PhysiciansCommittee
for Responsible Medicine
PCRM.ORG
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RE: ICCVAM draft guidance; Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies

Dr. Nicole Kleinstreuer
Director
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Submitted to Ms. Amber Daniel via email at amber.daniel@inotivco.com

Dear Dr. Kleinstreuer,

On behalf of the Physicians Committee for Responsible Medicine, and its nearly one million members and supporters worldwide, thank you for the opportunity to provide input on the ICCVAM draft guidance document, *Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies*. Establishing confidence is key to the uptake of new approaches that may improve testing outcomes while reducing and replacing animal use. We commend the work of NICEATM and ICCVAM agencies to reimagine these evaluation concepts and processes.

We agree with many key points made in this guidance document, including that:

- the processes used for validation should allow for efficient and timely development of NAMs that are fit-for-purpose, reliable, and provide information relevant to the species of interest,
- establishing confidence should be viewed as an evolving and iterative process,
- the possibility that NAMs provide better quality and more relevant information for regulatory decision-making must be acknowledged,
- consideration of the biology of the species of interest is important when assessing a NAM,
- anchoring a NAM to an established AOP can help demonstrate biological relevance of a NAM,
- efforts should be made to identify chemicals with human effects related to the outcome or mechanism being predicted by the NAM under development,
- using reference data from the species of interest allows the assessment of a NAMs against the species-relevant response,
- agencies should coordinate with international regulatory authorities to help ensure ! harmonization, which is important for industry adoption of NAMs, !
- communication from agencies about the acceptability of specific NAMS and training on NAMs can facilitate their use.

We have two main concerns with the document:

1. ! Definition of NAMs: Consistency in language is important, yet the term NAM currently holds various meanings. As defined in this guidance, the term NAM would deviate from previous ICCVAM use and that of the Environmental Protection Agency, which define NAM to mean 'nonanimal'. In its 2018 *Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States*, ICCVAM defined NAMs as "any non-animal technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment."[1] In its 2021 *New Approach Methods Work Plan*, the EPA, a United States agency that has taken a leading role in the evaluation and integration of NAMs, defined NAMs as "any technology, methodology, approach, or combination that can provide information on chemical hazard and risk assessment to avoid the use of animal testing."[2] We request that this guidance define 'NAMs' as 'nonanimal'.

2. ! Comparison of NAMs to Traditional Animal Test Data: We appreciate that the guidance states that the reliance and reproducibility of reference animal test methods should be considered, because to understand how a NAM compares, the capabilities and limitations of a comparator method must be understood. Assuming inherent validity of animal testing, or confidence based on prior use is problematic. Benchmarking the performance of NAMs against existing animal methods to illustrate 'equal or better' predictability should require an analysis of the statistical validity and reliability of both animal and nonanimal methods. In cases where these data are not available for animal studies, an assumption of test method validity is not a robust means of determining if a new approach is 'equal or better' as a predictor. Integrated approaches to testing and assessment (IATA) and weight of evidence approaches are essential in such cases to building confidence in nonanimal methods, and animal data without equal or better statistical analyses than nonanimal study data should hold less weight than other comparative methods.

Thank you for taking on this important issue, which must be addressed in order to more quickly and safely integrate NAMs. To help promote industry use, when NAMs are found to be scientifically valid, agencies must issue clear policies on acceptance. We greatly appreciate that the guidance stresses the importance of global harmonization of accepted methods, as companies are most likely to test for the lowest common denominator. We encourage ICCVAM agencies to work at international level to share information about specific validated/qualified NAMs to more quickly harmonize acceptance.

Please be in touch to discuss any of these issues further.

With best regards,

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[1] Interagency Coordinating Committee on the Validation of Alternative Methods. A Strategic Roadmap for Establishing New Approach to Evaluate the Safety of Chemical and Medical Products in the United States, 2018, available at < https://ntp.niehs.nih.gov/whatwestudy/niceatm/natl-strategy>.

[2] United States Environmental Protection Agency. New Approach Methods Work Plan, 2021, available at <https://www.epa.gov/system/files/documents/2021-11/nams-work-plan_11_15_21_508-tagged.pdf>.

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