A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States

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INTERAGENCY COORDINATING COMMITTEE ON THE VALIDATION OF ALTERNATIVE METHODS

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Preface

This Strategic Roadmap is a resource to guide U.S. federal agencies and stakeholders seeking to adopt new approaches to safety and risk assessment of chemicals and medical products that improve human relevance and replace or reduce the use of animals. This document was developed by representatives from 16 federal agencies and multiple interagency workgroups with input from the public. As such, it represents a consensus perspective, does not necessarily reflect opinions or policy of any specific agency or workgroup, and should not be taken as a commitment by any federal agency.

Introduction

Regulatory agencies in the United States are charged with protecting human health and the environment. To this end, agencies must determine the health hazards presented by substances such as pesticides, consumer products, cosmetics, pharmaceuticals, medical devices, and workplace chemicals. Testing these substances provides information about possible hazards and enables informed decisions regarding responsible manufacture, use, storage, and disposal.

Many currently accepted methods for assessing potential hazards use laboratory animals. However, animal-based testing has a number of recognized limitations: it can be expensive and time consuming, it raises moral and ethical issues, and it does not always identify toxic effects relevant to humans.

A more efficient, predictive, and economical system for assessing the effects of chemical substances on human health was envisioned in the seminal National Research Council report, Toxicity Testing in the 21st Century: A Vision and a Strategy (NRC 2007). In the decade since this report was published, investments in technology development and biomedical research have produced transformative scientific breakthroughs. However, these advances have not yet resulted in similar improvements in our ability to predict adverse human health effects caused by exposure(s) to chemicals and medical products. This limited translational impact can be partly attributed to the inability of relevant institutional practices to keep pace with rapid scientific advancements. Left unaddressed, the growing disparity between the capabilities offered by 21st century science and continued reliance on animal data for safety evaluations could impede our ability to capitalize on the remarkable progress made by, for example, the ToxCast and Tox21 programs, the National Institutes of Health (NIH) Tissue Chip program, and the Precision Medicine Initiative.

Alternative test methods *replace* animal use with non-animal test systems or use of phylogenetically lower species, *reduce* the number of animals required for a specific test, or *refine* animal use to lessen or avoid pain and distress. Replacement, reduction, and refinement of animal use, known as the 3Rs, have been important principles in biomedical research for over 50 years. More recently, the term “new approach methodologies” (NAMs) has been adopted as a broadly descriptive reference to any non-animal technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment. These new approaches include integrated approaches to testing and assessment (IATAs), defined approaches for data interpretation, and performance-based evaluation of test methods.

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was formally established in 2000 by the ICCVAM Authorization Act (ICCVAM Authorization Act 2000) as a permanent committee of the National Institute of Environmental Health Sciences (NIEHS). ICCVAM’s mission is to facilitate the development, validation, and regulatory acceptance of test methods that replace, reduce, or refine the use of animals. The committee is composed of representatives from 16 U.S. federal agencies that use, generate, or disseminate toxicological and safety testing information. The National Toxicology Program Interagency

Center for the Evaluation of Alternative Toxicological Methods (NICEATM)[1] provides scientific and administrative support to ICCVAM. The ICCVAM Authorization Act also specified the establishment of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), representatives drawn from specific stakeholder groups that advises ICCVAM and NICEATM on activities relevant to the act.

During its first 15 years, ICCVAM's evaluations of new methods followed a linear, stepwise validation model that proved to be lengthy, inefficient, and resource-intensive. This validation paradigm can no longer be solely relied on to meet the needs of federal agencies. Moreover, it is not compatible with many modern approaches to toxicity testing, which place less emphasis on replacement of *in vivo* tests with a single alternative method and more emphasis on NAMs that incorporate batteries of assays, *in silico* approaches, and computational models. It is important to understand and address the shortcomings of the historical approach as we move forward with a new paradigm for establishing confidence in NAMs.

- In the past, development of alternative methods was often initiated by researchers and test method developers with little input from the end users: federal agencies and regulated industries. This lack of understanding of regulatory needs, and particularly the various contexts of use, tended to produce methods that did not adequately meet the testing requirements of end users. Consequently, these methods were either not accepted by federal agencies or accepted by the agencies but not used by the regulated community. The likelihood of regulatory acceptance and industry adoption would be greatly increased if NAMs are developed "with the end in mind" to ensure fitness for purpose, which requires end users to be actively engaged during the research and development process. Likewise, it is critical that federal agencies provide clear guidance on their information needs, context of use, and willingness to accept NAMs in place of traditional animal-based tests.
- Previous validation efforts coordinated by ICCVAM typically adhered to principles described in Guidance Document (GD) 34, Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment, issued by the Organization for Economic Co-operation and Development (OECD) (OECD 2005). GD34 provides guidance on the design and conduct of validation studies, including the assessment of reliability, reproducibility, and relevance. Conforming to GD34 was intended to improve the expediency and efficiency of regulatory acceptance and incorporation of new methods into OECD test guidelines. While GD34 allows a great deal of flexibility via a "modular approach" to validation, this flexibility was not usually applied to ICCVAM-coordinated validation studies, a practice that contributed greatly to the expense and duration of these studies. In addition, GD34, published in 2005, does not fully address all considerations required for the effective evaluation of many modern technologies and approaches. Although GD34 will continue to serve as the default validation standard for the near future, the timely incorporation of 21st century science into modern risk assessment and hazard identification will require new

[1] https://ntp.niehs.nih.gov/pubhealth/evalatm/index.html.

approaches for establishing confidence in NAMs that incorporate the overarching principles described in GD34 in a more flexible and efficient manner.

– Historically, most validation studies were coordinated by a central organization (i.e., NICEATM). In many cases, it may be more appropriate for other organizations or agencies to coordinate the evaluation of NAMs. Moving forward, the United States needs to develop an approach for establishing confidence in NAMs that is better suited to capitalize on its vast but highly decentralized resources.

In 2013 ICCVAM underwent a strategic shift aimed at adjusting the validation paradigm for new test methods to be more productive, more responsive to stakeholders, and more engaged internationally. This shift led the ICCVAM to consider how a comprehensive U.S. national strategy could facilitate realization of the vision articulated in the 2007 National Research Council report. The concept of developing a strategic roadmap to establish new approaches for toxicity testing in the United States was proposed and endorsed at the 2015 SACATM meeting[2] and further developed at the 2016 SACATM meeting.[3] Acting on this endorsement, federal scientists from 16 agencies and multiple interagency workgroups met in February 2017 at NIH in Bethesda, Maryland, to discuss and develop the key elements of a new strategy for toxicity testing that would improve human relevance and reduce the use of animals.

The primary objective of this strategy, details of which are presented in subsequent sections, is to expedite the development and utilization of NAMs that provide information more relevant to human health than existing animal-based methods. While the current focus is on human health, the generalized framework could be applied to other disciplines within toxicology such as ecological toxicology. It is anticipated that focusing on human relevance will in time obviate the need for testing in animals, while also reducing the cost of product development and registration. A strategic roadmap will help establish the use of these new approaches by providing a conceptual framework to support the development, evaluation, and utilization of NAMs and facilitate communication and collaboration within and between government agencies, stakeholders, and international partners.

Strategic Roadmap

To expedite the use of 21st century science to protect and improve public health, federal agencies and stakeholders will work together to build a new framework to enable development, establish confidence in, and ensure utilization of new approaches to toxicity testing that improve human health relevance and reduce or eliminate the need for testing in animals. The successful development and implementation of these new approaches will require coordinated efforts that address the three strategic goals described below.

(1) Connect end users with the developers of NAMs. The successful implementation of NAMs will depend on research and development efforts developed cooperatively by industry partners and federal agencies. Currently, technologies too often emerge in search of a problem to solve. To increase the likelihood of NAMs being successfully developed and implemented, regulatory

[2] https://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2015/september/minutes20150902_508.pdf.
[3] https://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2016/september/minutes20160927_508.pdf.

agencies and the regulated industries who will ultimately be using new technologies should engage early with test method developers and stay engaged throughout the development of the technologies.

- **Identify anticipated testing requirements.** Agencies and industry stakeholders need to work together to identify and communicate their anticipated science and technology needs for safe product development and registration.
- **Encourage the establishment of grant review criteria tailored to the development of alternative methods.** Funding development of NAMs should begin as early in the research and development process as possible. However, most current grant review processes are tailored to reward highly innovative research and typically do not place the same value on research that does not rely on the use of animals. To better support NAM development, processes for influencing the distribution of funding by the federal government should be explored.
- **Develop mechanisms to improve communication between end users and researchers.** One of the most cost-effective and impactful actions that can be taken immediately is to foster efforts that improve the dialog between end users and test method developers. Federal agencies and industry stakeholders should collaborate to develop programs and processes that encourage an open dialog between test method developers and end users. For example, end users could host workshops or webinar series aimed at identifying agency and industry priorities with accompanying examples of use cases within or outside of regulated testing space.

(2) Foster the use of efficient, flexible, and robust practices to establish confidence in new methods. Stakeholders and federal agencies should work together to establish confidence in NAMs using flexible, robust, and integrated approaches spanning from early product development to the ultimate intended use.

- **Clearly delineate testing requirements and context of use.** Validation, by definition, is establishing fitness for a specific, intended purpose. However, data from a single guideline animal test can be used for multiple purposes, all of which need to be considered when developing a replacement. Failure to consider the ultimate context of use is one of the most frequently cited reasons for lack of agency and industry adoption of NAMs. It is therefore essential that agencies clearly communicate their needs along with all possible contexts for which data from both the existing animal study and NAM would be used.
- **Promote the use of new approaches for establishing confidence.** Agencies and stakeholders should use past experience as a guide for developing more flexible and efficient processes to evaluate fitness for purpose of a particular NAM. Developing these new approaches should be done in a collaborative, transparent, and inclusive manner. Activities to accomplish this might include:
    - Investigating approaches to establish confidence in NAMs that are driven by human biology, exposure, and mechanistic relevance (e.g. mode-of-action, adverse outcome pathways) and do not rely on animal data as the reference for

evaluating performance.

- Establishing forums to discuss best approaches to expedite regulatory acceptance of methods already in use for in-house screening by industry.
- Providing agency and stakeholder case studies illustrating how alternative approaches have successfully been evaluated or implemented.

– **Utilize public-private partnerships to promote cross-sector communication and cooperation.** The successful development of NAMs will depend on the ability of federal agencies and stakeholders to work closely together via public-private partnerships that facilitate the sharing of both knowledge and data. Extending collaborations into the private sector will allow knowledge and experience gained throughout the product development and registration cycle to be incorporated into new test method development and application. Such collaborations will also allow the resources and collective expertise of ICCVAM agencies and their stakeholders to be leveraged to address parallel testing needs and requirements across product sectors, providing opportunities to impact alternative test method research and development, acceptance, and implementation. These collaborations could, for example:
  - Identify and collate sources of high-quality human toxicological and exposure data.
  - Create centralized data access points that are publicly available and easily accessible.
  - Actively solicit the submission and collation of parallel data from animal studies and alternative methods.

(3) Encourage the adoption and use of new methods and approaches by federal agencies and regulated industries. Federal agencies and stakeholders need to take an active role in facilitating the successful adoption and use of NAMs, both within the federal government and internationally.

– **Provide clear language regarding the acceptance of NAMs.** Industry stakeholders indicate that lack of clear guidance on the status of regulatory acceptance is a significant factor impeding the use of NAMs. Industries cannot be expected to use new methods if they are uncertain about whether the data will be accepted by regulators. To facilitate use by industry, agencies should provide clear guidance on the use and acceptance of data from NAMs.

– **Collaborate with international partners to facilitate global harmonization and regulatory acceptance**. In a global economy, efforts by individual countries to develop NAMs will have little impact without international adoption of the new methods, as companies will always test according to the requirements of the most conservative country. Frequent and transparent communication with international partners will ensure that development and evaluation of NAMs are harmonized, where feasible, to account for international regulatory requirements. A forum for such a collaboration

already exists in the International Cooperation on Alternative Test Methods (ICATM), which was created to foster dialog among national validation organizations. In addition to its interaction with ICATM partners, federal agencies will also continue to be highly engaged with the OECD Test Guidelines program, placing increased emphasis on the need to develop new approaches for establishing confidence in NAMs, including the use of performance-based evaluation of test methods.

- **Explore processes to incentivize and promote the use of NAMs.** Simply establishing scientific confidence is often not sufficient justification for federal agencies or industry partners to abandon animal-based approaches in favor of NAMs. There are many practical non-scientific factors that must be considered prior to committing to the use of NAMs, such as confidence in historical results, legal considerations, and harmonization issues. The successful implementation of NAMs will depend on agencies and stakeholders working together to identify these factors and developing solutions that enable the widespread utilization of NAMs. For example, training programs on the use of a new method should be established for personnel who conduct or review toxicology studies.
- **Identify appropriate metrics for prioritizing activities, monitoring progress, and measuring success.** A challenge faced by all 3Rs efforts is determining the actual impact on the stated objective, whether it be reducing animal numbers or improving human relevance. Measuring the impact of implementation of new testing approaches is particularly difficult in the United States due to the limited ability to quantify animals used for toxicity testing. Despite these obstacles, agency-specific mechanisms often exist that can be used to estimate the impact of a given activity, such as tracking the number of waivers granted for a particular animal test. In order to assess the impact of this national strategy, effective mechanisms need to be created to track progress and identify objective criteria for measuring success.

Implementation

ICCVAM establishes temporary ad hoc workgroups to perform specific tasks identified by the committee as being important for the development or validation of NAMs and it is envisioned that ICCVAM workgroups will play a key role in implementing the goals of the Strategic Roadmap. The workgroups are chaired by representatives from agencies that use or require data from the topic of interest. The chairs are responsible for developing the group's scope and charge, which is then reviewed and approved by ICCVAM. ICCVAM member agencies and ICATM partners (EURL ECVAM, the Japanese Center for the Evaluation of Alternative Methods, the Korean Center for the Evaluation of Alternative Methods, and Health Canada) are then invited to participate in the workgroup.

ICCVAM workgroups will develop detailed implementation plans to address roadmap goals, tailored to specific toxicological endpoints of concern. These implementation plans will include four key elements: (1) definition of testing needs; (2) identification of any available alternative tests and computer models; (3) a plan to develop IATAs and defined approaches for

interpreting data; and (4) a plan to address both scientific and non-scientific challenges, including regulatory challenges such as international harmonization.

Given the critical importance of stakeholder engagement in the roadmap process, a communication plan will be developed to broaden awareness and invite engagement with the Strategic Roadmap. The goal of the communication plan will be to ensure timely, project-specific communication about activities and accomplishments relevant to the Roadmap throughout the stakeholder community. Building on the regular ICCVAM public event schedule (which includes annual meetings of SACATM, the ICCVAM Public Forum, and the ICCVAM Community of Practice Webinars), the communication plan will leverage a variety of mechanisms to facilitate the broad communication of ideas related to the roadmap's implementation, which could include focused workshops, webinars, news articles and other messages distributed via email, and web-based questionnaires and comment forms.

Development of the Strategic Roadmap

ICCVAM presented the concept for a coordinated strategy and roadmap to SACATM[4] in 2015. While acknowledging a number of challenges that would need to be considered, SACATM expressed support for the roadmap effort. "A Strategy for Implementing the Vision for Regulatory Toxicity Testing in the 21st Century" was the main focus of the 2016 SACATM meeting[5]. Discussions at this meeting centered on moving away from animal models for toxicity testing, impediments to adoption of alternative approaches, approaches to establishing public/private partnerships, and next steps toward developing a national strategy.

With the continued support of SACATM expressed at its 2016 meeting, ICCVAM entered into a yearlong process to develop the Roadmap goals with the participation of representatives from 16 federal agencies and multiple interagency workgroups.

During the first quarter of FY2017, ICCVAM drafted a mission and vision statement. The mission and vision statement was released to a larger Roadmap Planning Group prior to a workshop held in February 2017. The Roadmap Planning Group consisted of an expanded group of federal employees from both the ICCVAM member agencies and federal agencies outside the usual ICCVAM membership. At the February 2017 meeting, the Roadmap Planning Group reviewed and commented on the mission and vision statements and began developing an outline for the Roadmap.

The first opportunity for public comment on the development of the Roadmap occurred at the 2017 Annual meeting of the Society of Toxicology during a National Toxicology Program-hosted session, "Developing a Strategic Roadmap to Establish New Approaches for Evaluating the Safety of Chemical and Medical Products in the United States." Subsequent opportunities for public comment during the development of the Roadmap occurred at the ICCVAM Public

[4] https://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2015/september/minutes20150902_508.pdf
[5] https://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2016/september/minutes20160927_508.pdf

Forum[6] (May 24 at NIH in Bethesda, Maryland) and the National Toxicology Program Board of Scientific Counselors meeting[7] (June 29 at NIEHS in Research Triangle Park, North Carolina).

A draft of the Roadmap for public comment was released on the ICCVAM webpage on August 14 and this draft was discussed at the 2017 SACATM meeting[8] (September 18–19 at NIH in Bethesda, Maryland). Comments collected from SACATM and the public were considered and incorporated into a final draft that was reviewed by ICCVAM committee members.

Three Federal Register Notices were published during this time period that reference the Roadmap effort:

1. 82 FR 19071 – ICCVAM Notice of Public Meeting; Request for Public Input (NIH 2017a).
2. 82 FR 20484 – National Toxicology Program Board of Scientific Counselors; Announcement of Meeting; Request for Comments (NIH 2017b).
3. 82 FR 37885 – SACATM; Announcement of Meeting; Request for Comments (NIH 2017c).

[6] https://ntp.niehs.nih.gov/pubhealth/evalatm/3rs-meetings/past-meetings/pubforum-2017/iccvamforum-2017.html
[7] https://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2017/june/minutes20170629_508.pdf
[8] https://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2017/september/minutes20170918_508.pdf

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Acronyms & Abbreviations

3Rs	replace, reduce, and refine animal use in research and testing
EURL ECVAM	European Union Reference Laboratory for Alternatives to Animal Testing
GD	guidance document
IATA	integrated approaches to testing and assessment
ICATM	International Cooperation on Alternative Test Methods
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
NAMs	new approach methodologies
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NIEHS	National Institute of Environmental Health
NIH	National Institutes of Health
OECD	Organization for Economic Co-operation and Development
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
Tox21	Toxicology Testing in the 21st Century
ToxCast	EPA Toxicity Forecaster
U.S.	United States