DRAFT

A New Vision and Direction for ICCVAM

Introduction

In 2000, Congress passed the ICCVAM Authorization Act and established ICCVAM (Interagency Coordinating Committee on the Validation of Alternative Methods) as a permanent interagency committee composed of the heads (or their designees) of 15 Federal regulatory and research agencies that require, use, generate, or disseminate toxicological and safety testing information. NICEATM [NTP (National Toxicology Program) Interagency Center for the Evaluation of Alternative Toxicological Methods] of the National Institute of Environmental Health Sciences (NIEHS) provides scientific and operational support for ICCVAM's technical evaluations and related activities. ICCVAM and NICEATM work together to promote the development, validation, and regulatory acceptance of new and revised regulatory test methods and integrated testing and decision strategies that replace, reduce, and refine the use of animals in testing while maintaining and promoting scientific quality and the protection of human health, animal health, and the environment. In response to requests from Congress, ICCVAM prepared the 2008-2012 Five-Year Plan in collaboration with relevant Federal agency program offices. The 2008-2012 Five-Year Plan described the priorities for evaluating test methods and performing test method reviews. Efforts between 2008 and 2012 led to reviews of the validation status and regulatory acceptance for a number of *in vitro* alternatives, including ocular toxicity, pyrogenicity assessment, and *Leptospira* vaccine potency testing.

In May 2012, ICCVAM published a draft 2013-2017 Five-Year Plan for public comment and for review by the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM). Subsequently, Linda Birnbaum, the Director of NIEHS and NTP, and ICCVAM announced that ICCVAM and NICEATM would be making significant changes to the focus and priorities of both groups (*http://iccvam.niehs.nih.gov/announcements/ICCVAM-all/2013-02-06-EHP.htm*). In time, these changes are intended to better align ICCVAM and NICEATM with the vision laid out by the National Academy of Sciences in the 2007 NRC Report on Toxicity Testing in the 21st Century (NRC, 2007) while simultaneously fulfilling the mission of ICCVAM to implement the 3Rs of toxicity testing (*i.e.,* replace, reduce, and refine) in accordance with the ICCVAM Authorization Act of 2000. Implementing the NRC vision will take time. In the shorter term, ICCVAM and NICEATM are working together to improve the process and procedures to augment efficiency and productivity.

The present document describes the initial steps towards a new strategic direction for ICCVAM. Specifically, this document discusses: (1) ICCVAM priority setting and areas for scientific focus for immediate resource investment; (2) plans to improve communications with stakeholders and the public; and 3) exploration of new paradigms for the validation and utilization of alternative toxicological methods.

ICCVAM priority setting and areas for scientific focus for immediate resource investment

As part of the new direction for ICCVAM, member agencies will take a more active role in priority setting and operations of the Committee. These changes will allow more effective resource investment in projects of interest and utility to the agencies. One aspect of these changes is a re-orientation of resources invested by member agencies. The draft 2013-2017 Five-Year Plan described numerous projects that ICCVAM would be participating in, thus diluting limited resources over many projects. Currently, ICCVAM is considering an alternative strategy to identify priority areas for enhanced, immediate resource investment where there is an expectation of short-term success (< 5 years, see below). In order to maintain a high level of awareness of scientific advances in the key areas of relevance to ICCVAM, member agencies will play a larger role in communicating needs specifically related to their agency.

ICCVAM is developing revised procedures for the submission/nomination of new assays or projects. These revised procedures will be shared with the public for comment in the future. A key change to the process, however, will be the need for documented support by at least one federal agency. This federal agency will take the role of 'sponsor' for the proposed project, thereby ensuring that work done by ICCVAM is aligned with the needs of the agencies.

NICEATM will continue to provide administrative and scientific support to ICCVAM. However, a significant amount of NICEATM resources will now be allocated to utilizing computational toxicology, data mining, and cheminformatics approaches to identify and evaluate methods that can replace or refine toxicity tests currently performed using animals. NICEATM will also work closely with the NTP Biomolecular Screening Branch in supporting the interagency Tox21 consortium (*http://tox21.org*).

As described above, ICCVAM has identified several projects where the science has advanced substantially and where there is a reasonable likelihood of success with a reasonable timeframe (1-5 years) for implementation into regulatory use. As a result, ICCVAM and NICEATM are initiating efforts to increase resources towards the following projects:

- *Biologics: Leptospira vaccine potency.* The US Department of Agriculture's Animal and Plant Health Inspection Service (USDA-APHIS) is committed to decreasing the number of hamsters used in *Leptospira* vaccine potency testing. The Department is also developing a mechanism to use fewer hamsters in the maintenance of the *Leptospira* challenge cultures. The effects of this change on hamster usage will be monitored over the next 5 years. A 25%-30% decrease in animal usage by the industry is anticipated.

- *Acute oral and dermal toxicity testing.* The US Environmental Protection Agency (EPA) is working with NICEATM to evaluate the relative contribution of acute and dermal Lethal Dose (LD50) tests in providing information related to hazard labeling and use of personal protective equipment. In addition, ICCVAM is working with NICEATM to assess the utility of *in vitro* assays (e.g. 3T3 NRU) for predicting oral LD50 values.

- *Skin sensitization.* Great strides have been made in putting together an *in silico/in chemico/in vitro* battery for the assessment of skin sensitization. Such animal alternative assays have been developed for the various key events in the adverse outcome pathway for skin sensitization. ICCVAM is developing a strategy for how it plans to evaluate skin sensitization test methods and to make progress towards skin sensitization testing without the use of intact animals. ICCVAM will request input from the public and SACATM on the development of this strategy.

The identification of these areas does not mean that ICCVAM and NICEATM will no longer be engaged in following the advancement of science for other alternative approaches. On the contrary, ICCVAM is moving towards better coordination with on-going international activities, and agency representatives will be expected to update ICCVAM and NICEATM regularly on activities in their agencies. As other alternative approaches are developed and show promise, ICCVAM and NICEATM will maintain flexibility to reorient efforts to maximize potential progress towards implementing the 3Rs. For example, historically, ICCVAM has taken an approach oriented around a one-to-one replacement of an *in vivo* test with an alternative assay. As suggested by the skin sensitization effort noted above, this approach is changing. In the future, as alternative methods move into the area of assessment of repeated-dose, more complex batteries of tests that evaluate systemic toxicity will need to be assembled. As a consequence, there will be less emphasis by ICCVAM and NICEATM on one-to-one replacement of an *in vivo* toxicity endpoint with a single alternative assay and more emphasis on batteries of assays and *in silico* approaches to interpret and analyze such batteries.

Plan to improve communications with stakeholders and the public

One of the roles of ICCVAM is to promote the scientific validation, regulatory acceptance, and industry utilization of alternative toxicological methods that replace, reduce, or refine animal use. To accomplish this role, ICCVAM needs to improve communications regarding efforts by federal agencies to implement the 3Rs and to improve acceptance of these efforts by both regulators and the regulated community. To accomplish this, ICCVAM is making plans to:

- *Improve Agency-specific 3R content on the ICCVAM website.* Federal Agencies are actively engaged and leading efforts to improve and fundamentally change regulatory toxicity testing. The ICCVAM website will be updated for easier navigation and to provide a venue for greater transparency about current agency activities and accomplishments. Although the public is aware of some efforts such as EPA's ToxCast and the National Institute of Health's Tox21 projects, many efforts are not as well publicized. Therefore, the ICCVAM website will be used as a single repository for highlighting all efforts by federal agencies to implement the 3Rs.

- *Achieve broader engagement with the scientific community and stakeholders (e.g., the regulated community, public interest groups) to advance regulatory science and encourage*

broader application of alternative methods in regulatory decision-making. ICCVAM intends to engage stakeholders though a number of different mechanisms including: focused workshops with well-defined objectives, community of practice webinars, and web-based questionnaires and comment forms. In addition, ICCVAM will seek to have more interaction with stakeholders via face-to-face forums that facilitate the direct communication of ideas and suggestions.

- *Increase agency awareness of international 3R efforts.* In order to increase participation with 3R projects coordinated by the Organization for Economic Co-operation and Development (OECD), the US national coordinator for OECD will become an *ad hoc* member of ICCVAM. The national coordinator will provide frequent updates on topics of interest to federal agencies and also use ICCVAM as a forum to provide feedback on those activities to OECD.

New paradigms for regulatory acceptance and utilization of alternative methods

There is significant worldwide interest in developing an understanding of how biological pathways become engaged in toxicity responses. The aim is that knowledge about these pathways will lead to predictive, integrated testing strategies that will likely combine *in silico* approaches and multiple *in vitro* or high throughput assays with limited, targeted testing in laboratory animals. There are various statistical approaches to assembling components of a "most predictive" test battery that warrant consideration by ICCVAM, as well as statistical models for integration of all relevant information and assay results. In addition, significant efforts are being put into *in silico* and *in vitro* approaches for screening and prioritization. Given the important differences in these applications (regulatory testing for safety evaluation or risk assessment vs. screening/prioritization) of alternative assays, the concept of validation needs to be re-considered. In the area of validation, ICCVAM and NICEATM have roles to play in these paradigm shifts, although those roles are not completely clear at this time. ICCVAM and NICEATM will be engaging the public to reconsider the concept of validation along with their roles in this new paradigm.

In addition to changing the concept of validation, ICCVAM member agencies recognize that re-evaluating standing policy in response to new data could also have a substantial impact on the number of animals used for regulatory safety testing.