ISCTM
THE INTERNATIONAL SOCIETY FOR CNS
CLINICAL TRIALS AND METHODOLOGY

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15 May 2026

To: Food and Drug Administration, HHS

Re: Docket No. FDA-2025-D-6131-0002

The International Society for CNS Clinical Trials and Methodology (ISCTM) welcomes this opportunity to respond to the FDA request for comment regarding the draft guidance document: *General Considerations for the Use of New Approach Methodologies in Drug Development Guidance for Industry.*

The ISCTM offers these comments for consideration based on our experience and expertise in human CNS research. The ISCTM is an independent organization focused on advancing the development of improved treatments for CNS disorders. No member of this Working Group, comprised of scientists, clinicians, trialists, and drug developers from both industry and academia, received compensation for comments provided. Comments represent individual opinions and not that of the institution, agency, or company affiliation of group members.

The ISCTM formed a group, led by Debra Hoffmeyer and Geoff Varty, to review and provide comments on behalf of the Society. The authors (in alphabetical order) of the comments provided below are:

Ryan Berry, MD, *Authority Health, Michigan State University*
Durga Bestha, MD, *Atrium Health*
Marc Cantillon, MD, *Rutgers RWJ Medical School*
Debra Hoffmeyer, MA, *Little Bear Pharma (co-chair)*
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COMMENTS ON GENERAL CONSIDERATIONS FOR THE USE OF NEW APPROACH METHODOLOGIES IN DRUG DEVELOPMENT GUIDANCE FOR INDUSTRY:

General Comments:

ISCTM welcomes this guidance and is encouraged by the FDA's commitment to providing a framework that supports the use of New Approach Methodologies (NAMs) in drug development. The guidance represents a meaningful step toward enabling sponsors and investigators to adopt scientifically rigorous,

human-relevant alternatives that reduce reliance on traditional animal studies while advancing the predictive toxicology needed to support safe and efficient clinical development.

ISCTM respectfully suggests that FDA consider clarifying how this guidance aligns with existing international frameworks, including those of the International Council for Harmonisation (ICH), the European Medicines Agency (EMA), and the Pharmaceuticals and Medical Devices Agency (PMDA). As NAMs are increasingly developed and applied across global drug development programs, harmonized expectations regarding validation standards, acceptable methodologies, and regulatory submission requirements would reduce duplicative effort, facilitate multinational development programs, and accelerate the broader adoption of these approaches. ISCTM would welcome further guidance or a dedicated appendix addressing points of convergence and divergence with key international regulatory frameworks. The ISCTM respectfully asks if the FDA could clarify whether The Center for Biologics Evaluation and Research (CBER) has collaborated with CDER on this draft guidance?

ISCTM respectfully suggests that FDA consider establishing a publicly accessible registry or dashboard to track NAMs that have been reviewed or accepted in the context of regulatory submissions. Unlike the current publication of biomarker qualification decisions, there is currently no analogous transparency mechanism for validated or accepted NAMs. A centralized FDA NAMs registry would serve multiple important purposes: it would reduce duplication of validation efforts across sponsors, provide the field with actionable precedent, and accelerate adoption of fit-for-purpose methodologies. ISCTM is encouraged by recent FDA initiatives in regulatory transparency and views a NAMs dashboard as a natural and valuable extension of those efforts.

Finally, ISCTM respectfully suggests that FDA consider whether the scope of this guidance would benefit from more explicit treatment of the qualification process as it relates to NAMs. As currently drafted, the guidance addresses validation considerations in substantive detail; however, qualification—which establishes that a drug development tool and its proposed context of use can be relied upon for a specific regulatory interpretation—is acknowledged but not elaborated upon. Given that sponsors may seek to pursue both validation and qualification of a NAM as complementary pathways toward regulatory acceptance, ISCTM recommends that FDA consider articulating the relevant considerations for qualification within this guidance, or alternatively, provide clear cross-references to qualification-specific guidance to assist sponsors in navigating both processes in a coordinated and efficient manner.

Specific comments:

Proposed recommendations for deletion marked as strikethrough, Italics and bold text.

Proposed recommendations for addition marked as Italics and bold text.

ISCTM respectfully suggests the FDA consider the following:

Section	Page Number	Line Number	Comment / Proposed Revision	Rationale / Justification
I. INTRODUCTION	1	19–26	Add examples and delete language: The purpose of this guidance is to provide drug developers with a validation framework for new approach methodologies (NAMs) used in drug	IND applications are required for drugs that are either NCEs or those that are being studied for a new use or at a new dose range or frequency that has the potential to substantially effect

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			development to improve predictive toxicology in humans, inform clinical development, and move away from reliance on animal testing.[2] NAMs include a broad range of methods such as complex in vitro, 2D in vitro, in chemico, in silico, ***and real-world evidence (RWE) studies, including but not limited to target trial emulation, synthetic control arm simulation, disease progression models, novel endpoints, and safety signal simulation studies.*** This guidance describes the Center for Drug Evaluation and Research's (CDER's) general recommendations to consider for validating NAMs when ~~***nonclinical NAMs***~~ data are provided in support of a ~~***drug application***~~ ***regulatory submission*** or regarding an order issued under section 505G of the FD&C Act for an OTC monograph.[3]	safety or efficacy. In the case of the latter, human data may exist from RWE or pharmacovigilance surveillance, representing prior knowledge that may adequately address specific toxicological concerns, and should be specified as a potential NAM. Removing "nonclinical" from the statement ensures that it can encompass prior knowledge regardless of human, in vitro (with cells or tissue of human origin), or in vivo (human or animal) origin. Potential inputs for in silico modeling may include human PK data based on biological samples, RWE, in vitro data, or in vivo findings. This is better aligned with the 21 CFR 312.23(a)(9) regulation which includes: "Previous human experience with the investigational drug". Additionally, replacing "drug application" with "regulatory submission" is a more applicable reference.
II. BACKGROUND	2	56-58	Remove the word "nonclinical": Under the regulations governing investigational new drug applications, drug sponsors must submit ~~***nonclinical***~~ data regarding their proposed product's pharmacology and toxicology before the proposed product can proceed to clinical trials.	Please see above rationale for removing "nonclinical" for lines 19-26.

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II. BACKGROUND		Footnote 7	Add additional subpart: CFR 312.23(a)(8), ***and 21 CFR 312.23(a)(9)***	The addition of subpart (9) ensures that "prior knowledge," as stated in the draft guidance, may be considered regarding previous human experience to be used as inputs for in silico modeling NAMs.
II. BACKGROUND	3	73-75	Add statement: Therefore, CDER encourages the use of NAMs in regulatory submissions, especially when they improve the predictivity, reliability, and human relevance ***of prior knowledge*** or nonclinical tests and therefore enhance the safety of subsequent clinical trials.	The addition of "prior knowledge" ensures that the guidance is not overly emphasizing nonclinical tests as the only avenue for potential NAMs. A common issue is that safety data from clinical trials is difficult to interpret in the absence of RWE in larger numbers, and improving the predictivity of data submitted to justify the IND may require prior knowledge to detect and predict rare adverse events from comparable products.
II. BACKGROUND	3	76-80	Remove phrase: CDER also encourages sponsors to consult with the applicable review division ~~***if there is uncertainty***~~ about the suitability of the method for regulatory use…	As written, the phrase is too open-ended. Sponsors would benefit from clearer guidance on when additional engagement is expected.
II. BACKGROUND	3	81-83	Replace “nonclinical”: A variety of different types of NAMs data can be included as part of ~~***nonclinical***~~ ***regulatory submissions***; this guidance provides general considerations regarding validation principles that are broadly applicable to all NAMs.	The replacement of nonclinical submissions with "regulatory submissions" broadens the inclusion of data from NAMs into IBs, INDs, NDAs/BLAs and other regulatory submissions.
II. BACKGROUND	3	88-90	Remove the word “nonclinical”: As a drug development program continues, other	The removal of "nonclinical" from the sentence broadens the types of NAMs that

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			~~nonclinical~~ tests may be needed to support clinical trials (e.g., carcinogenicity studies, developmental and reproductive toxicity studies).	can be used to provide insights to key issues in drug development
II. BACKGROUND	4	106-109	Edited text: ***Data supporting qualification and validation should be provided to establish the reliability of NAM data for specific situations. CDER will review data supporting qualification and validation of NAMs used in a drug development program to determine whether its use is appropriate in the context and fit-for-purpose.***	On Line 36-37, the guidance states that a fit-for-purpose NAM, even if not validated, may adequately address specific toxicological concerns. Then on Lines 107-109, the guidance states that validation is critical to establishing the reliability of NAM data for specific situations. These statements contrast one another. Edits have been proposed to resolve the discrepancy.
III. VALIDATION AND CONSIDERATIONS C. Technical Characterization	7	211	Proposed bullet insertion: ***Quantitative benchmarks based on multiple independent controlled data should be presented for interpretability of performance.***	Absence of benchmarks prevents proper study design and powering.
III. VALIDATION AND CONSIDERATIONS C. Technical Characterization	7	214	Proposed bullet insertion: ***High levels of reproducibility and transferability should be specified to give necessary confidence in complex NAM platforms.***	Critical gap for complex NAM platforms.

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