The U.S. Strategic Roadmap: New Approaches to Evaluate the Safety of Chemicals and Medical Products

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Preface

The U.S. strategic roadmap is intended as a resource to help guide the efforts of federal agencies and stakeholders seeking to adopt new approaches for use in safety and risk assessment. This document was developed by representatives from 16 federal agencies and multiple interagency workgroups. 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, 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 safety-testing methods 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 xenobiotics on human health was envisioned in the seminal National Research Council (NRC) report, *Toxicity Testing in the 21st Century: A Vision and a Strategy*. In the decade since this report was published, investments in technology development and biomedical research have produced the transformative scientific breakthroughs necessary to begin realizing the NRC vision. However, these advances have not yet resulted in similar improvements in our ability to predict adverse human health effects caused by exposures to chemicals. 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, Human Tissue Chips, 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 procedure, or *refine* animal use to lessen or avoid pain and distress. Replacement, reduction, and refinement of animal use, known as the 3Rs, have been guiding principles in biomedical

research for over 50 years. More recently, the term "new approach methodologies" (NAMs)[1] has been adopted[1] as a broadly descriptive reference to any nonanimal technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard assessment.

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was formally established in 2000 by the ICCVAM Authorization Act 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) provides scientific and administrative support to the committee. The act also specified the establishment of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), a group of representatives of 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 approach to validation no longer meets the needs of federal agencies and is not compatible with 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 these and other shortcomings as we move forward with a new paradigm for establishing confidence in NAMs:

- In the past, development of alternative methods has often been initiated by researchers and test method developers with little input from federal agencies and regulated industries. This lack of understanding of regulatory needs 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 and if end users are actively engaged during the research and development process.

- Past validation efforts coordinated by ICCVAM typically adhered to processes 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 Organisation for Economic Co-operation and Development (OECD). GD34 provides guidance on factors such as the design and conduct of validation studies, independent

[1] https://echa.europa.eu/documents/10162/22816069/scientific_ws_proceedings_en.pdf/a2087434-0407-4705-9057-95d9c2c2cc57

evaluation of validation studies, international harmonization, and documentation used to support validation studies. Conforming to GD34 was intended to improve the expediency and efficiency of regulatory acceptance and incorporation of new methods into the 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 aspects required for the evaluation of more modern technologies and approaches. The United States needs an approach for establishing confidence in NAMs that incorporates many of the overarching principles described in GD34 in a more flexible and efficient manner.

- The validation process previously employed by ICCVAM was compartmentalized and linear: methods were developed, then validated, then accepted by regulators, and finally adopted by industry. The discretization of these steps often resulted in poor communication between key participants regarding needs and expectations, which led to inefficiencies in the validation process, ultimately contributing to the lack of acceptance and utilization of NAMs.

- Although the acronyms are similar, the organizational structures and funding models of international "validation organizations" (EURL ECVAM, ICCVAM, JaCVAM, KoCVAM, etc.) vary greatly in both scope and scale. For example, ICCVAM is a coordinating committee and makes recommendations on the acceptability of new test methods; it has no labs, no budget, and no authority. The European Union Reference Laboratory for Alternatives to Animal Testing (EURL-ECVAM), on the other hand, is a true "validation center" with a staff of dozens, a Good Laboratory Practice (GLP)-compliant in vitro laboratory, a high throughput screening facility, and a network of 37 GLP-compliant labs that provide dedicated support for validation studies. It is not realistic to expect one model of validation to work for, for example, both ICCVAM and EURL-ECVAM. While fully recognizing the value of validation models being applied in other regions or by other validation organizations, the United States needs to develop an approach to establishing confidence in NAMs that is better suited to capitalize on its vast but broadly distributed resources.

In 2013 ICCVAM underwent a strategic shift aimed at changing the validation paradigm for new test methods to be more productive, more responsive to stakeholders, and more engaged internationally. This shift led the committee to consider how development of a comprehensive U.S. national strategy could facilitate realization of the vision articulated in the 2007 NRC 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 and further developed at the 2016 SACATM meeting. Acting on this endorsement, federal scientists from 16 agencies and multiple interagency workgroups met in February 2017 to discuss and develop the key elements of a national strategy for toxicity testing that would improve human relevance and reduce the use of animals.

The primary objective of this strategy is to expedite the development and utilization of NAMs that provide information more relevant to human health than existing animal-based methods, although the generalized framework could be applied to any discipline of toxicology (i.e., ecological toxicology). It is anticipated that focusing on human relevance will 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 Outline

To expedite the use of 21st century science to protect and improve public health, federal agencies and stakeholders will work together to establish a new framework that directs the development of enabling technologies and promotes strategies to 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 being guided by industry partners and federal agencies. Currently, technologies too often emerge in search of a problem to solve. Providing early guidance on the specific needs of the safety / risk assessment community and maintaining a presence during the evolution of a technology should significantly increase the likelihood of successful NAMs being developed and implemented.

- **Identify anticipated testing requirements.** Agencies and industry stakeholders should 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 must 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 intended for applied toxicity testing. 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 a workshop or webinar series aimed at identifying agency and industry priorities along with 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, integrated approaches to testing that span from early 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 one existing guideline study 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:
    - 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 more human-relevant approaches to toxicity testing 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. 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 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 must take an active role in processes required for the successful adoption and use of NAMs, both within the federal government and internationally.

- **Agencies should adopt 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 start using new methods if they are uncertain about whether the data will be accepted by regulators. In order to facilitate use by industry, agencies should provide clear guidance on the use and acceptance of data from NAMs.

- **Agencies should 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. Additionally, the expertise and resources vary significantly between regions. This diversity of resources should be leveraged to expedite the incorporation of NAMs into a modern risk assessment framework. 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 framework for such a collaborative effort already exists in the International Cooperation on Alternative Test Methods (ICATM), which was created to foster such dialog among national validation organizations. The United States also will 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. These new approaches will include integrated approaches to testing and assessment (IATAs), defined approaches for data interpretation, and performance-based evaluation of test methods.

- **Agencies and stakeholders should work together to 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.

- **All stakeholders should endeavor to identify appropriate metrics for prioritizing activities, monitoring progress, and measuring success.** A challenge faced by all 3Rs

efforts, including those conducted internationally, is determining the actual impact on the stated objective, whether it be reducing animal numbers or improving human relevance. The difficulty of measuring the impact on animal usage, in particular, is exacerbated in the United States due to limitations imposed by the Animal Welfare Act. Despite these difficulties, 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 working groups to perform specific tasks that have been identified by the committee as being important for the development or validation of NAMs. The workgroups are chaired by representatives from agencies that use or require data from the topic of interest. The chairs are responsible for developing a scope and charge for the group, which is 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 offered the opportunity to participate in the workgroup.

Detailed implementation plans developed by ICCVAM working groups to address roadmap goals 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. A draft implementation plan outline is provided in Appendix 1.

Current ICCVAM working groups focus on the following areas: reference chemicals, skin sensitization, acute systemic toxicity, ocular and dermal irritation, developmental and reproductive toxicity, in vitro to in vivo extrapolation (IVIVE) and read-across. Implementation plans developed by these groups will be will be made available to the public. ICCVAM is also evaluating processes that will facilitate public-private collaborations that can support working group efforts.

Communication Plan

A key role of ICCVAM is to promote the scientific validation, regulatory acceptance, and industry utilization of NAMs. Given the critical importance of stakeholder engagement in the roadmap process, a communication plan will be developed which ensures timely, project-specific communication to and from the scientific 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 Webinar), a variety of mechanisms including focused workshops, webinars, news articles, and other messages distributed via email, and web-based

questionnaires and comment forms will be considered in facilitating the broad communication of ideas related to the roadmap's implementation.

APPENDIX 1

Implementation Plan Template:

Coordinate activities via ICCVAM Working Groups (including ICATM partners)

- Prioritize based on agency needs, expected impact on animal usage, mechanistic understanding, ability to mitigate obstacles, and available resources
- Coordinate efforts with international partners (e.g. OECD)

Draft Scoping Document:

- Identify all agency requirements / expectations
    - Classification & labeling system(s) (GHS, EPA, CPSC)
    - Legal framework for acceptance of alternative methods
- Define chemical and regulatory space for each agency
- Identify validated alternatives and status of acceptance by agency
- Identify gaps associated with the suite of available alternatives (i.e., adequate AOP coverage)
- Identify obstacles to implementation

Coordinate efforts with stakeholders:

- Establish public/private partnerships
- Organize workshops to discuss state of the science and implementation progress

Identification, acquisition, and curation of high quality data (in vitro and in vivo):

- Facilitate agency-driven data-sharing initiatives
- Leverage partnerships with industry
- Curate the scientific literature and publicly available databases

Identify and develop approaches:

- Develop defined approaches using in silico and/or in vitro features
- Review literature for published defined approaches that can be evaluated
- Interrogate in vivo variability to provide context for confidence in alternative approaches

Gain regulatory acceptance and use:

- Validate defined approaches for regulatory decision contexts
- Develop training materials and assist agencies in issuing guidance