Summary Minutes

Scientific Advisory Committee on
Alternative Toxicological Methods Meeting
September 11-12, 2025
Virtual Meeting Hosted at
National Institute of Environmental Health Sciences
Research Triangle Park, NC

I. Contents

II. Location of Background Materials and Presentations

Background materials and presentations for the 2025 Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) meeting are available on the National Toxicology Program website (see "Past SACATM Meetings" at https://ntp.niehs.nih.gov/events/past/index.html?type=SACATM).

III. Frequently Used Abbreviations

3Rs	replacement, reduction, or refinement of animal use in research or testing
3RsC	3Rs Collaborative
ADME	absorbance, distribution, metabolism, and excretion
ARDF	Alternatives Research and Development Foundation
CAMERA	Collection of Alternative Methods for Regulatory Application
CDEs	common data elements
CDE-WG	ICCVAM Common Data Elements Workgroup
Complement-ARIE	Complement Animal Research in Experimentation
DPCPSI	Division of Program Coordination, Planning, and Strategic Initiatives (National Institutes of Health)
ENTRÉE	Engaging NAMs for Toxicant Regulation and Effects
EPA	U.S. Environmental Protection Agency
FAIR	findability, accessibility, interoperability, and reusability
FDA	U.S. Food and Drug Administration
GD 34	"Guidance Document 34"; formally, OECD's Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment
GHS	United Nations Globally Harmonized System of Classification and Labelling of Chemicals
HPPT	human predictive patch test
HTS	high-throughput screening
IATA	integrated approach to testing and assessment
ICCS	International Collaboration on Cosmetics Safety
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ICE	Integrated Chemical Environment
IIVS	Institute for In Vitro Sciences
ISTAND	Innovative Science and Technology Approaches for New Drugs

IVIVE	in vitro to in vivo extrapolation
NAMs	new approach methodologies
NICEATM	National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
OECD	Organisation for Economic Co-operation and Development
OPERA	Open (Quantitative) Structure–activity/property Relationship App
ORIVA	Office of Research Innovation, Validation, and Application (National Institutes of Health)
PBPK	physiologically based pharmacokinetics
PETA	People for the Ethical Treatment of Animals
QSAR	quantitative structure–activity relationship
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
SARA–ICE	Skin Allergy Risk Assessment–Integrated Chemical Environment
VQN	Validation and Qualification Network

IV. Attendance

SACATM convened in a virtual meeting hosted at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, NC, on September 11 and 12, 2025. In addition to the participants named below, many individuals viewed the webcast — more than 300 on September 11 and more than 170 on September 12. The SACATM Chair and Designated Federal Officer were present at NIEHS to manage the meeting. All other SACATM members and the ad hoc member participated remotely. Speaker presentations, oral public comments, and SACATM discussions were held via the webcast.

SACATM Members

Antonio Baines, PhD, North Carolina Central University

Kambez Benam, DPhil, University of Pittsburgh (ad hoc)

Ellen Berg, PhD, Alto Predict LLC

Corie Ellison, PhD, Procter & Gamble

Sue Marty, PhD, MPH, DABT, The Dow Chemical Company (Chair)

Kristini Miles, PhD, DABT, Miles Consulting LLC

Adrian Nañez, PhD, Exelixis, Inc.

Nathan Price, PhD, Buck Institute for Aging and Thorne HealthTech

Patricia Silveyra, MS, PhD, Indiana University Bloomington

Sally Thompson-Iritani, DVM, PhD, University of Washington and 3Rs Collaborative

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Principal Representatives

Warren Casey, PhD, DABT, NIEHS

Brian Cholewa, PhD, National Cancer Institute

Suzanne Fitzpatrick, PhD, U.S. Food and Drug Administration (FDA), ICCVAM Co-chair

John Gordon, PhD, U.S. Consumer Product Safety Commission

Alison Harrill, PhD, U.S. Environmental Protection Agency (EPA; acting principal representative)

Steve Hwang, PhD, U.S. Department of Transportation

Shannon Marko, DVM, U.S. Department of Defense

Dina Paltoo, PhD, MPH, National Library of Medicine

Barnett Rattner, PhD, U.S. Department of the Interior

Patricia Ruiz, PhD, Agency for Toxic Substances and Disease Registry

Cassandra Tansey, DVM, Department of Veterans Affairs Office of Research and Development

Menghang Xia, PhD, National Center for Advancing Translational Sciences

Other ICCVAM Representatives

Anna Lowit, PhD, EPA

Natalia Vinas, PhD, EPA, ICCVAM Co-chair

Stephen Ferguson, PhD, NIEHS

National Institutes of Environmental Health Sciences Staff

Kristine (Gayle) Bernabe, DrPH

Helena Hoegberg-Durdock, PhD

Kamel Mansouri, PhD

Mary Wolfe, PhD, Designated Federal Officer

Rick Woychik, PhD

Pei-Li Yao, PhD

NIEHS Support Contractors

Ella Darden (Inotiv, contractor supporting the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods [NICEATM])

Victoria Hull, MS (Inotiv, contractor supporting NICEATM)

John Maruca (Image Associates, contractor supporting the NIEHS Office of

Communications and Public Liaison)

Nathan Mitchiner (NTT DATA, contractor supporting the NIEHS Office of Communications and Public Liaison)

Steven Morefield, MD, (Inotiv, contractor supporting NICEATM)

Katie Needham, PhD, (Axle, contractor supporting NIEHS Division of Translational Toxicology)

Emily Reinke, PhD (Inotiv, contractor supporting NICEATM)

Chris Schnur (NTT DATA, contractor supporting the NIEHS Office of Communications and Public Liaison)

Catherine Sprankle, MS (Inotiv, contractor supporting NICEATM)

Public

David Allen, PhD, International Collaboration on Cosmetics Safety

Naomi Charalambakis, PhD, Americans for Medical Progress

Jonathan Freedman, PhD, PrecisionTox Consortium

Katherine Groff, MS, People for the Ethical Treatment of Animals

Steven Hermansky, PhD, FDA Human Foods Program

Tracy Beth Hoeg, MD, PhD, FDA Office of the Commissioner and Center for Biologics Evaluation and Research

Vicki Katrinak, Humane World for Animals

Shagun Krishna, PhD, Physicians Committee for Responsible Medicine

Megan LaFolette, PhD, The 3Rs Collaborative

Sue Leary, Alternatives Research and Development Foundation

Shaun McCullough, PhD, RTI International

Margaret Ochocinska, PhD, National Institutes of Health

Vanitha Sekar, PhD, FDA Center for Drug Evaluation and Research

Geetha Senthil, PhD, National Center for Advancing Translational Sciences

Kristie Sullivan, MS, Institute for In Vitro Sciences

September 11, 2025

V. Welcome and Opening Remarks

Dr. Sue Marty, Chair of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), called the meeting to order at 10:07 a.m. on September 11.

In welcoming remarks, Dr. Rick Woychik, Director of the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program, reviewed the purpose of SACATM and the goals of this meeting, noting the importance

of SACATM's advice to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). As many ICCVAM agencies are turning to an emphasis on human-based methods, this advice is additionally important. Acknowledging recent changes in leadership, he congratulated former NICEATM director Dr. Nicole Kleinstreuer on her new role at the National Institutes of Health (NIH) and Dr. Helena Hogberg on her elevation to acting director of NICEATM. He also thanked Dr. Warren Casey, NIEHS, for returning to the role of Executive Director of ICCVAM. Reviewing the agenda, he asked SACATM members for their candid feedback on how ICCVAM can be most effective in both the near and long term. He closed by acknowledging continuing collaborations with international partners.

SACATM members and in-person attendees introduced themselves.

Dr. Mary Wolfe, NIEHS, SACATM Designated Federal Officer, read the conflict-of-interest statement and reviewed meeting logistics.

VI. Session IA: Updates, Roadmaps, and Collaborations

NICEATM and ICCVAM and NIH Prioritization of Human-based Research

Dr. Casey noted that he is currently on full-time detail to the NIH Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI). While the agenda had originally included an update on NICEATM and ICCVAM activities, these would be described in detail later in the meeting, so his presentation would focus on NIH's recent activities to prioritize human-based research technologies.

Activities in 2024 and continuing under the current administration have laid the groundwork for recent high-profile announcements of activities around new approach methodologies (NAMs). The 2024 recommendations by the Advisory Committee to the NIH Director catalyzed the development and use of NAMs. Additionally, NIH accepted the proposal for the Complement Animal Research in Experimentation (Complement-ARIE) Common Fund program to support the regulatory adoption of NAMs. Dr. Casey reviewed Complement-ARIE's purpose and goals. Another important accomplishment in 2024 was publication of the ICCVAM document "Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies."[1] This guidance document is unique in that it was written by regulators who will evaluate the data from these methods and make decisions based on them. In reviewing the priorities of the current NIH Director Dr. Jay Bhattacharya, Dr. Casey noted the relevance of two of them to ICCVAM: "reproducibility and rigor" and "innovation and collaboration." The April 10, 2025, announcement from the U.S. Food and Drug Administration (FDA)[2] on its "Roadmap to Reducing Animal Testing in Preclinical Safety Studies"[3] was groundbreaking in that it stated an explicit intention to work with ICCVAM. The April 29, 2025, NIH announcement[4] confirmed the partnership with FDA and also announced

[1] Available at https://doi.org/10.22427/NICEATM-2.

[2] Available at https://www.fda.gov/news-events/press-announcements/fda-announces-plan-phase-out-animal-testing-requirement-monoclonal-antibodies-and-other-drugs.

[3] Available at https://www.fda.gov/media/186092/download?attachment.

[4] Available at https://www.nih.gov/news-events/news-releases/nih-prioritize-human-based-research-technologies.

establishment of the NIH Office of Research Innovation, Validation, and Application (ORIVA).

ORIVA is pending approval at NIH but organization and initiation activities are underway. ORIVA will reside within DPCPSI, which has a $1.8 B budget and oversees the NIH Common Fund and other large programs. Dr. Casey reviewed the DPCPSI director's priorities, emphasizing "accelerate translation through practical solutions" and noted that in practice this means investing in activities with the potential to have impact within the next five years. The scope and charge of ORIVA will encompass addressing all 3Rs. Presenting a schematic of a NAMs development and implementation pipeline, Dr. Casey noted that ORIVA will provide support for the biomedical research phase of this pipeline. However, in addition to the increased funding that NIH will provide to develop these early technologies, commitments are needed from federal agencies to support development of these approaches. This has already happened with FDA and the U.S. Environmental Protection Agency (EPA) but participation by more agencies is needed. Examples of recent NIH–FDA interactions include a July joint workshop[5] and a recent Memorandum of Understanding.[6]

An example of the infrastructure that NIH is creating to support this effort is the Standardized Organoid Modeling Center, a federally funded resource to help standardize organoid models. Development of this Center is being supported via $60 M in-kind resources from NIH centers and an additional $10-15 M from DPCPSI. The Center will be housed at the National Cancer Institute's Frederick National Laboratory. Dr. Casey closed his presentation by summarizing an April 29 NIH announcement that notes that all notice of funding opportunities must address explicitly how NAMs were considered.[7] The intent of this requirement is not that NIH will not fund future animal studies, but to ensure that the best research models are considered, regardless of what has been done previously.

Clarifying questions and comments: Dr. Ellen Berg asked Dr. Casey to describe the envisioned relationship and overlaps between DPCPSI, ORIVA, NICEATM, and ICCVAM. Dr. Casey responded that NICEATM and ICCVAM will continue in their current roles, and DPCPSI will provide funding. Dr. Marty asked if there is a timeline for the Standardized Organoid Modeling Center activities; Dr. Casey said that the Center has been established physically and an announcement with activity timelines should be communicated soon.

Public Comments

Public comments for this session were combined with those for the following session.

[5] Details at https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/fda-nih-workshop-reducing-animal-testing-07072025.

[6] Available at https://www.fda.gov/about-fda/domestic-mous/mou-225-25-012.

[7] Available at https://www.nih.gov/news-events/news-releases/nih-prioritize-human-based-research-technologies.

VII. Session IB: Roadmaps and Collaboration

FDA Roadmap Implementation to Reducing Animal Testing in Preclinical Safety Studies

Dr. Tracy Beth Hoeg, FDA Office of the Commissioner and Center for Biologics Evaluation and Research, referred to the groundbreaking nature of the FDA Roadmap and acknowledged the input of Dr. Kleinstreuer in its development. FDA conducted a listening tour of drug developers and industry leaders that has reinforced the acceptance of NAMs throughout industry and acknowledgement that their use is the best path forward to advance drug development. The recent Memorandum of Understanding between NIH and FDA includes development of a list of validated NAMs that FDA would like to see applicants use. This list will be included in a forthcoming guidance document, which is intended as an evergreen resource for regulated companies.

Addressing the question of why implementing NAMs has not progressed more to date, Dr. Hoeg noted that, in the past, communication with FDA prior to application submission could be challenging and time-consuming for sponsors. This and the lack of incentives for including NAMs in applications discouraged sponsors from abandoning animal testing. FDA is aware of this issue and is considering safe harbor approaches that have been adopted elsewhere to address it. There is also a misapprehension that NAMs must be prequalified by FDA. To address this, FDA now requires that a submission include NAM data when any of three conditions is met:

1. FDA has already accepted data from a NAM for that endpoint.
2. The NAM is recognized as validated by U.S. or international regulators.
3. The submission includes accompanying data for reviewers.

Showing the FDA list of qualified drug development tools, Dr. Hoeg noted FDA will provide this list to reviewers. To address the challenge of communication with FDA, the Administration is evaluating a model used in Australia—a decentralized review process that involves external experts. FDA centers are working together to increase public awareness that they would like to see data from NAMs instead of animal tests in cases where animal testing does not add value. Other efforts include educating reviewers, trying to publicize success stories, and implementing a hotline or consultation service. FDA is considering incentives to encourage the inclusion of NAMs data in submissions, such as the aforementioned safe harbor practice, priority review for submissions including NAMs, and a request that sponsors provide NAMs data when animal data are insufficient.

Dr. Hoeg acknowledged the inefficiency of the Innovative Science and Technology Approaches for New Drugs (ISTAND) program currently used to qualify new drug development tools. FDA is working to streamline this program and raise awareness that the prequalification of tools is not required. FDA is also asking Congress to amend Section 351(a) of the Public Health Service Act for biologics to allow waivers of nonhuman primate testing when other supporting data are available from approved products or in the scientific literature. Efforts are also underway to update guidance from the International Council for Harmonisation to support waiving the two-species

requirement for safety testing. FDA is collaborating with the Advanced Research Projects Agency for Health and NIH to develop a model for predicting toxicity, which will leverage FDA internal data, and is seeking private partners for this effort. These initiatives will improve toxicity and efficacy testing, save time and money, and support goals toward replacing, reducing, and refining animal use (3Rs).

FDA's Innovative Science and Technology Approaches for New Drugs (ISTAND) Program

Dr. Vanitha Sekar, FDA Center for Drug Evaluation and Research, noted that ISTAND was launched as a pilot in 2020 and was converted to a permanent program in 2025. ISTAND, which includes assessment of drug development tools for nonanimal models, is a separate program under FDA's drug development tool qualification programs. In FDA context, qualification is a formal conclusion that a drug development tool can be used reliably for its stated context of use in drug development and regulatory review. Key to qualification is establishing a specific context-of-use. The qualification pathway has three major steps:

1. Submission of a letter of intent.
2. Development of a qualification plan.
3. Submission of the full qualification package.

The process is iterative and allows refinement. After the full qualification package is submitted, it is reviewed by subject matter experts from across all FDA centers to determine whether the tool meets the standards for qualification for the proposed context-of-use.

Examining the review process in more detail, Dr. Sekar noted that the initial assessment for each step is targeted to be done within 30 days of receipt. Turnaround time for the subsequent compressed review is targeted at three months for the letter of intent, six months for the qualification plan, and 10 months for the full qualification package. FDA utilizes a fit-for-purpose principle to tailor evidentiary expectations to each drug development tool's context of use. Delays can result if the FDA advises that more robust studies or additional supporting data are required to justify a particular context of use. For transparency, details of ISTAND submissions are posted on the FDA website within 30 days of a major milestone. FDA is looking for ways to refine the review process so it moves forward more efficiently. Reviewing ISTAND evaluations to date, Dr. Sekar noted the large number of microphysiological systems and artificial intelligence/machine learning tools. Important considerations for drug development tool qualification include relevance to regulatory decision-making, potential to advance 3Rs goals, improvements to current models, and usefulness in weight-of-evidence strategies. Notably, research-oriented methods used internally by drug developers for discovery are outside of ISTAND's scope. Dr. Sekar closed by emphasizing that FDA encourages early engagement through pre-submission meetings to discuss potential qualification pathways.

Engaging NAMs for Toxicant Regulation and Effects (ENTRÉE): A Draft Pilot Program for US FDA Human Foods Program (HFP) – How to Qualify a New Approach Method (NAM) for Food Safety Use

Dr. Steven Hermansky, FDA Human Foods Program, reviewed FDA's Engaging NAMs for Toxicant Regulation and Effects (ENTRÉE) program, which is a pilot program that builds on the 2024 ICCVAM report on validation and the ISTAND program. He reviewed the concept of qualification in the FDA context and how it is different from validation, emphasizing that data from a qualified NAM will be accepted by FDA without further justification. Qualification begins with the regulatory question or gap, not the tool method or test, and focuses on the specific information that the NAM provides. For example, less data are required for a screening method than a method intended to replace a pivotal nonclinical study, and the evaluation of food ingredients requires consideration of the complexity of food products and their interaction with biological systems. Initial steps for the ENTRÉE program will focus on applications to review safety of substances already in the food supply. FDA is encouraging communications with sponsors before submission. The letter of intent is a very important part of the process, and Dr. Hermansky reviewed specifically what it should address. A key element of the letter of intent is an outline of the training that will be provided to encourage use and acceptance once the NAM is qualified. More broadly and in general, the key steps of ENTRÉE mirror those of ISTAND and consist of informal discussions with FDA followed by submission of a letter of intent, a qualification plan, and finally a full qualification package. Development of the ENTRÉE program has considered the use of proprietary information, which recognizes both that sponsors may have a financial stake in keeping certain aspects of their methods confidential and that FDA cannot accept methods for which it is unclear how the information was developed. The intent is to address these issues through appropriate confidential business information agreements. Dr. Hermansky closed his presentation by outlining how ENTRÉE will be integrated into Human Foods Program submissions. Review of a method will involve subject matter experts both within and outside of FDA, training materials will be developed concurrently with that review, and accepted methods will be announced on the FDA website.

Clarifying questions and comments: Dr. Berg asked Dr. Hermansky to clarify the role of the FDA vs. the test method developer in defining the context-of-use. Dr. Hermansky replied that FDA will work with test method developers to create a relevant context of use. FDA will outline information on developing a context of use and post it on their website along with other information for the ENTRÉE program. He encouraged sponsors to proactively discuss projects with FDA to help define appropriate contexts-of-use. Dr. Kambez Benam asked Dr. Sekar whether requests to the ISTAND program were welcomed from academic as well as private entities, and she responded affirmatively. Dr. Benam then asked whether there is an expectation to benchmark NAMs against an animal model. Dr. Sekar responded no and noted that FDA would prefer to see demonstration of activity with known compounds.

ICCVAM Roadmap and Increased Opportunities

Dr. Hoegberg-Durdock noted that the 2023 SACATM meeting reviewed the progress toward replacement of animal use for acute toxicity "six-pack" endpoints. Her presentation focused on how SACATM's recommendations from that meeting have

been implemented and was organized according to those recommendations' relevance to the three key goals of the 2018 ICCVAM Strategic Roadmap.[8]

Strategic Roadmap Recommendation 1: Connect end users with the developers of alternative methods. SACATM comments indicated that more communication was needed between method developers and regulators and among stakeholders from different industries. Dr. Hoegberg-Durdock also noted current comments about the need for training method developers and broader education of stakeholders. In response, ICCVAM launched the Method Developers Forums[9]—events that allow regulators to clearly communicate their testing and information needs and method developers to explain how their methods address those needs. She reviewed organization of the forums, which are geared toward clearly defining regulators' needs in a specific focus area and providing a specific framework to ensure method developers address those needs. NICEATM and ICCVAM are engaged in discussion around strategies to improve follow-up from the forums, such as the development of manuscripts or follow-up workshops.

Strategic Roadmap Recommendation 2: Establish new validation approaches that are more flexible and efficient. SACATM comments emphasized centralizing context-of-use and biological relevance and moving away from benchmarking against animal tests and are addressed in the 2024 ICCVAM validation document. SACATM also noted the need for a common standard for characterizing NAMs that bridges the gap between toxicology and medical research, as well as a better understanding of data curation and review approaches. These needs are being addressed by the Complement-ARIE program and a new ICCVAM workgroup on common data elements, both of which will be discussed in more detail in Session 2 of this SACATM meeting.

Strategic Roadmap Recommendation 3: Ensure adoption and use of new methods by both regulators and industry. SACATM comments noted that validation is not sufficient for a new test method to be broadly adopted and that more guidance is needed on how to use in vitro and in silico approaches, in particular outside the context of the one-to-one replacement for an animal test. To address these needs, NICEATM is developing computational tools that make it easier for end users and regulators to understand and use these data. The tools will be discussed in more detail in Session 3 of this SACATM meeting. NICEATM also has ongoing collaborations with the Organisation for Economic Co-operation and Development (OECD) in their integrated approach to testing and assessment (IATA) case studies program.

Other comments from SACATM at the 2023 meeting focused on activities for ICCVAM engagement beyond replacement of the six-pack. SACATM's input included the development of human-based testing approaches for more complex endpoints, such as carcinogenicity, cardiotoxicity, and developmental neurotoxicity, for which leveraging human data will be important. Dr. Hoegberg-Durdock noted that the first Method Developers Forum focused on carcinogenicity and the next one is on cardiovascular toxicity testing, which NICEATM plans to hold in 2026. She reviewed other NICEATM activities around cardiovascular endpoints, including development of an adverse

[8] Available at https://ntp.niehs.nih.gov/whatwestudy/niceatm/natl-strategy.
[9] Details at https://ntp.niehs.nih.gov/go/developers-forums.

outcome pathway for one mechanism of development of atherosclerosis.[10] NICEATM is also working on mapping ToxCast/Tox21 assays to key characteristics of carcinogens. Dr. Hoegberg-Durdock highlighted ongoing in vitro to in vivo extrapolation (IVIVE) modeling efforts for developmental neurotoxicity and noted a manuscript describing this would be published soon. In collaboration with the European Food Safety Authority and FDA, NICEATM is establishing a training set of compounds for the laboratory transfer exercise of the developmental neurotoxicity in vitro battery and undertaking other activities to support these assay transfers. A 2024 NICEATM publication described applying the developmental neurotoxicity IATA to prioritization of testing of organophosphorus flame retardants.[11] Dr. Hogberg closed by referring to spring 2025 press releases about activities and collaborations between NIH and FDA. Open communication within and among agencies will support harmonization and this engagement among agencies will help support adoption of NAMs by agencies that lack a research component.

Clarifying questions and comments: There were no clarifying questions.

Public Comments

Written public comments were submitted for all sections from 28 private citizens and the following organizations:[12]

- The 3Rs Collaborative
- Americans for Medical Progress
- Humane World for Animals/Humane World Action Fund
- People for the Ethical Treatment of Animals
- Physicians Committee for Responsible Medicine
- PrecisionTox Consortium
- RTI International

Oral Public Comments

Oral public comment speakers registered in advance of the meeting and upon recognition by the SACATM Chair presented their comments remotely.

Dr. Megan LaFolette, The 3Rs Collaborative (3RsC), provided an overview of this U.S.-based nonprofit focused on facilitating collaborations in the 3Rs space. 3RsC had three key recommendations for SACATM and ICCVAM:

- **Increase federal partnership with and funding for 3RsC:** 3RsC's work is non-partisan, balances all 3Rs, includes all stakeholders, and addresses issues key to all 3Rs. Dr. LaFolette noted 3RsC's ongoing collaborations with FDA, NIH, and EPA and their representation on many federal advisory boards. Their ultimate goal is to be established as an official 3Rs center in the U.S., similar to

[10] Described in Ehrlich et al. 2024, https://doi.org/10.14573/altex.2403211.
[11] Described in Kreutz et al. 2024, https://doi.org/10.3390/toxics12060437.
[12] Written public comments are available at https://ntp.niehs.nih.gov/events/past/index.html?type=SACATM (click the link "Meeting Materials" in the far-right table column).

the UK National Centre for the 3Rs. 3RsC also recommends mandating comprehensive 3Rs training as part of responsible conduct of research training, a requirement that their 3Rs Certificate Course could fulfill.

- **Prioritize strategic partnerships across all scientific research:** This is needed to promote meaningful culture change, in particular engaging with communities that are not currently included in this effort. It is important to avoid overpromising the current capacity of NAMs to avoid alienating communities dependent on animal models.
- **Focus on the most predictive models that incorporate all 3Rs to advance public health and patient outcomes:** Prioritizing research with the highest scientific merit and potential impact will require pursuing all 3Rs with well-designed research.

Clarifying questions and comments: There were no clarifying questions by SACATM.

Ms. Kristie Sullivan, Institute for In Vitro Sciences (IIVS), acknowledged a renewed sense of motivation to incorporate nonanimal models into research and testing. In particular, she welcomed the emphasis on collaboration and knowledge sharing. Training in NAMs will be key to transferability and is essential to progress. Training infrastructure is already available through Institutional Animal Care and Use Committees, the National Library of Medicine, and the U.S. Department of Agriculture, and she encouraged use of these existing resources to provide training on how to find and implement alternatives. The Standardized Organoid Modeling Center will be a good way to do this for NAMs, and NIH can engage in other activities to connect researchers with resources, e.g. for availability of human tissues, which could be a focus activity for ORIVA. International harmonization will be important to avoid duplication of effort, and standardization efforts exist that can be utilized to avoid this. Consistent collection of metrics can support better understanding of what is and is not working, and NIH can focus on grant submissions and other activities to clarify this. Ms. Sullivan noted Dr. Hoeg's findings on how the pharmaceutical industry supports use of NAMs, and she encouraged SACATM to consider how to further foster that trust and use of NAMs. ISTAND so far has been burdensome for industry to utilize, and she encouraged revision of that program with input from industry, test method developers, and testing laboratories. She closed by emphasizing the importance of providing scientists and reviewers within FDA the resources to incorporate new decision-making tools into their daily work.

Clarifying questions and comments: There were no clarifying questions by SACATM.

Ms. Sue Leary, Alternatives Research and Development Foundation (ARDF), noted that her foundation focuses on funding the development of nonanimal methods for biomedical research, primarily through a network of researchers in the U.S. and Europe. Activities being discussed at this meeting represent the culmination of efforts ongoing since publication of the Strategic Roadmap. She felt that the Standardized Organoid Modeling Center will be a great resource for those developing organoid models for both regulatory and biomedical research applications. She echoed comments by others on the importance of collaboration and engagement among all ICCVAM agencies and the need for these efforts to be appropriately resourced.

Clarifying questions and comments: There were no clarifying questions by SACATM.

Ms. Katherine Groff, People for the Ethical Treatment of Animals (PETA), noted that the progress over the previous year by ICCVAM and NICEATM reflects the expertise and commitment of the people participating in this effort. ORIVA's goal to serve as a central hub to coordinate efforts to develop, validate, and scale the use of nonanimal methods is well-placed to drive meaningful improvements in health outcomes. The Standardized Organoid Modeling Center has the potential to become an impactful, science-driven program. PETA supports FDA's new initiatives around advancing NAMs and would like to see more efforts to clarify guidance in areas including safety testing for sunscreens, screening for skin irritation and pyrogenicity in both pharmaceuticals and medical devices, and anticaries effectiveness in dental products. ENTRÉE should collaborate with existing programs in FDA such as ISTAND and the program for qualifying medical device development tools to enable all of these programs to improve their effectiveness. Collecting and publicly sharing metrics on the use of animal and nonanimal methods would highlight both successes and gaps representing opportunities for development of new methods.

Clarifying questions and comments: There were no clarifying questions by SACATM.

Comments from Designated SACATM Discussants

Discussants for "Session I: Updates, Roadmaps, and Collaboration" were asked to consider the following questions:

- The ICCVAM Roadmap has three overarching principles: (1) connect end users with the developers of NAMs, (2) identify anticipated testing requirements, and (3) encourage the establishment of grant review criteria tailored to the development of alternative methods.
    - Given the recent announcement of agencies NAM priorities, are the three primary principles within the ICCVAM roadmap still relevant and are there additional concepts and stakeholders to consider?
    - What are the primary endpoints of interest for chronic diseases that NAMs can address? What are key areas of focus for NAMs development to address these endpoints?
- How can ICCVAM and NICEATM optimize collaborative efforts with FDA on their roadmap and further support ICCVAM's goals?

Dr. Wolfe noted that Dr. Sally Thompson-Iritani would not participate in the SACATM discussion for Session 1 due to the appearance of a conflict given her role as President of 3Rs Collaborative that made public comments in this session.

Dr. Antonio Baines, first discussant, noted the increase in collaborations among federal agencies during his tenure on SACATM, which is really driving the science forward. The Strategic Roadmap continues to be relevant to advancing NAMs and the document can continue to guide activities in the future. He noted, however, that other concepts could be considered. For example, inclusivity is important, and NICEATM and ICCVAM should reach out to colleges and universities to make sure future researchers understand these methods and concepts so they can incorporate them into their research. Veterinarians and Institutional Animal Care and Use Committee members need to be in these

conversations, as well as science communicators. Understanding mechanisms of disease is important, and needs to encompass population diversity and differences in exposure by different populations. It is also important to consider how ancestral exposure and historic injustices could be modeled or characterized. Dr. Baines agreed with commenters' assertion that animal models should still be used when appropriate, while still fully embracing the 3Rs. He closed by reiterating the importance of clear communication and transparency on this point.

Dr. Kristini Miles, second discussant, agreed with many points made by Dr. Baines. While the Strategic Roadmap continues to be relevant, to strengthen the framework and increase adoption, ICCVAM needs to engage early and intentionally with universities, scientific societies, trade associations, and industry consortia. These groups can ensure that NAMs address real-world concerns, which will help promote broad uptake. Engagement with nongovernmental organizations, patient advocacy groups, and public health groups will also help to promote trust in NAMs, as they can provide valuable insight into the public's perception on scientific integrity and trust and help develop priorities. She suggested there might be a need for a long-term strategy for stakeholder development and training that recognizes the different but interconnected needs of developers and users and regulators and gives everyone confidence in interpreting and applying NAMs data. These initiatives could also improve stakeholders' abilities to communicate science in a way that builds trust and collaboration. She identified a need for infrastructure and data repositories that enable sharing to allow end users to compare performance, refine methods, and identify gaps. Endpoints of interest for chronic diseases include nervous, immune, and endocrine system endpoints, which would be supported by the development of models for neurodegeneration and neurotoxicity, efforts to address chronic inflammatory and immunosuppressive activity, and the identification of substances that could contribute to obesity and metabolic disorders. Broader areas of NAMs development might include developing models to simulate chronic diseases or conditions and repeated low-dose exposure, leveraging artificial intelligence and in silico modeling, and further developing regulatory and validation frameworks. She encouraged development of case studies showing how NAMs can predict endpoints relevant to FDA's and other guidelines, which should also include negative cases to understand their limitations so that the methods can be further refined. To advance the FDA roadmap, she encouraged collaboration on aligning strategic priorities and fostering a culture that values quality, scientific integrity, and continuous improvement. She reiterated the need for workshops and webinars to support training on data interpretation, which should engage academic institutions, nongovernmental organizations, and patient advocacy groups. Collaboration could also be advanced by coordinating research and validation projects and by sharing and publishing case studies using NAMs for common toxicity endpoints.

Additional SACATM Comments

Dr. Benam noted the difficulty of modeling long-term (years and decades of) exposure, which is relevant to many diseases of concern. He suggested engaging researchers using animals and chemical researchers to discuss how to develop surrogates for these models and encouraged FDA, NIH, and others to provide funding for developing these surrogates.

Dr. Berg recognized NICEATM efforts to develop computational tools. She identified a need for a framework for contexts-of-use across agencies, and suggested a centralized group to develop chemical sets for qualification and prequalification.

Dr. Patricia Silveyra noted the uncertainty around how NAMs will be evaluated, which causes concern among researchers. NAMs integrating multiple organs and representing complex physiology are not fully developed or validated, and this represents a limitation for understanding the development of chronic disease. Researchers fear that the inclusion of experimental or unvalidated NAMs in their grant applications could weaken their proposals or compromise funding chances, which ironically would discourage the very innovation we are trying to promote. She suggested that funding proposals should encourage development of NAMs alongside animal models; the best approach forward is for NAMs to complement animal research.

Summarizing the morning session, Dr. Marty commented on how well ICCVAM activities are supporting the roadmap goals. In particular, she noted agencies' activities around data sharing, publishing lists of accepted NAMs, and publicizing case studies. Early engagement of stakeholders is important, and agencies clearly recognize this need. International harmonization is going to be important to eliminate the continued need for animal testing in different arenas. Emphasis on all 3Rs will continue to be important, and sharing metrics publicly will support adoption of NAMs. Incorporation of NAMs for complex endpoints will require engagement with all experts in these areas.

VIII. Session II: Data Standards, Validation, and Qualification

Validation and Qualification Network (VQN) Public–Private Partnerships for Adoption and Implementation of New Approach Methodologies (NAMs)

Dr. Margaret Ochocinska, NIH, provided an update on the Complement-ARIE program and its Validation and Qualification Network (VQN). DPCPSI was established in 2006 to administer the NIH Common Fund, which advances the NIH mission through collaborations within NIH and through public–private partnerships. Dr. Ochocinska reviewed the purpose and goals of Complement-ARIE.[13] The work products of Complement-ARIE are envisioned to be validations of individual and combinatorial NAMs. The program builds on several existing programs across NIH, including development of complex in vitro systems, digital twin models, in chemico screening, and in silico models. Since last year's SACATM meeting, the program has completed strategic planning activities and held a prize competition that resulted in $1 M in awards to 20 teams. They also launched the VQN, a public–private partnership with the Foundation for the NIH. The design phase for the VQN is under way, with over 50 public, industry, and nonprofit partners participating. The other Complement-ARIE components, the Technology Development Center and the NAMs Data Hub and Coordinating Center, are scheduled to launch in FY26. The NIH–FDA partnership discussed earlier advances the goals of Complement-ARIE, and a similar Memorandum of Understanding has been established with EPA.

Dr. Ochocinska discussed in greater detail the components of Complement-ARIE. All of

[13] Detailed at https://commonfund.nih.gov/complementarie.

these will support and encompass community engagement, training, and workforce development, and all activities are being undertaken with the end user in mind. The Technology Development Centers will stimulate the development of NAMs to fill in areas of greatest need. The NAMs Data Hub and Coordinating Center will create integrated data structures, including standards for model credibility and a searchable NAMs repository. The VQN is a partnership between NIH and the Foundation for the NIH, with the goals of accelerating the adoption of NAMs by ensuring NAMs are robust, reliable, and reproducible, demonstrating biological relevance of NAMs, and ensuring each is fit-for-purpose. Activities supporting this include establishing common data elements and standardized reporting, ensuring NAMs have well-described protocols, designing and funding transferability studies, and conducting quality assessments. The public–private partnership model allows Complement-ARIE to leverage precompetitive data sharing and coordinate activities. While Complement-ARIE is coordinating development of the VQN, the VQN is meant to be a resource for all to support validation of novel combinatorial NAMs. Cost sharing with NIH will support significantly expanded efforts for validation and qualification studies. It also allows for the creation of a precompetitive space for establishing consensus validation-qualification frameworks. The VQN is currently in the design phase to plan development of the network and hold workshops with stakeholders; this was launched in April.[14] A steering committee has been established. Implementation will be a two-phased process that will initially fund four to eight validation case studies that will be processed through the VQN for submission to either FDA or EPA, depending on the context-of-use. Submissions of NAMs for initial validation were due August 31 and are currently being reviewed, with another round of submissions due December 31, 2025. Dr. Ochocinska closed by reiterating the broad range of partnerships participating in the VQN, including government entities from other countries active in the NAMs space,and will build upon existing U.S. and international efforts to ultimately provide more cost-effective, rapid, human-relevant NAMs for drug discovery, chemical safety testing, and wider biomedical research approaches to bring NAMs products to market.

Clarifying questions and comments: There were no clarifying questions or comments.

International Harmonization of Test Methods Validation – The Role of Readiness Criteria to Amplify Success

Dr. Alison Harrill, EPA, began by noting the relevance of her presentation to international harmonization, which has been identified as a priority by public commenters. A project began in 2023 to modernize OECD guidance for validating new or updated test methods for its Test Guidelines Programme. Current guidance,[15] referred to informally as Guidance Document 34 (GD 34), is 20 years old and doesn't adequately represent advances such as in silico tools, defined approaches, or artificial intelligence. This and other concerns prompted the modernization effort.

Dr. Harrill reviewed the GD 34 validation process. Focusing on the issue of readiness

[14] Information at https://fnih.org/our-programs/validation-qualification-network-design-phase/.

[15] "Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment;" available at https://www.oecd.org/en/publications/guidance-document-on-the-validation-and-international-acceptance-of-new-or-updated-test-methods-for-hazard-assessment_e1f1244b-en.html.

criteria, she described the example of the MCF-7 estrogen receptor transcriptional activation method, whose multi-year validation failed because of minor differences in lab practice. Such examples suggest that developing readiness criteria, establishing a protocol early, and incorporating training steps may help to improve a method's chances of success and speed validation. OECD stakeholders' workshops in 2022 and 2023 examined key questions around validation, such as how processes are evolving and key pain points. Concurrently, OECD issued a statement calling for greater financial support of validation studies.[16] Dr. Harrill summarized the communities represented at the workshops, including study managers, participating labs, and regulatory stakeholders. Positive aspects of the current validation paradigm include the involvement of a national validation organization and regulatory guidance, the expertise of an experienced validation management team, the availability of grants to support the study, effective coordination of shipping, and coding of chemicals, and data review. Challenges include funding and budgeting, changes in staffing, difficulties with international shipping of reference chemicals, and facilitating knowledge sharing and the crucial aspects of training.

The outcome of these discussions was a vision of a more streamlined validation workflow that importantly includes both evaluation of the method's relevance to the decision context and protocol optimization. Dr. Harrill showed a pipeline diagram that includes points at which different levels of readiness could be evaluated. She emphasized that while this is being presented in the context of OECD test guidelines, this process could be applicable to other validation contexts such as those for EPA and FDA. Background documents that informed this approach include the ICCVAM validation document and a publication with multiple ICCVAM authors, which describes a technical framework for enabling high-quality NAMs measurements.[17]

Dr. Harrill then discussed in more detail what readiness criteria constitute. They provide a starting point for assessing whether the method is worth prioritizing for a validation program and help regulators get a sense of the status of the method. Different criteria might be required for different method types. Assessment could be qualitative or quantitative but needs to be sufficient to inform on where the method falls in a validation continuum. The validation project team has drafted templates for in vitro and in silico/computational test methods, which are envisioned to become annexes to the updated GD 34. Key components of regulatory assessment include method relevance; test method characterization; data management, evaluation, and interpretation; reproducibility within and between labs; and completion of an independent audit. Validation of computational models has some specific requirements, including detailed descriptions of the algorithm, well-defined and quality-controlled inputs and outputs with appropriate metadata, documented versioning and dependencies, and a risk assessment evaluation. The templates to evaluate readiness criteria in the GD 34 update will be intended for use as a starting point and can be modified as necessary. Lessons learned from developing the readiness criteria are being shared with Complement-ARIE to help them optimize their method review processes, and Dr. Harrill noted that several people are involved in both the OECD validation project team and

[16] Available at https://web-archive.oecd.org/2023-01-23/650072-urgent-mobilisation-national-regional-resources-to-support-the-validation-of-new-methods-safety-testing-of-chemicals.pdf.
[17] Petersen et al. 2023. https://doi.org/10.14573/altex.2205081.

Complement-ARIE.

Clarifying questions and comments: Dr. Nathan Price asked whether the reproducibility issue with the MCF-7 assay was addressed sufficiently to validate the method. Dr. Casey replied that the specific issue was identified as a probable cause. Further development of the method ceased because funding ended and there was uncertainty whether there would be additional issues to address.

ICCVAM Common Data Elements (CDE) Workgroup

Dr. Geetha Senthil, National Center for Advancing Translation Sciences, is co-chair of the newly established ICCVAM Common Data Elements Workgroup (CDE-WG). This workgroup provides input to Complement-ARIE to ensure that validation and qualification activities meet agency-specific regulatory standards. The CDE-WG was established in June 2025 to guide the development of structured data elements to support NAMs development activities across Complement-ARIE. Common data elements (CDEs) are standardized terminologies and formats that are essential to providing consistency, comparability, and interoperability of NAMs data across studies. Dr. Senthil reviewed the CDE-WG's membership, which includes seven ICCVAM agencies. The CDE-WG will coordinate with Complement-ARIE to develop unified and implementable data standards that consider the needs of both U.S. and international stakeholders. She reviewed the workgroup's charges:

1. Identify existing CDEs by agency and NAM modality: this will consider types of NAM, context-of-use, relevant endpoints, technical characterization, human relevance, and reference data.
2. Identify CDEs used by key international organizations.
3. Identify conflicting terms.
4. Identify gaps where CDEs are needed.
5. Propose harmonized nomenclature for new CDEs.

The workgroup is still being organized. An early activity is anticipated to be a standardized survey for agencies, using the FDA letter of intent and EPA requirements as examples.

Clarifying questions and comments: Dr. Berg asked how this work is aligning with similar activities at FDA, and Dr. Senthil replied that the group would need to consider this.

Public Comments

Oral Public Comments

Ms. Sullivan, IIVS, noted IIVS' three decades of experience testing with NAMs. IIVS has learned a lot from bringing NAMs into a Good Laboratory Practice environment, and it shares those learnings with others. She emphasized that more resources are needed for validation; there are many methods that could be incorporated into decision-making but aren't because they haven't been validated. Current validation approaches are too slow and the bar is too high. She encouraged validation to explicitly state a context-of-use such as within an IATA or for screening. Extensive validation procedures

are not needed for some contexts-of-use. She also encouraged caution about consideration of applicability, which should be based on chemical properties rather than the specific chemicals tested during the validation, and cited the example of testing mixtures as an area where this is often a barrier. The new ICCVAM workgroup's efforts could help increase understanding of the applicability of methods across different sectors. She closed by expressing support for broader implementation of published, good in vitro methods practices, which will help ensure readiness of new methods.

Clarifying questions and comments: There were no clarifying questions.

Ms. Leary, ARDF, welcomed the developments described in this session. ARDF is participating in the Complement-ARIE VQN, and she anticipates that the public–private partnership model will be very productive. Data standards will be key to building confidence in new methods and will also increase efficiency; she supported this as an appropriate and relevant activity for ICCVAM.

Clarifying questions and comments: There were no clarifying questions.

Dr. Shaun McCullough, RTI International, noted RTI International's support for ICCVAM activities, which are laying the groundwork for increased progress in advancing NAMs. Initiatives such as Complement-ARIE build on past ICCVAM activities to provide the infrastructure needed for efficient, science-based validation of NAMs. RTI International encourages ICCVAM and NICEATM to continue prioritizing these objectives:

1. Establish clear criteria for a method's suitability for a particular context-of-use.
2. Expand cross-agency harmonization of data and metadata standards and reporting frameworks.
3. Embed transparency and reproducibility into all validation and qualification processes to reinforce public trust in regulatory and clinical science.
4. Support validation of in vitro methods to ensure rigor and reproducibility in both regulatory applications and basic science research.

Validated context-specific methods are needed to support good decision-making. In an era when the credibility of information is being threatened by misuse of data and technology, ICCVAM can be a role model in setting high standards for methods, validation, and data integrity, which are essential to optimal decision-making.
Dr. McCullough described human-derived co-culture models for inhalation toxicity, citing them as examples of systems that allow mechanistic exploration at the molecular and cellular level and the capture of differences across populations and can be used with IVIVE to support decision-making. He also noted RTI International's support for data harmonization and standardization efforts and closed by emphasizing RTI International's commitment to continue engaging with ICCVAM, NICEATM, and SACATM to advance their shared priorities.

Clarifying questions and comments: There were no clarifying questions by SACATM.

Dr. Jonathan Freedman, PrecisionTox Consortium, noted the continued usefulness of in vivo models. PrecisionTox Consortium was established as part of the European Union's Horizon 2020 program and focuses on the application of small model organisms, which are not classified as animals in the European Union. He expressed concern that the

current NIH definition of NAMs excludes these models, which are useful in evaluating complex endpoints. This exclusion is problematic because it doesn't align current U.S. efforts with activities in the European Union and other jurisdictions. In the context of its chemicals legislation, the European Commission is advancing the use of NAMs, including small model organisms. Small model organisms can serve as an important complement to in vitro and in silico NAMs.

Clarifying questions and comments: There were no clarifying questions by SACATM.

Comments from Designated SACATM Discussants

Discussants for "Session II: Data Standards, Validation, and Qualification" were asked to consider the following questions:

- What are the primary considerations for data format to meet FAIR principles and ease of data collection? How do you translate easy data collection by a human to easy data storage and accessibility?
- What should be considered when developing requests for proposals for methods to meet the needs of preclinical or early development safety assessment in a regulatory context?
- What lessons learned from regulatory validation practices, e.g. OECD Guidance Document 34 readiness criteria, could be applicable to qualification of biomedical approaches?

Dr. Price, first discussant, felt that both support for principles of findability, accessibility, interoperability, and reusability of data (FAIR principles) and facilitation of data collection are best served by first establishing an overarching structure and then developing tools, such as spreadsheets, to address the needs articulated through the structure. Metadata are important as are quality control and provenance. He supported the concept of an integrated data ecosystem and noted the need for strong governance and tools for gathering different types of data. He identified a need to consider how to integrate and validate combinatorial NAMs; if these are to be considered in the context of standard approaches, it's important to consider what "better" means in this context. Requests for proposal should specify context-of-use of a NAM as well as its limitations. Reproducibility within and across labs should be specified, which departs from traditional grants that tend to emphasize novelty. For artificial intelligence and machine learning models, he stressed awareness of how small differences in models can lead to big differences in outcome and interpretation. With regards to application of GD 34 readiness criteria to biomedical approaches, he noted as important elements reliability, relevance, robustness, performance standards, transparency, and a big emphasis on repeatability. Artificial intelligence methods will provide the opportunity to pull together different threads of evidence and also accelerate regulatory reviews.

Dr. Berg, second discussant, reiterated the need for metadata and common standards for reporting data. Centralized registries are important to support these; however, establishing them will be a substantive task and collaboration to do this is important. Spending time up front to establish good processes will support future reuse of data.

Regarding requests for proposals, she reiterated the importance of specifying context-of-use; performance standards and reference chemicals, which are sufficient to cover the envisioned applicability domain, are important. Methods should also inform on therapeutic or toxicity mechanisms, because such methods tend to be more valuable in tiered assessments or combinatorial approaches. Also, the request for proposal needs to be clear about what existing methods the proposed method is going to be compared against and how that comparison will be made. Lessons learned from GD 34 show that methods should not be entering the validation process too soon. It would help to have a standardized expectation for what is expected in the way of qualification data. Lab transfer should not be attempted too soon, and a higher expectation for quality systems is needed in general. Consider centralizing the distribution of reference chemicals. Method developers need more guidance in prequalification. Tiered sets of reference chemicals could help with the refinement of performance issues. She encouraged greater standardization of the process with templates and checklists and less emphasis on narrative descriptions of methods.

Dr. Benam, third discussant, noted that a key aspect of data collection is structured but flexible formats for data storage. Data collection should be automated and machine-readable in formats that are interoperable among repositories. He stressed the importance of capturing metadata that describe items such as species cell source, chip type, and exposure conditions. Use of controlled vocabularies is important. Automation should be a priority, and he encouraged the use of direct-from-instrumentation pipelines. Data collection formats must respect the realities of bench science: if data entry is cumbersome, compliance will fail. Requests for proposals should include specific context-of-use, fit-for-purpose performance standards including go/no-go gates, and specify use of the FAIR principles. Software should use validated pipelines and reproducible containers, and validation should be robust and reproducible. Requests for proposals should also insist on human relevance and translational anchors; the biological mechanism should be justified. Ethical sourcing should be documented in metadata. Proposals should articulate the value proposition; that is, how the new method compares to the next best thing. Scalability is important, as are data deliverables that are realistic, machine readable, and can be easily stored and accessed. Proposals should also be built on early engagement with end users. Lessons learned from GD 34 indicate again a need to articulate context-of-use and performance criteria up front, as well as to demonstrate reproducibility and transferability. The applicability domain should be clarified in the context of where the method does and does not work. Also important are using well-characterized benchmark controls, comparing to clinical outcomes, and maintaining data integrity and transparency.

Additional SACATM Comments

There were no additional SACATM comments.

In summarizing the session, Dr. Marty noted that a potentially useful aspect of Complement-ARIE will be the development of orthogonal NAMs that reinforce our understanding of biology. She noted support for efforts to make data more broadly available. She concurred with Dr. Berg's comment about the importance of taking the time to make sure the development of CDEs is done well, in particular with an eye toward supporting comparisons across data sets, which will maximize the utility of NAMs

and also help identify data gaps. Major lessons learned from previous validation efforts are to not allow NAMs to enter validation too soon, and to recognize the importance of defining context-of-use up front, which also plays a role in determining the validation strategy. She noted the support for automating approaches to capturing data and expressed support for the update of GD 34 and the broader acceptance of good in vitro methods practices.

Dr. Wolfe and Dr. Marty thanked the day's presenters and discussants; Dr. Marty adjourned the meeting for the day at 3:26 p.m.

September 12, 2025

Dr. Marty called the second day of the meeting to order at 10:04 a.m. SACATM members and in-person attendees introduced themselves. Dr. Wolfe reviewed meeting logistics and read the conflict-of-interest statement.

IX. Session III: Computational Resources

Collection of Alternative Methods for Regulatory Application (CAMERA)

Dr. Katie Needham, Axle, is project manager for CAMERA, a new resource for qualified and validated NAMs. The beta version of CAMERA is planned for launch later this year. CAMERA was developed in response to a need identified by ICCVAM for a single resource that enhances accessibility to qualified and validated NAMs for regulatory application. The resource is being developed by NICEATM under an ICCVAM steering committee. Collaborators include NIEHS and developers from Dynanet. CAMERA will be a free, publicly accessible resource. It will use the ICCVAM definition of NAMs: "any technology, methodology, approach or combination thereof that can be used to provide information on chemical hazard and risk assessment and supports replacement, reduction, or refinement of animal use." CAMERA will provide access to test method details such as applicability domain, mode of action, and reference chemicals. It will support comparison of test methods and provide documentation such as standard operating procedures, validation study reports and data, access to related PubMed publications, and information on relevant guidelines and regulatory guidance.
Dr. Needham emphasized that CAMERA will not interpret regulatory guidance and will simply provide information available publicly from federal agencies. Where available, contact information for follow-up questions will be provided. User features will include full-text search for chemicals or test methods; filtered search dropdowns for test method type, test method endpoint, or regulatory agency to refine search or browse the database; tooltips providing definitions; data visualizations; and content download capabilities. Reference chemical tables include quick links to the NICEATM Integrated Chemical Environment (ICE). At beta deployment, CAMERA is expected to include 27 NAMs covering endpoints including skin sensitization, irritation, and corrosion.
Dr. Needham reviewed the use cases that CAMERA is intended to address. End users will include method developers, nongovernmental organizations, Institutional Animal Care and Use Committees, funding organizations, educators, regulated industries, regulatory agencies, and biomedical researchers. The ICCVAM steering committee includes members from the U.S. Consumer Product Safety Commission,

U.S. Department of Defense, EPA, Occupational Safety and Health Administration, three offices of NIH, and five centers within FDA. She acknowledged the nongovernmental organizations, companies, and academic institutions that have provided input and feedback on CAMERA. CAMERA is intended to serve as the final repository for methods validated through Complement-ARIE.

Clarifying questions and comments: In response to Dr. Corie Ellison, Dr. Needham noted that CAMERA has not yet officially launched. Dr. Nañez asked if there will be a way to query CAMERA for methods approved by a specific agency for a specific endpoint, and Dr. Emily Reinke, Inotiv, replied that that would not be a capability at launch but is envisioned for the future. Dr. Marty asked whether CAMERA would provide templates, and Dr. Needham replied that the goal is for CAMERA to capture as much data as possible in a standardized format. CAMERA's developers will inform data formatting but not necessarily drive it. Dr. Miles asked if CAMERA would incorporate international guidelines in the search fields, and Dr. Needham responded that CAMERA currently includes OECD guidelines and is open to future expansion to include other information.

Updates to the Integrated Chemical Environment (ICE)

Dr. Kamel Mansouri, NIEHS, highlighted recent updates to ICE. ICE is a web-based platform that integrates chemical safety data with tools for data exploration. There were two updates in 2025, version 4.1.1 in February and version 4.2 in July. ICE data follow FAIR principles, which support both human- and machine-driven discovery and reuse of data. Dr. Mansouri reviewed the breadth of curated in vitro and in vivo data in ICE. In addition to data from literature sources and validation studies, ICE houses a curated set of high-throughput screening (HTS) data from Tox21 and ToxCast, aligned with the current release of EPA's InvitroDB. ICE also provides in silico predictions of toxicity, human exposure, and absorbance, distribution, metabolism, and excretion (ADME) properties. The 4.2 ICE release added the ClassyFire chemical taxonomy, a structure-based automated classification system with 11 hierarchical levels that cover more than a million chemicals. This taxonomy is valuable for grouping, read-across, and identifying gaps in data set coverage. ICE 4.2 also aligned its Chemical Quick Lists with InvitroDB v.4.2.

Dr. Mansouri then reviewed specific ICE tools, noting recent improvements.

- The Search tool, improved to facilitate use of Chemical Quick Lists, returns results in tabular form and as interactive data visualizations.
- The Chemical Quest tool allows identification of chemicals in the ICE database that are similar to a chemical of interest.
- The Chemical Characterization tool allows the user to explore physicochemical properties and use categories for single chemicals or one or two sets of chemicals. The Chemical Characterization tool's principal component analysis plots were updated in ICE 4.2.
- Curve Surfer supports exploration of HTS data concentration–response curves, with details on points-of-departure added in ICE 4.2.
- The Physiologically Based Pharmacokinetics (PBPK) tool allows users to predict

behavior of chemicals administered via the oral, intravenous, and inhalation exposure routes and includes in utero embryo/fetal exposures. ICE 4.2 updates enabled the user to upload their own data for ADME and physicochemical parameters.

- The ICE IVIVE tool generates estimates of equivalent administered doses that would result in plasma concentrations equal to an in vitro activity concentration. As for the PBPK model, ICE 4.2 updates enabled the user to upload their own data for ADME and physicochemical parameters.

ICE includes extensive documentation, and ICE help videos were updated in ICE 4.1.1. NICEATM welcomes user input with suggestions of new features and data to add to ICE, and provides custom training on request.

Clarifying questions and comments: There were no clarifying questions.

New Apps for Skin Sensitization

Dr. Reinke, Inotiv, noted that defined approaches enable integration of data from multiple sources to faciliate a decision about chemical hazard or potency. Several options now exist to apply defined approaches to predict skin sensitization potential, including options that leverage human data. Application of defined approaches for skin sensitization is described in OECD Guideline 497,[18] and a recent update of this guideline includes a wide range of test methods providing 24 different combinations to predict hazard, as well as the Skin Allergy Risk Assessment–Integrated Chemical Environment (SARA–ICE) model for point-of-departure predictions. Dr. Reinke reviewed NICEATM tools to make these methods more accessible to a broad range of users.

- The DASS App, launched in 2023, allows users to apply the defined approaches in the original Guideline 497. Updates in 2024 and 2025 made the app more user-friendly, including simplified handling of borderline calls. DASS App allows the user to evaluate performance using their own reference data and/or data from ICE chemical reference lists. Dr. Reinke reviewed the DASS App user interface and how a user would set up a query. DASS App provides a data template and the option to select the assays from which the data are taken. Reference data can be imported from ICE. Outputs are provided as tables and interactive graphics.
- The SARA–ICE model for derivation of a point-of-departure was initially developed by Unilever; a collaboration with NICEATM expanded the database to 434 chemicals and added a number of different assay types. This year, SARA–ICE was accepted into Guideline 497, and NICEATM launched the SARA–ICE app to facilitate its application. The app has two modes; the "TG 497" mode, which aligns with the Guideline 497 criteria, and the "Extended Version," which allows the user to make a hazard determination as well as generate a point-of-departure. Decision models can be adjusted to different sensitivities and specificities. The TG 497 mode is static because it is based on the guideline; however, the Extended Version could be modified in the future to add in more test methods or outputs. Dr. Reinke showed sample outputs from both modes. Outputs include a graphic

[18] Available at https://www.oecd.org/en/publications/guideline-no-497-defined-approaches-on-skin-sensitisation_b92879a4-en.html.

representation of the uncertainty distribution and a tabular report of the probability distributions for various classifications. Future development may add methods to the extended model, in silico reactivity structural alerts, extrapolation of population-level effects, a user input feature, and a downloadable local version. Speaking to that last point, Dr. Reinke emphasized that the SARA–ICE tool does not store user-provided data.

- Finally, Dr. Reinke reviewed the HPPT App, which was released last week. This app is based on a human predictive patch test (HPPT) database compiled by NICEATM and collaborators at the German Federal Institute for Risk Assessment.[19] A 2024 paper[20] describes a modified decision framework to use such data to inform United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS) potency classifications. The HPPT App makes this approach broadly available. Dr. Reinke reviewed the HPPT App decision tree, sample input data, and the output options for potency measure. Like the other apps, the HPPT App provides a template for input data. Outputs are provided as interactive tables.

In summary, NICEATM's work focuses on the development of computational tools to help make regulatory decisions or complex models more available to stakeholders.

Clarifying questions and comments: Dr. Ellison asked whether the tools flag questionable data. Dr. Reinke confirmed that the DASS App and SARA–ICE both flag questionable input data.[21] None of the tools have output flags, and NICEATM may consider adding that feature in the future.

Public Comments

Oral Public Comments

Ms. Vicki Katrinak, Humane World for Animals, acknowledged the work that NICEATM and ICCVAM have done this year to advance NAMs. It is important for agencies to devote appropriate resources to advance NAMs acceptance, particularly updating guidance and training of reviewers. Agencies need to prioritize discussions with international regulators to promote harmonization. Clear goals, timelines, and metrics are also needed to provide measures of success. Humane World welcomes the news that ICCVAM will continue to hold Method Developers Forums and that ICCVAM is exploring how to follow up on these events more effectively. Humane World also welcomes FDA addressing barriers to using NAMs in drug development and in particular, plans to update guidance, implement safe harbor practices, and establish a hotline to assist with using NAMs. It is exciting to see the advances in computational tools, and Ms. Katrinak encouraged EPA to issue communications on acceptance of the Collaborative Acute Toxicity Modeling Suite for pesticide hazard assessment. She also asked for updates on the Collaborative Modeling Project of Acute Inhalation Toxicity. It is important to communicate effectively to the public how the work NICEATM and ICCVAM are doing supports better human health protection in addition to reducing

[19] Strickland et al. 2023. https://doi.org/10.1007/s00204-023-03530-3.
[20] Herzler et al. 2024. https://doi.org/10.1007/s00204-023-03656-4.
[21] Information received from the app developer after the meeting confirmed that the HPPT App also flags questionable input data.

animal use. Policy makers must be part of the discussion so that they can better understand how to support the continued advancement of this work, and Humane World is happy to support these communication efforts.

Clarifying questions and comments: There were no clarifying questions by SACATM.

Dr. Shagun Krishna, Physicians Committee for Responsible Medicine, noted that ICCVAM has been instrumental in driving acceptance of NAMs and building trust in these approaches. She welcomed the new collaborations between NIH and FDA. Responding to Dr. Hoeg's presentation, she emphasized the importance of highlighting success stories and providing practical support to FDA reviewers. Physicians Committee is excited to see the progress made so far on CAMERA and would like to see cardiovascular endpoints included in this resource, as well as more human-relevant methods. They would also welcome more clarity on how CAMERA data will be used in regulatory decision-making; Dr. Krishna encouraged development of specific guidance on how to use CAMERA data. She closed by noting that Physicians Committee would be presenting a webinar on SARA–ICE on October 1.[22]

Clarifying questions and comments: There were no clarifying questions by SACATM.

Comments from Designated SACATM Discussants

Discussants for "Session III: Computational Resources" were asked to consider the following questions:

- For the tools discussed, i.e., ICE, SARA–ICE, and CAMERA, what are the primary areas for enhancement to increase their impact and functionality?
- What data sets should be added to these tools to address stakeholder needs and drive future innovations in toxicological assessments?
- Where would the development of other tools facilitate access to computational models such as PBPK, IVIVE, DASS App, and HPPT App?

Dr. Ellison, first discussant, said that it is very exciting to see the improvements in ICE made in response to SACATM's suggestions such as input of users' own physicochemical properties data. The ICE Chemical Quest tool could be improved by using approaches other than Tanimoto scores to determine similarity; for example, adding chemical structural alerts based on expert-driven rules to identify specific functional features. He suggested adding to ICE EPA genomics and pharmacokinetic data sets, which represent many species and chemical types. The PBPK models could be improved by adding the dermal exposure route. As the number of available tools grows, he highlighted the potential for user confusion about how the tools and models in ICE differ from the models available from other platforms such as the OECD Toolbox or EPA CompTox Dashboard, and noted this could be problematic for weight-of-evidence analyses. For example, if a user runs the same model on different platforms they may think they're getting predictions from different models, leading to bias favoring the prediction from the model available on multiple platforms. Applicability domain limitations need to be highlighted. CAMERA has potential to be a good landing point for

[22] Information available at https://www.pcrm.org/ethical-science/animal-testing-and-alternatives/nura/sara-ice.

validated methods, and it will be important to clearly articulate how qualification (in the FDA sense) differs from validation. Qualification starts with context-of-use, which isn't always the case with validation. It is important to capture the context-of-use to avoid potential misuse. For the skin sensitization tools, Dr. Ellison expressed an interest in seeing assessments of data quality and flags for trends and anomalies. He also asked whether these tools incorporate metabolism, for example, for prohaptens.

In response, Dr. Mansouri agreed with the comments on Chemical Quest and noted that improvements are in progress, including an endpoint-agnostic similarity for exploratory search and an endpoint-specific similarity search for predictive grouping. The EPA genomics data are being considered for inclusion in an upcoming ICE release. Dr. Mansouri agreed that some clarification is needed about the use of different versions of the same model on different platforms, although to a certain extent, he proposed that users document the platform version used for an analysis. The Open (Quantitative) Structure–activity/property Relationship App (OPERA) is available on several platforms but in different versions Thus, for example, an OPERA prediction of partition coefficient obtained via ICE might differ from one obtained via the CompTox Dashboard because the two platforms are using different versions of OPERA. Information on applicability domain is provided in OPERA's knowledge base, as well as accuracy estimates and an uncertainty range. Some of this information is only available on certain platforms and output formats. Dr. Reinke agreed that the terms qualification and validation are often conflated and that the CAMERA developers are trying to make sure the tool clarifies the specific context-of-use of each method. Regarding the skin sensitization models, she noted that in vivo data will by nature incorporate metabolism but the in vitro data do not. A current priority for these tools is to incorporate data from 3D models such as EpiSens and SENS-IS that might have limited metabolic capability, as well as computational models that could predict whether a substance might be a prehapten or prohapten.

Dr. Adrian Nañez, second discussant, prefaced his remarks by noting they represent the point of view of the early-career toxicologist and the naïve end user in pharma and product safety trying to determine how to use these tools for decision-making. CAMERA has great potential, and suggested that it might be of interest to capture information on methods with validation in progress. For ICE, being able to query novel compounds is useful, and structural similarity tools will help. He agreed with the importance of incorporating metabolism. He noted the recent improvement of these tools, and stressed the importance of communicating how the tools can be used and connecting with potential users to demonstrate utility.

In response, Dr. Reinke agreed with the importance of training and noted that recent NICEATM training activities would be discussed during the afternoon session. NICEATM tailors training to users by incorporating relevant case studies. They also present demonstrations at meetings and are interested in opportunities to connect with stakeholders. Dr. Nañez suggested doing training at Society of Toxicology meetings. Dr. Needham stated that she would take Dr. Nañez's comments on CAMERA back to the Steering Committee and noted that CAMERA is meant to be fully interoperable with ICE. Dr. Suzanne Fitzpatrick, FDA, ICCVAM Co-chair, noted the current interest in chemicals in food and invited stakeholder participation in identifying knowledge gaps.

Additional SACATM Comments

Dr. Berg expressed interest in seeing metrics on these tools; for example, how many people are using ICE versus just downloading the data. She felt that the ICE interface is not user-friendly for biologists and asked if training on use of the data might be provided on the landing pages. CAMERA should include a formal registry of context-of-use, and it would be good to standardize this across agencies, which would provide a measure of progress and also identify gaps. Regarding the CDE effort, she felt that making this information and the associated data dictionary publicly available, even in draft, would support broader standardization and harmonization efforts. Too often this information is buried where only the developers can find it, and making this information publicly available would help train biologists in data literacy. She closed by identifying some data sets of interest, including EPA's pharmacokinetics data and data from human studies of drugs. In response, Dr. Reinke agreed with the importance of metrics on ICE. She noted that these data are currently collected; however, there are issues with the data that must be resolved. Dr. Hogberg added that NICEATM recently had a meeting with FDA to figure out how they can apply their PBPK models to FDA data, and she would be open to suggestions of data they should consider.

Dr. Benam suggested raising awareness of these tools among academics and other stakeholders besides chemical companies and regulators. Computational methods and platforms are evolving very fast, and the tools discussed today need to evolve to incorporate new knowledge and technology. It is also important to clarify how "human-relevant" the in vitro data are.

Dr. Sally Thompson-Iritani, noted that the Federal Demonstration Partnership (FDP) is supporting the development of a platform that supports reproducibility and standardization of procedures for IACUC protocols. The project is called CUSP (Compliance Unit Standard Procedures). There could be an opportunity to expand this to other procedures that address all 3Rs. The tool will be launched on September 15. She invited collaboration to broaden access to these tools.

In summary, Dr. Marty noted the excitement around CAMERA but emphasized that to be useful it must clarify the difference between qualification and validation and highlight context-of-use. Suggestions on new approaches to search for similar chemicals in ICE are already being addressed by NICEATM. Commenters also noted the importance of clarifying the versioning of tools and including data quality assessments. Many remarks emphasized the importance of and interest in training, and she encouraged NICEATM to keep in mind established users that may not be aware of new tool features when developing training programs. She emphasized that metrics will support the continued development and use of these tools.

X. Session IV: ICCVAM Public Outreach and Education

ICCVAM Public Forums

Dr. Anna Lowit, EPA, reviewed the history and purpose of the ICCVAM Public Forum, held annually since 2014. A new vision for ICCVAM articulated by then-NIEHS Director Linda Birnbaum in 2013 emphasized that ICCVAM communication with stakeholders needed to become more bidirectional and collaborative, and the Public Forum was

established to help address that need. The 2014 Public Forum included updates on NICEATM and ICCVAM activities, presentations from a few agencies, and a few public comments. Data on Public Forum agendas over the years shows that both the length of the program and the number of presentations have increased, with some agencies in some years giving multiple presentations. In most years the Public Forum has been presented both in person and online, with online attendance generally increasing each year. The length of the agenda has varied from one to two days depending on the number of presentations. Reports from outside the ICCVAM member agencies have included updates from international forums such as OECD, the International Council for Harmonisation, and GHS, as well as summaries on Tox21 and related activities. Agencies have used the Public Forum as a venue to announce new initiatives or programs.

Dr. Lowit noted the importance of the Public Forum for engaging with the public to develop the Strategic Roadmap. The 2017 Public Forum solicited public input on development of the roadmap, the publication and implementation plan were announced at the 2018 Public Forum, and implementation plan updates were presented in 2019-2021. Every Public Forum has included public comments, with the number being consistent over time. Although most comments have been presented by animal welfare groups, recently more method developers presented comments, which prompted, in part, development of the ICCVAM Method Developers Forum.

Dr. Lowit then reviewed a sample agenda from 2023, soliciting specific recommendations from SACATM on how the event could be improved going forward. She noted that each presentation is about 15 minutes long, so it is is a "very packed" agenda. The agenda has no theme; rather, the agencies are free to present on what they would like to bring forward to the public at the time. Public comments are integrated into the agenda in various ways, sometimes in a single session and sometimes in multiple sessions. While the Public Forum can be viewed as a show-and-tell opportunity for the agencies, there have been several important initiatives that arose from it. For example, Public Forum comments requested detailed tracking of numbers of animals used for testing. Because this tracking is not possible under current U.S. regulations, the ICCVAM Metrics Workgroup subsequently developed other measures of success that have been recognized by stakeholders and prompted a more nuanced and constructive dialogue on this topic. Comments in the Public Forum have also highlighted the need for opportunities for method developers to engage with regulators, which is a key goal of the Strategic Roadmap. In addition to the Method Developers Forum, FDA has initiated its own alternative methods webinar series through which agency staff can engage with methods developers. The update of the ICCVAM validation document was also in response to recurring needs articulated by stakeholders at the Public Forum.

Clarifying questions and comments: There were no clarifying questions.

ICCVAM Communities of Practice Webinars

Dr. Natalia Vinas, EPA, ICCVAM Co-chair, reviewed the history and purpose of the ICCVAM Communities of Practice webinar series, held annually since 2015. With the SACATM meeting and the Public Forum, this webinar provides a third annual opportunity for ICCVAM to engage with the public. It addresses a need identified by ICCVAM for an event that provides a close examination of current topics in alternative methods with

regulatory application. The first Communities of Practice webinar, held in January 2015, was on the topic of reverse toxicokinetics and attracted over 250 viewers. Registration and attendance have been consistent throughout the series. A review of webinar topics throughout the series' history have shown both diversity and timeliness. Like the Public Forum, the Communities of Practice webinars have stimulated follow-on activities. The first webinar on toxicokinetics prompted a webinar series and workshop on IVIVE in 2016. The 2016 presentation on quantitative structure–activity relationship (QSAR) models preceded collaboration with University of North Carolina-Chapel Hill to develop QSAR models for a number of endpoints. Presentation in 2019 of a human-relevant model for inhalation toxicity led to the model's publication as a case study by OECD and its use to support an EPA risk assessment. Dr. Vinas closed by requesting SACATM's input on how to improve the webinar series and what topics might be considered in the future.

Clarifying questions and comments: There were no clarifying questions.

Engaging the Public: Trainings, Workshops, and Demonstrations of NICEATM Tools

Ms. Victoria Hull, Inotiv, summarized recent public outreach activities undertaken by NICEATM. Public outreach is important to build confidence in NAMs, establish collaborations, increase accessibility of complex models, and democratize access to data. A timeline for 2024-2025 noted 18 public outreach events focused on NICEATM activities and tools, including training provided and specifically tailored to individual stakeholders. She discussed a few examples in depth:

- The ICCVAM Method Developers Forum, launched in 2024, is a proactive effort to highlight and implement the recommendations detailed in the 2024 ICCVAM's Validation guidance document. It provides an opportunity for NAMs developers to present their methods and discuss regulatory issues with relevant stakeholders. The first forum was presented in August 2024 on the topic of carcinogenicity testing; the next forum will focus on cardiovascular toxicity.
- An October 2024 EPA workshop supported by NICEATM focused on probabilistic methods for chemical risk assessment, with the goal of helping to make these methods more understandable by and accessible to a broad audience.

NICEATM training takes a cyclical approach that uses audience feedback to inform training materials and tool updates. Training plans are updated and adapted to each audience. Training topics include NICEATM tools, computational methods, and NAMs for general risk assessment. Training is provided in several formats.

- **In-person events** recently included an ICE presentation at the inaugural conference of the International Collaboration on Cosmetics Safety (ICCS), a continuing education course at the 2024 annual meeting of the American Society for Cellular and Computational Toxicology, and an ICE training session at the headquarter of NSF International (National Sanitation Foundation). The advantages to in-person training are many, including that it's interactive, it can be adjusted in real time to accommodate the audience, and it provides the best opportunity to get high-quality feedback from the trainees.

- Examples of recent **virtual trainings** include demonstrations to FDA, the Massachusetts Department of Environmental Protection, and the OpenTox Summer School. These events included some interactivity with live question-and-answer sessions as part of the program. Virtual training sessions allow NICEATM to access diverse audiences with minimal expenses or travel cost and the audience is typically larger than for in-person events.
- **Demonstration booths** at scientific meetings provide opportunities to provide overviews to new users as well as answer specific questions from current users.

Other recent public engagement activities include interactions with international stakeholders, interactions via the ICE help email, and updates of ICE documentation. Future training activities are slated to include more static training modules such as help videos and slide decks, more training that targets early-career scientists, development of more case study demonstrations, and identification of new approaches for audience feedback. Those interested in engaging NICEATM for training should contact NICEATM.[23]

Clarifying questions and comments: There were no clarifying questions.

Public Comments

Oral Public Comments

Ms. Leary, ARDF, noted her organization's frequent engagement with the Public Forum and especially appreciated the opportunity to interact in person with ICCVAM members and other stakeholders. She encouraged agencies to make participating in the Public Forum a priority going forward. She welcomed the future directions described in Ms. Hull's presentation, which will better leverage ICCVAM's leading role in public outreach.

Clarifying questions and comments: There were no clarifying questions.

Dr. David Allen, ICCS, noted the number of thought leaders that have been involved in the Communities of Practice webinars. ICCS develops animal-free approaches that can be applied to regulatory decision-making. ICCS's goal is to provide a forum for collaborative work across government and industry to facilitate the scientific and technical steps that are necessary for the adoption of NAMs and next-generation risk assessment frameworks. ICCS has published the first in an envisioned series of guidance documents to support a global transition to animal-free safety science. These are especially suited for safety assessors new to NAMs. The first guidance document focuses on skin sensitization; other documents are planned on topics including skin and eye irritation, read-across, and thresholds of toxicological concern. ICCS recently partnered with NICEATM to do a landscape analysis of acute toxicity and will continue to pursue collaborations with NICEATM, ICCVAM, and others to support educating safety assessors on animal-free approaches. He echoed the support voiced by others for in-person meetings and suggested that ICCVAM events be aligned with other events to facilitate travel approval.

Clarifying questions and comments: There were no clarifying questions by SACATM.

Ms. Groff, PETA, encouraged regulatory bodies to support training of test method users

[23] Email ICE-support@niehs.nih.gov.

and reviewers, which is the only way new methods are going to be fully implemented. Direct comparison to animal data delays the implementation of new methods, and education on different methods of validation and qualification, as articulated in the ICCVAM validation document, is key to advance the adoption of NAMs. International harmonization, standardization, and data sharing are all essential to advancing science, and achieving these in turn relies on education, training, and coordination across agencies and stakeholders. She closed by encouraging NICEATM and ICCVAM to continue to have an in-person option for SACATM and the Public Forum, and suggested adding a panel discussion to the Public Forum.

Clarifying questions and comments: There were no clarifying questions by SACATM.

Dr. Naomi Charalambakis, Americans for Medical Progress, described this nonprofit as having a mission to support medical advances through education and policy programs that build awareness of the importance of investing in biomedical research to improve public health. She presented three specific requests for SACATM and ICCVAM:

- Standardize definition of NAMs to "new approach methodologies." The acronym currently has different meanings and definitions across federal agencies and stakeholders, leading to misinterpretations and conflicting policy expectations. The definition "new approach methodologies" accurately captures the full scope of the scientific and ethical commitments of this work without oversimplifying.
- Ensure that expansion of ICCVAM activities includes adequate expertise and resources for biomedical research. ICCVAM has made an impact on advancing nonanimal models in toxicology but the role of NAMs and animal models differs across scientific disciplines. ICCVAM can help reinforce the concept that different approaches can complement each other.
- Provide clear communication and set realistic expectations for NAMs. To maintain credibility with the public it is important not to overpromise or oversimplify these technologies and to acknowledge that there are still areas where animal research is necessary.

In summary, research policies and tools should serve the science rather than define it.

Clarifying questions and comments: There were no clarifying questions by SACATM.

Comments from Designated SACATM Discussants

Drs. Baines, Berg, and Marty attended the 2025 ICCVAM Public Forum[24] and were asked to share their thoughts about that event.

Dr. Baines emphasized the importance of being inclusive in communications with academia, in particular to include liberal arts universities and smaller institutions with relevant graduate programs. He encouraged consideration of how to use different communication channels, such as popular science magazines and textbooks, to raise awareness of NAMs. While he acknowledged the broader reach of virtual programs, he stressed the advantages of in-person engagement. He suggested NICEATM and ICCVAM reach out to a broader range of professional society meetings, including the

[24] Materials available at https://ntp.niehs.nih.gov/go/iccvamforum-2025.

American Association for Cancer Research and Society of Toxicology chapter meetings.

Dr. Berg noted the difficulties that the current situation with the government presented at this year's Public Forum but still found it very timely and interesting.

Dr. Marty congratulated the ICCVAM committee on putting together a great Public Forum this year despite challenges within the government. Highlights of the Public Forum included progress on the developmental neurotoxicity in vitro battery and updates on PBPK models of brain and adipose tissue; she expressed interest in development of a lactation model. The presentations on Tox21 assays were interesting but their limitation continues to be the physiological relevance of assays that don't integrate codependent pathways. She noted recent progress in development of liver and kidney models and expressed particular interest in seeing further development of the kidney model. The presentation on the human thyrocyte model validation study noted the tradeoff between predicting a range of responses within a human population and the reproducibility of the assay due to the diversity of the donor cells. Thyrocyte cellular responses across multiple donors were carefully characterized to establish assay qualification criteria and set benchmark ranges for responses. Balancing diversity with reproducibility is going to be a key consideration for human models.

Drs. Thompson-Iritani and Nañez attended the 2025 Communities of Practice webinar[25] and were asked to comment on that event.

Dr. Thompson-Iritani felt that Dr. Danilo Tagle of the National Center for Advancing Translational Sciences effectively showed how translation opportunities can be incorporated and gave some examples of effective outreach. Dr. Ivan Rusyn from Texas A&M described some very effective collaboration efforts. Dr. Thompson-Iritani noted in particular the relatively low cost of entry to the network compared to other similar efforts. Dr. Remi Villenave from Roche represented the pharma space and highlighted areas where no models are available and additional work is needed. The robust question-and-answer focused on the timeline for progression, with commenters agreeing that validation and adoption of these models will take longer than expected and any attempt at imposing a timeline would just create anxiety. Commenters also stressed the need to be careful about benchmarking and context-of-use. Making the recording and slides available is helpful because they contain so much information.

Dr. Nañez encouraged ICCVAM and NICEATM to explore more ways to publicize these important events. The data on submissions presented by Dr. Villenave were very interesting. This presentation emphasized considering ways to measure progress, and the biosafe survey that was cited is a good example. Dr. Rusyn's presentation was an overview of a very active area that provided good consideration of how to build confidence in these methods. There is value in being able to explore utility of the models before committing to them.

Discussants for "Session IV: ICCVAM Public Outreach and Education" were asked to consider the following questions:

- What are some focal points (e.g., venues, meetings, educational institutions) to

[25] Materials available at https://ntp.niehs.nih.gov/go/commprac-2025.

increase ICCVAM's and NICEATM's engagement and outreach on NAMs?

- How might ICCVAM improve public access and educational opportunities on NAMs?
- Which recent outreach efforts have been most effective in guiding ICCVAM and NICEATM activities?

Dr. Thompson-Iritani, first discussant, felt that connecting with people who don't currently feel like they're part of the conversation should be prioritized. Attendance at different conference venues would help. Improving public access includes addressing the issue of information overload. ICCVAM is a trusted resource but clarifying its role might be helpful, as many potential partners might not understand how ICCVAM relates to them, particularly those in the discovery science area. She stressed the importance of making sure NICEATM and ICCVAM are accessible.

Dr. Silveyra, second discussant, agreed that while presenting at scientific society meetings is important, so is getting NAMs into graduate curricula. Engaging with accreditation bodies and professional organizations, and fostering international collaboration is important. Having a centralized, user-friendly NAMs hub would help with accessibility of the tools. Such a hub would also be a good venue to share case studies and success stories. Online modules and toolkits would support adoption of NAMs. She encouraged NICEATM and ICCVAM to develop accessible resources such as infographics and brief summaries. Stakeholder listening sessions are important outreach for understanding the needs of academia, industry, and advocacy groups.

Additional SACATM Comments

Dr. Berg agreed with the need to manage information overload. NICEATM and ICCVAM need to consider how to curate and prioritize material, and she agreed that a centralized hub would be helpful. She also encouraged consideration of how artificial intelligence can be leveraged and used going forward.

Summarizing the session, Dr. Marty noted that part of its purpose was to solicit specific suggestions on how ICCVAM can better communicate with stakeholders, and she encouraged SACATM members to follow up with additional suggestions. Points made in this session included recognition of the value of in-person meetings and the suggestion to incorporate question-and-answer sessions or panel discussions to further encourage engagement. Connecting with a broader range of stakeholders is a continuing theme, and having materials readily available online supports that. In particular, Dr. Marty encouraged NICEATM and ICCVAM to keep students and academic training programs in mind when developing training materials and outreach strategies.

XI. Adjournment

Dr. Wolfe thanked the SACATM members for their participation in the meeting and the time they spent preparing for the meeting.

Dr. Marty thanked the committee for their thoughtful and actionable comments that challenge ICCVAM and NICEATM to improve their efforts. She thanked the presenters for their carefully prepared presentations and the organizers for their efforts in putting

together the meeting. Drs. Vinas, Hogberg, and Casey also extended their thanks to the participants; Dr. Casey added that standardizing the definition of NAMs within NIH is an active area of effort.

Dr. Marty adjourned the meeting at 2:39 p.m.

These summary minutes for the SACATM meeting on September 11-12, 2025, have been read and approved by the chair.

[redacted]

Signed,
Sue Marty, PhD
SACATM Chair
Date: December 16, 2025