information on the original cell type	Add additional recommendation on validating appropriate cellular and genetic identity, as well as relevant tissue- and physiological features of the NAM, to prove COU-dependent *in vivo* fidelity/relevance
Section III.D Fit-for-Purpose (lines 256–258)	Current language emphasizes comparison to traditional comparator methods, which may not be applicable for NAMs addressing	Clarify that comparative performance against traditional methods should be applied when appropriate, and that for NAMs addressing data gaps or human-specific mechanisms where no suitable comparators exist, alternative validation

	novel biology or contexts where no suitable traditional models exist	approaches (e.g., mechanistic relevance or concordance with clinical or human data) may be sufficient to demonstrate fitness-for-purpose
Section II / III	Role of NAMs within WoE not fully defined	Expand to clarify that NAMs may serve as primary, complementary, or mechanistic evidence
Throughout	Limited reference to computational/AI approaches	Add explicit recognition of AI/ML and hybrid modeling approaches