PhysiciansCommittee
for Responsible Medicine
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Dr. Helena Hoegberg-Durdock
Acting Director
Division of the National Interagency Center for the Evaluation of Alternative Test Methods (D-NICEATM)

Dr. Warren Casey, Ph.D., DABT
ICCVAM Executive Director
National Institute of Environmental Health Sciences
P.O. Box 12233, Mail Drop K2-16
Durham, NC 27709

Re: 2026 Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Public Forum

Dear Dr. Hoegberg-Durdock, Dr. Casey, and ICCVAM Committee Members:

The Physicians Committee for Responsible Medicine appreciates the opportunity to provide comments for the 2026 ICCVAM Public Forum. We commend ICCVAM, D-NICEATM, and its member agencies for the significant progress made over the past year in advancing the development, validation, and regulatory implementation of New Approach Methodologies (NAMs).

In particular, we applaud the establishment of the National Institutes of Health (NIH) Office of Research Innovation, Validation, and Application (ORIVA), the continued implementation of the Food and Drug Administration (FDA) Roadmap to Reducing Animal Testing in Preclinical Safety Studies, and the renewed commitment by the Environmental Protection Agency (EPA) to phasing out mammalian testing by 2035. These initiatives demonstrate strong federal leadership and reflect an important shift toward more human-relevant, efficient, and predictive approaches for biomedical research and regulatory decision-making.

As these initiatives mature, the focus should now shift from launching new programs to ensuring their successful implementation. This includes developing clear regulatory pathways to reduce animal use in testing, expanding reviewer training, strengthening interagency coordination, increasing transparency through measurable outcomes, and continuing to invest in the scientific validation and regulatory acceptance of NAMs that reduces and replaces animal use.

The Physicians Committee remains committed to working collaboratively with ICCVAM and its member agencies by providing scientific expertise, regulatory training, and international collaboration to support the successful transition toward nonanimal science. We respectfully offer the following comments and recommendations to support this shared goal.

1. Agency-Specific Updates

1.1. NIH: Prioritizing Human-Based Research

1.1.1. The Arrival of ORIVA

We applaud the steps the NIH has already taken to implement the agency-wide initiative to prioritize human-based research, including: (a) establishing ORIVA in the Office of the Director, (b) investing $150 million in human-based research projects under the Complement-ARIE program, (c) developing NAMs infrastructure like the Standardized Organoid Modeling Center, (d) and launching new NAMs funding opportunities, like one that was released in March 2026 to facilitate the construction or modernization of biomedical research facilities—including for establishing new facilities focused on human-based methods or transitioning existing animal-based facilities.

ORIVA is well positioned for coordinating NIH-wide efforts, building momentum for human-based research across the NIH portfolio, and ensuring these innovative technologies reach their full potential in a wide variety of disease areas and research applications. It also serves a critical role as an interagency hub for NAMs to support parallel efforts at the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA), coordinating cross-agency validation efforts and ensuring efficient resource allocation to relevant test guidance updates. We encourage ORIVA to continue working closely with ICCVAM, FDA, EPA, and other federal partners to harmonize validation approaches, coordinate reviewer training, and promote consistent implementation of nonanimal methods across agencies. We look forward to seeing ORIVA continue to serve as a catalyst for the broader federal transition toward human-based science and to regularly communicate its progress and impact to the research community.

1.1.2. Phasing Out Nonhuman Primate Use

Building on the initiative to prioritize human-based research, the NIH should develop a plan to phase out research involving nonhuman primates, including the National Primate Research Centers. Widespread physiological and biochemical differences between primate species lead to poor translation to knowledge of human biology and clinical benefit. Reflecting the growing acknowledgement of the limited translatability of primate experiments, last year, the Center for Disease Control announced the end of its primate experiments, and earlier this year the NIH entered into discussions with leadership at Oregon Health and Science University, home of the largest of the National Primate Research Centers, regarding transitioning the center into a sanctuary.

Existing funds for primate experiments, including those reserved for the P51 grants, should be used to transition towards more infrastructure, training, and research focused on human-based approaches.

Furthermore, as NAMs continue to advance, NIH should clarify that nonhuman primates should not be used to validate these methods. Validation frameworks increasingly emphasize demonstrating human biological relevance, reliability, and fitness for purpose, rather than concordance with historical animal data. Using nonhuman primate studies to validate human-based methods would perpetuate reliance on animal-based methods with known translational limitations.

1.1.3. Replacing Canine Testing

There is a growing interest among the public, lawmakers, and agency leadership in reducing or eliminating dog experiments in biomedical research and regulatory testing. A cursory evaluation of NIH-funded projects involving dogs in NIH's grant database, RePORTER, reveals that a large portion of these projects justify dog experiments as being necessary for Investigational New Drug (IND)-enabling preclinical testing.[1] Some projects even note that dog experiments are conducted at the request of the FDA, despite there being no regulatory requirement for dog experiments. As these IND-enabling experiments and projects are being funded by the NIH, the NIH has discretion to introduce policies to address the continued financial support of such experiments.

The FDA does not require dog experiments for regulatory testing. We recommend that the NIH update the Grants Policy Statement Section 4.1.1 to clarify that the FDA does not require dog testing and that grant applicants cannot justify the use of dogs based on FDA requirements. This clarification should also be incorporated into descriptions and review criteria of new funding opportunities and conveyed to scientific review officers to ensure agency staff, reviewers, and investigators are aware that dog testing is not required by the FDA.

1.2. FDA: Moving from Roadmap to ImplementationProgress on the FDA Roadmap

- Regulations

[1] E.g., National Institutes of Health. Drug development of RK-33 for breast cancer treatment. RePORTER. Accessed July 16, 2026. https://reporter.nih.gov/search/L6-staWUVEqJEBnzHCd0NA/project-details/11183284; National Institutes of Health. Fabl Inhibitors as Potent, Gut Microbiome-Sparing Antibiotics. RePORTER. Accessed July 16, 2026. https://reporter.nih.gov/search/gY2coAG7GEy4DASJY_Cj2Q/project-details/11327635; National Institutes of Health. IND-enabling studies of KTX-1161, a novel NRF2 activator for corneal endothelial disease. Accessed July 16, 2026. https://reporter.nih.gov/search/L3pNxSaNG0m-W59Y9U7WWw/project-details/11251478; National Institutes of Health. Development of Cobinamide as a Cyanide Antidote: Completion of pre-IND Studies. RePORTER. Accesed July 16, 2026. https://reporter.nih.gov/search/Q8CoAO2a00uSDa3V2HdMyg/project-details/11182935

    - Integrated Review Teams
- **FDA–ORIVA Collaboration**
    - Encourage formal FDA–ORIVA collaborations.
    - Joint scientific workshops.
    - Shared validation projects.
    - Cross-agency reviewer training.
    - Joint qualification pathways.
- **Updating FDA Guidance**

1.2.1. Progress on the FDA Roadmap

The FDA has made remarkable progress implementing the Roadmap to Reducing Animal Testing in Preclinical Safety Studies.[2] The April 2026 Year One Report documented substantial advances, including establishment of Integrated Review Teams (IRTs) to support review divisions in evaluating NAMs, expansion of the now permanent Innovative Science and Technology Approaches for New Drugs (ISTAND) Drug Development Tool qualification program, and publication of multiple draft guidances advancing human-relevant approaches to regulatory decision-making.[3]

Among these, we particularly commend FDA's draft guidance, *General Considerations for the Use of New Approach Methodologies (NAMs) in Drug Development*, which furthers FDA's priority to move away from reliance on animal testing toward human-centric methods. Our public comments on the draft guidance place its recommendations within the broader context of building confidence in the use of NAMs for regulatory decision-making by emphasizing that a NAM need not be validated to be considered for review; that confidence can be achieved through flexible, fit-for-purpose strategies that consider the intended application of the NAM; and that comparisons between NAMs and historically used methods should be guided by relevant human evidence, when available, and by the human regulatory question each method is intended to inform.

Since publication of the Year One Report, FDA has continued this momentum through the release of two particularly significant draft guidances. The draft guidance on Quantitative Systems Pharmacology (QSP)-Based Dose Selection for Minimum Anticipated Biological Effect Level (MABEL) in First-in-Human Clinical Trials establishes a framework for integrating mechanistic modeling, human-derived experimental data, and clinical knowledge for first-in-human dose selection.[4] Likewise, the draft guidance Oncology Pharmaceuticals: Streamlined Nonclinical

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[2] U.S. Food and Drug Administration, *Roadmap to Reducing Animal Testing in Preclinical Safety Studies* (April 10, 2025), https://www.fda.gov/media/186092/download?attachment.
[3] U.S. Food and Drug Administration, *Quantitative Systems Pharmacology (QSP)-Based Dose Selection for Minimum Anticipated Biological Effect Level (MABEL) in First-in-Human (FIH) Trials: Guidance for Industry*, draft guidance (June 2026), https://www.fda.gov/media/193230/download.
[4] U.S. Food and Drug Administration, *Oncology Pharmaceuticals: Streamlined Nonclinical Safety Studies for Biologics and Conjugated Products: Guidance for Industry*, draft guidance (May 2026), https://www.fda.gov/media/192723/download.

Safety Studies for Biologics and Conjugated Products recognizes that, where no pharmacologically relevant animal species exists, safety assessments may be supported through an integrated weight-of-evidence assessment in lieu of animal toxicology studies through fit-for-purpose NAMs.

Taken together, these actions reflect a broader shift in regulatory science, from viewing animal studies as the default foundation of preclinical safety evaluation toward an integrated framework in which complementary human-relevant evidence streams, including experimental NAMs, computational approaches, mechanistic biology, and existing clinical knowledge, collectively inform regulatory decision-making through a fit-for-purpose weight-of-evidence assessment.

To fully realize this transition, the FDA should continue focusing on implementation. Priorities should include 1) establishing cross-center NAM coordination, 2) publishing decision frameworks describing how integrated evidence is evaluated, 3) expanding reviewer training, 4) increasing transparency through case studies and performance metrics, and 5) continuing to modernize guidance across therapeutic areas, particularly small molecules. These efforts will help ensure that scientifically valid, human-relevant methods rather than historical precedent determine the evidence used to support regulatory decisions.

1.2.2. FDA-ORIVA Collaboration

The establishment of the NIH ORIVA creates an unprecedented opportunity to strengthen coordination between the nation's largest biomedical research funder and its primary medical product regulator. As NIH accelerates development and validation of human-relevant methodologies, close collaboration with FDA will be essential to ensure these technologies are translated efficiently into regulatory practice.

FDA should dedicate personnel and resources to a formal FDA–ORIVA collaboration focused on accelerating the evaluation, qualification, and implementation of New Approach Methodologies. Priority activities should include joint scientific workshops, shared validation studies, coordinated reviewer and investigator training, development of common evaluation frameworks, and collaborative qualification pathways for emerging technologies. Formal coordination between FDA and ORIVA will improve regulatory efficiency, reduce duplication of effort, and accelerate adoption of scientifically robust, human-relevant approaches across the biomedical research enterprise.

1.2.3. Endotoxin Guidance Follow-up

We appreciate the FDA’s intention to provide flexibility for manufacturers to transition to the use of recombinant endotoxin testing reagents via the March 2026 guidance revision of *Pyrogen and*

Endotoxins Testing: Questions and Answers.[5] However, we are concerned that these revisions are not sufficient to achieve this intended goal. As the revised guidance does not add any mention of recombinant methods (rBET) or reference Chapter <86> of the US Pharmacopeia (USP), the revised guidance provides neither industry nor FDA reviewers with the necessary direction to use and accept recombinant methods. We encourage the FDA to re-issue this guidance explicitly clarifying that appropriate rBET methods are accepted as equivalent to testing using horseshoe crab blood (LAL) for new and existing products and describing how companies can transition product registrations from LAL to rBET through an annual reportable when supported by appropriate method verification data as described in USP Chapter <86>. Doing so will help achieve the FDA's stated intention and will fulfill the congressional directive in FY 2026 appropriations that directs this guidance be updated to "include acceptance of appropriate rBET methods for endotoxins testing for new and existing products."[6]

1.2.4. Leveraging PDUFA VIII to Advance NAMs

The reauthorization of the Prescription Drug User Fee Act (PDUFA) for fiscal years 2028 through 2032 presents an opportunity to deliver on goals to enhance the use of NAMs and reduce animal testing, while making the drug review process more efficient, predictive, and responsive to patient needs. As the FDA drafts its PDUFA commitment letter, we urge the agency to consider how it can include goals to support the transition to NAMs, and allocate user fees for this work where appropriate. We urge PDUFA VIII to include commitments on: providing clear guidance on using NAMs, providing early FDA-sponsor consultation meetings regarding NAMs use, providing FDA reviewer training on interpreting NAMs data, establishing incentives for sponsors who submit NAMs data, establishing a data sharing system for preclinical and clinical drug data, and ensuring international clinical safety data can be used in place of animal testing where sufficient.

1.2.5. Clarifying FDA Policy on Dog Testing

As discussed above, there is growing interest in reducing and replacing the use of dogs in experiments. To ensure there is clear understanding among reviewers and drug sponsors on FDA requirements with regard to using dogs, we urge the FDA to release a statement clarifying that the agency does not require testing on dogs and encouraging the submission of NAMs data. We also urge additional communication with reviewers to ensure dog tests are not being requested by default.

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[5] U.S. Food and Drug Administration. FDA Clarifies Current Thinking on Pyrogen and Endotoxins Testing. March 18, 2026. Accessed May 12, 2026. https://www.fda.gov/science-research/advancing-alternative-methods-fda/fda-clarifies-current-thinking-pyrogen-and-endotoxins-testing

[6] U.S. House of Representatives, Committee on Appropriations. *H. Rept. 119-172 - Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, 2026.* June 25, 2025. Accessed May 12, 2026. https://www.congress.gov/119/crpt/hrpt172/CRPT-119hrpt172.pdf

1.2.6. FDA Database of Regulatory NAM Case Studies

A key step to accelerate adoption of NAMs is the establishment of a publicly accessible FDA database of anonymized regulatory case studies describing NAM approaches that have been accepted for safety, efficacy, quality, or batch testing. Rather than cataloging technologies, the database should document the regulatory question addressed, the context of use, the human-relevant evidence submitted, the FDA's evaluation of that evidence, and the role it played in the final regulatory decision. Structured data describing preclinical testing strategies, predictive performance relative to clinical outcomes, and regulatory outcomes should also be included.

This database will provide practical precedents for sponsors, encourage consistent review practices across FDA centers and review divisions, reduce uncertainty regarding appropriate contexts of use for NAMs, and strengthen confidence in integrated human-relevant evidence. This recommendation meets industry recognition of the need for greater transparency of the review and use of NAMs.

1.3. EPA

1.3.1. Supporting EPA's Efforts to Advance NAMs

We enthusiastically welcome EPA’s recommitment to phasing out mammalian animal testing by 2035 as well as the progress the agency has already made in meeting this goal. On June 2, EPA updated its list of acceptable alternatives to animal studies under the Toxic Substances Control Act for the first time in five years, adding 13 NAMs, including a method to evaluate eye hazards with reconstructed human cells, a method to evaluate phototoxicity using a 3D human cell-based tissue model, and a computational approach to identify dermal sensitization hazard and potency using *in vitro* and *in chemico* test data. Importantly, EPA also launched a streamlined process for researchers, companies, and non-governmental organizations to nominate NAMs for inclusion in this list. In addition, EPA developed a nonanimal testing framework for identifying skin irritation and corrosion hazards that prioritizes data from human cell-based tissue models, an approach on which we collaborated with the agency. By informing more reliable, relevant, and timely evaluations of chemical risk, nonanimal NAMs translate gold standard science into regulatory practice that better protects human health and the environment.

We are especially encouraged that EPA is already applying this gold standard science in its chemical risk evaluations. In April through June 2026, the agency released nine draft risk evaluations and hazard assessments for public comment and consideration by its independent Science Advisory Committee on Chemicals. In these risk evaluations, the agency used a computational model to help calculate protective limits for skin exposure based on *in vitro*, *in chemico*, and other available information, applied the Rethinking Chronic Toxicity and Carcinogenicity Assessment for Agrochemicals project (ReCAAP) weight of evidence framework to conclude that new cancer studies would not add value to certain assessments, found that one

chemical was not likely to cause cancer in humans after a literature review and gene expression analysis indicated that the biological mechanism was not relevant to humans, and used its Screening Tool for Inhalation Risk (STIR) to model inhalation hazard for avian taxa. These examples show how NAMs can help EPA meet its statutory obligations by allowing the agency to review more chemicals in less time with fewer resources.

1.3.2. Advancing In Vitro Transcriptomics

In addition, we are especially pleased by the publication of memos rescinding avian testing requirements for two chemicals. However, we note that to support hazard assessments of two chemicals, EPA used 5-day in vivo transcriptomic studies. While this approach may reduce and refine animal use when it replaces studies that use greater numbers of animals and longer durations of exposure to measure apical endpoints, these studies used numbers of rodents comparable to those used in sub-chronic toxicity studies in rodents. We urge EPA to intensify efforts to develop and implement methods that assess transcriptomics *in vitro*.

We look forward to an update of EPA's NAMs Work Plan and progress report, as called for by the House Committee on Appropriations. We encourage EPA to resume its regular Conference on the State of the Science on Development and Use of NAMs for Chemical Safety Testing. This conference has served as an important forum for sharing scientific advances, regulatory case studies, updates on implementation of the EPA NAMs Work Plan, and stakeholder feedback. Reinstating this conference would strengthen transparency, scientific exchange, and stakeholder engagement while supporting continued implementation of NAMs.

1.3.3. Advancing Physiologically Based Toxicokinetic (PBTK) Modeling

We commend EPA for its longstanding leadership in developing and advancing physiologically based toxicokinetic (PBTK) modeling to support modern chemical risk assessment. Through the development of the high-throughput toxicokinetic (HTTK) model, a publicly available computational tool, EPA has helped establish the scientific foundation to translate human-relevant *in vitro* data into human *in vivo* exposure scenarios. These efforts have enabled more efficient, mechanistically informed, and human-relevant safety assessments while reducing reliance on animal studies. We encourage EPA to continue investing in the development, evaluation, and regulatory implementation of PBTK models, including expanding chemical coverage and increasing transparency and confidence in model evaluation to support broader regulatory acceptance.

1.3.4. Completing the 90-Day Dog Study Waiver Project

Advancing NAMs requires dedicated agency resources to evaluate, implement, and accept these methods alongside continued investment in their development. During the 2023 ICCVAM Public Forum, the EPA described its efforts to develop waiver criteria for the 90-day dog toxicity study for pesticides. However, progress has remained limited. We urge EPA to dedicate the time and

resources needed to complete its retrospective analysis of the 90-day toxicity test in dogs, which uses as many as 58 dogs per pesticide, and to finalize waiver criteria.

2. International Harmonisation and the OECD

International harmonisation plays an important role in reducing duplicative animal testing, promoting regulatory efficiency, and ensuring that scientifically robust nonanimal methods are accepted across global markets. The Physicians Committee acts as secretariat for the International Council of Animal Protection in OECD Programs (ICAPO). We commend the United States for its continued leadership within the Organisation for Economic Cooperation and Development (OECD), especially through the Working Party on Hazard Assessment and the Test Guidelines Programme, and encourage its continued engagement in OECD activities that advance the development, validation, and regulatory acceptance of NAMs.

In collaboration with ICAPO, the US is leading the development of an integrated approach to testing and assessment (IATA) for respiratory sensitization, which will provide the first internationally harmonized framework for evaluating this endpoint using human-relevant approaches. The US also co-leads the development of an IATA for Systemic Toxicity with ICAPO and Canada, aiming to establish a novel plan for the nonanimal assessment of systemic toxicity. Continued commitment to these initiatives is critical to improving human health protection while reducing reliance on animal testing.

Additionally, the US co-leads important work on the "Revision of Guidance Document 34 on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment" and the "Revision of Guidance Document 331 on the Characterisation, Validation and Reporting of Physiologically Based Kinetic (PBK) Models for Regulatory Purposes". These projects will play an important role in strengthening international confidence in NAMs and facilitating their regulatory acceptance.

Finally, we note that updates on OECD activities have not been included on the ICCVAM Public Forum agenda since 2024. Given the important role that US agencies play in advancing international harmonization, we encourage ICCVAM to reinstate regular reporting on OECD activities and Test Guideline Programme outcomes during future Public Forums.

3. Training and Regulatory Capacity Building

Training is consistently identified as one of the greatest barriers to the successful implementation of NAMs. While significant progress has been made in developing and validating human-relevant methods, their regulatory adoption depends on ensuring that reviewers, risk assessors, and decision-makers have the knowledge and confidence to evaluate and apply these approaches consistently.

We encourage federal agencies to continue investing in training programs that build scientific and regulatory expertise in the application of NAMs. Such efforts should include endpoint-specific training, regulatory case studies, computational approaches, IATAs, and emerging technologies such as PBPK modeling and artificial intelligence where appropriate.

The Physicians Committee provides free training through our NURA program (NAM Use for Regulatory Application; www.pcrm.org/NURA). We greatly appreciate the willingness of federal agencies to present in these training webinars, including the recent NAM training on Sunscreens (www.pcrm.org/sunscreen). We encourage the agencies to continue their commitment to training on implementing NAMs and especially encourage engagement of the FDA (www.pcrm.org/FDA). The Physicians Committee remains committed to supporting US agencies by collaborating or developing targeted, free training on nonanimal methods to meet their individual needs. We look forward to continuing these collaborations to accelerate the implementation of human-relevant, nonanimal methods across the U.S. regulatory landscape.

We thank ICCVAM, NICEATM, and its member agencies for their continued leadership in advancing NAMs and for the meaningful progress made over the past year. We appreciate the opportunity to provide these comments and look forward to continued collaboration to accelerate the development, validation, and regulatory implementation of nonanimal approaches that better protect human health and the environment while reducing reliance on animal testing.

Sincerely,

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