PhysiciansCommittee
for Responsible Medicine
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July 15, 2025

Dr. Helena Hoegberg-Durdock, Acting Director
National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

Re: 2025 ICCVAM Public Forum

Dear Dr. Hoegberg-Durdock and ICCVAM Committee Members:

The Physicians Committee for Responsible Medicine appreciates the opportunity to provide input at the 2025 ICCVAM Public Forum. We commend The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and NICEATM for their continued leadership in advancing the development, evaluation, and implementation of New Approach Methodologies (NAMs) that improve scientific relevance while reducing reliance on animal testing.

We offer the following comments and recommendations to support your work and to promote the successful integration of human-relevant methods across federal agencies.

I. Agency-Specific Recommendations

FDA

We commend the U.S. Food and Drug Administration (FDA) for its leadership in advancing the development and use of NAMs, as reflected in its "Roadmap to Reducing Animal Testing in Preclinical Safety Studies." This agency-wide initiative has the potential to transform product development and regulatory decision-making by increasing the use of human-relevant, nonanimal test methods. We also applaud the recent FDA–NIH workshop highlighting collaborative efforts to accelerate the acceptance of nonanimal approaches across regulatory and research domains. To support effective implementation of the roadmap, we respectfully offer the following recommendations:

a. **Update Guidance Documents to Reflect NAMs Acceptance**
   We recommend FDA update its guidance documents to clearly define how NAMs can be used in regulatory submissions, including specific context of use and data interpretation, to reduce uncertainty and build sponsor confidence.
b. **Accelerate ISTAND Reviews and Expand Contexts of Use**
   FDA's ISTAND program is a key vehicle for advancing NAM qualification. We recommend increasing support for the program, specifically through dedicated reviewer funding and

expanding the contexts of use for NAMs to ensure that validated methods can be applied more broadly in drug and biologics development.

c. **Require NAMs for Sunscreen Product Approvals**
To modernize sunscreen product regulation and improve human relevance, we urge the FDA to require the use of nonanimal methods, including validated *in vitro* assays for skin absorption, phototoxicity, and related endpoints; for both initial approval and reformulation assessments. This would align FDA policy with global best practices in cosmetic and personal care product safety evaluation.

d. **Update Endotoxins Guidance to Accept Recombinant Methods for New and Existing Products**
Recombinant Factor C (rFC) has been extensively validated and is internationally accepted. We recommend guidance to explicitly support the use of rFC for endotoxin testing in both new and existing biologics and medical devices.

e. **Support In Vitro Methods for Assessing Protein Digestibility in Foods**
We support FDA's efforts to qualify *in vitro* methods for assessing protein digestibility as an ethical, human-relevant alternative to animal-based assays. We suggest the agency issue clear guidance to promote adoption and ensure consistent use in substantiating protein content claims for conventional foods.

NIH

Advancing NAMs at the NIH

The National Institutes of Health (NIH) is making significant strides in advancing the development and implementation of NAMs in biomedical research. **We commend the agency's commitment to shifting toward nonanimal, human-specific research through the establishment of the Office of Research Innovation, Validation, and Application (ORIVA)**. NIH Director Bhattacharya stated that this "will accelerate innovation, improve health outcomes, and deliver life-changing treatments." This initiative—together with the Complement Animal Research in Experimentation (Complement-ARIE) Common Fund Program and the work of the National Center for Advancing Translational Sciences (NCATS)—will be central to driving a meaningful transition toward nonanimal, human-specific research. NIH-wide investment in ethical, effective, and human-based methods will yield significant benefits for patients, public health, and the drug development economy. **The Physicians Committee commends these efforts to advance NAMs across the NIH.**

Recent progress at NCATS has laid a foundation for agency-wide momentum, particularly through the NIH's acceptance of the recommendations from the Advisory Committee to the Director Working Group on Catalyzing the Development and Use of Novel Alternative Methods. The launch of the Complement-ARIE Common Fund program builds on this progress by enhancing translational success, improving clinical outcomes, and streamlining the drug development pipeline—all while reducing and replacing animal use. Like NCATS, the Common Fund has prioritized inclusive public engagement, hosting listening sessions with a wide range of stakeholders to inform program goals and design. Its innovative crowdsourcing competition—the Complement-ARIE Challenge—recently awarded $1 million in prizes for novel NAMs concepts aimed at improving basic research, uncovering disease mechanisms, and advancing clinical

applications. These efforts are commendable examples of how federal programs can engage diverse voices and spark innovation. We appreciate the Validation and Qualification Networks (VQN) under the Complement-ARIE initiative as a mechanism to accelerate the regulatory readiness of NAMs. To better align with the scale of the need, we encourage implementation of a more ambitious phased timeline and the allocation of additional resources to support developers in reaching validation and qualification goals more efficiently. **The Physicians Committee encourages NCATS, Complement-ARIE, and ICCVAM to work with ORIVA and share these strategies with other NIH institutes, centers, and offices, as well as with the NIH-Wide Strategic Plan team, to promote broader adoption of such inclusive and transparent strategies.**

One key recommendation from the ACD NAMs Working Group is the role of scientific review in ensuring the success and proper evaluation of NAMs-based research. While the NIH Center for Scientific Review cannot directly train reviewers on how to assess NAMs, funding opportunity announcements can and should include specific review criteria that ensure these approaches are properly evaluated. The NIH Center for Scientific Review is already expanding its Bias Awareness and Mitigation Training for reviewers, chairs, and Scientific Review Officers to include information and vignettes about scientific bias—the preference for one's own science or approach—an umbrella concept under which animal methods bias can be considered. Additionally, a recent NIH Research Opportunity Announcement (ROA) for the Autism Data Science Initiative noted that the ROA would "not support data generation in non-human animal models." In July 2025, the NIH also stated that all new NIH ROAs would include language on NAMs, and that there would be no further proposals exclusively seeking projects involving animals. The NIH is therefore already making great strides to facilitate the development and use of NAMs, but to make further progress in supporting the equitable assessment of NAMs, the NIH should consider: **1) expanding its pool of reviewers with NAMs expertise, 2) establishing more NAMs-specific funding opportunities to avoid competition with animal-based projects across NIH institutes and centers, and 3) expanding training for reviewers to recognize and address animal methods bias.**

More broadly, **the NIH should develop a plan to phase out research involving nonhuman primates in line with Dr. Bhattacharya's initiative to prioritize human-specific research**. Many of the most significant areas of primate research and testing are replete with evidence of poor translation to human biology, disease, or benefit in the form of new, safe, and effective therapies. At the NIH, infectious disease and neurological research make up the two largest users of primates, yet the widespread and significant genetic and biochemical interspecies differences mean translation to human biological knowledge and clinical benefit will be difficult and rare. During the September 2024 Council of Councils meeting, former Council member Dr. Kevin Johnson, suggested that all scientists would benefit from technology like NAMs, and that one of the goals of the National Primate Research Center (NPRCs) should be to "not need NPRCs."

Furthermore, **we encourage the agency to halt funding for research using animals in foreign laboratories**. NIH has no effective mechanism to ensure that foreign institutions comply with U.S. animal welfare standards or to independently verify the claims made in grant applications and progress reports. This lack of oversight raises serious ethical, scientific, and accountability

concerns. One of the most immediate actions NIH can take to advance its new initiative is to stop funding animal experiments conducted outside the U.S.

As the NIH continues to implement the many recommendations from the Advisory Committee to the Director NAMs Working Group and the newly established ORIVA, **we encourage the agency to parallel the aforementioned spirit of robust public engagement and accountability by making as many metrics of progress, success, and impact publicly available as possible through data dashboards, frequent reports, webinars, and other venues.**

EPA

Advancing EPA's Commitment to NAMs and TSCA Mandates

The Physicians Committee appreciates the EPA's continued leadership of efforts to develop and implement alternative test methods and strategies that do not use animals for regulatory decision-making. We were encouraged by Administrator Zeldin's support of legislation protecting animals while representing New York's 1st congressional district and by reports of his commitment to getting the agency back on track to eliminate its reliance on animal testing. We urge the agency to prioritize reporting to the House Committee on Appropriations on progress made to reduce animal testing since 2021 and to reestablish a timeline for its eventual replacement.

The Physicians Committee looks forward to updates to the 2021 NAMs Work Plan and TSCA List of Alternative Methods and Strategies as well as the development of transparent processes for how alternatives are nominated and added to the list. To avoid a surge in animal use resulting from the implementation of the EPA Transcriptomic Assessment Product for data-poor chemicals, we recommend the agency prioritize efforts to develop *in vitro* methods for transcriptomics assessment.

Finally, we urge the EPA to issue a statement clarifying how the agency will continue to fulfill its TSCA mandate to reduce and replace vertebrate testing under its reorganization plans.

DOD

Encouraging Continued Department of Defense (DOD) Investment in NonAnimal Methods

We encourage the DOD to continue advancing its transition from animal-based studies towards NAMs particularly through Congressionally Directed Medical Research Programs (CDMRP) and Small Business Innovation Research (SBIR) grant preference for NAM-based biomedical research.

II. ICCVAM Strategic Initiatives & Tools

Sustaining the Method Developer Forum as a Standing Platform for Scientific Exchange

We are encouraged by the launch of the Method Developer Forum in 2024, particularly the inaugural effort focused on carcinogenicity. This initiative provides an important space for scientific exchange between method developers and regulatory stakeholders, which is essential for accelerating the development, refinement, and acceptance of NAMs. We noted that subsequent forums have not been scheduled, and we respectfully encourage ICCVAM and its partner agencies to consider re-establishing this platform as a regular engagement mechanism.

Advancing Regulatory Use of the CatMOS Model

The Physicians Committee encourages ICCVAM agencies, including EPA and NICEATM, to promote broader use of the CatMOS (Categorical Model for Systemic Toxicity) model. As a nonanimal, structure-based tool for predicting systemic toxicity categories, CatMOS holds significant promise for regulatory applications under TSCA, GHS, and prioritization frameworks. We see a valuable opportunity to expand its impact by supporting continued evaluation, showcasing real-world use cases, and offering training to facilitate integration into regulatory workflows. These efforts would help advance the shared goal of reducing reliance on animal testing while improving predictive capacity for human health outcomes.

Using human data for retrospective NAMs validation

To ensure that NAMs are evaluated based on their relevance to human biology, we encourage ICCVAM agencies to rely on human data (where available) for retrospective validation and performance assessment. Many NAMs are designed to overcome the limitations of animal experiments and validating them solely against animal data undermines their potential. Retrospective analyses using clinical, epidemiological, or human biomarker data can provide a more appropriate benchmark for evaluating NAMs intended for human health risk assessment. We urge ICCVAM and associated agencies to promote and coordinate such efforts across agencies to strengthen confidence in human-relevant science.

III. Enabling Adoption: Training, Transition & Transparency

Supporting the Transition to NAMs Through Leadership Engagement and Capacity Building

The Physicians Committee commends ICCVAM for its ongoing efforts to support the transition from animal-based research to NAMs, including training programs and cross-agency collaborations. We also applaud EPA for its leadership in offering accessible training on *in silico* tools through both virtual and in-person platforms. These programs are essential for increasing awareness, trust, and uptake of new methods across regulatory agencies.

We encourage ICCVAM to consider organizing regular engagement meetings with agency leadership and stakeholders to support the transition from animal-based research to NAMs. Platforms that already bring together academic researchers, scientists, and industry, such as the Physicians Committee's NURA program, could serve as a useful foundation for facilitating these cross-sector conversations and advancing shared goals.

Establishing transparent metrics to publicly report animal use numbers

With numerous promising initiatives that have been announced to reduce and replace animal use, it is essential to establish mechanisms for accountability and ways to measure progress toward these goals. Currently, the number of animals used in research and testing in the U.S. is not accurately tracked, and the total number remains unknown. For example, while the EPA provides notice of testing information received, it is not possible to determine whether such testing was conducted for TSCA. We acknowledge that there are inherent challenges with collecting and reporting this information, but transparently and comprehensively tracking animal numbers is necessary to stay accountable to agency commitments, identify additional opportunities to reduce animal use, and build public trust in federal research activities. We ask ICCVAM agencies to annually track the number of animals used in agency submissions based on species, test, and endpoint, and to make these metrics publicly available.

IV. International Collaboration & Emerging Innovation

Promoting Global Harmonization of NAMs Through Organisation for Economic Co-Operation and Development (OECD) Engagement

The Physicians Committee engages with international regulatory bodies, including the OECD, to advance the global adoption of nonanimal methods. We appreciate the U.S's strong history of leading and engaging in these important OECD projects, including the newly published SARA-ICE skin sensitization model and advancing globally harmonized efforts of a nonanimal respiratory sensitization and systemic toxicity. Inter-department efforts among U.S. agencies, including the U.S.' initiatives to update GD 34 on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment, are strong examples of global leadership that prioritizes human-relevant science and drives science and collaboration forward. The Physicians Committee looks forward to supporting the agencies with applicable training to accompany such innovative methods.

Support for ARPA-H CATALYST

We are strongly encouraged by the ARPA-H CATALYST moonshot program to completely replace animal testing with nonclinical *in silico* analysis. We look forward to the upcoming announcement of program participants.

We thank you for your continued commitment to advancing science that protects human health and the environment while reducing animal use. The Physicians Committee looks forward to continued collaboration with ICCVAM, NICEATM, and agency partners to support the implementation of innovative, ethical, and effective testing strategies.

Sincerely,

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