PhysiciansCommittee
for Responsible Medicine
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Dr. Warren Casey, Director
National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)
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Submitted via ICCVAMquestions@niehs.nih.gov

Dear Dr. Casey,

The Physicians Committee for Responsible Medicine is a nationwide nonprofit comprised of over 175,000 supporters advocating for efficient, effective and ethical medical practice, nutrition, and research. We appreciate the opportunity to provide written and oral input on NICEATM and ICCVAM-related activities over the past year.

We will start by offering our congratulations on the publishing of *A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States*. This plan for modernizing safety testing is commendable and reflects the hard work, dedication, and engagement of ICCVAM member agencies under NICEATM's leadership. We appreciate that the roadmap clearly aims to advance human relevant approaches that are efficient, predictive, and economical, given the limitations to animal-based testing.

Below, we offer feedback on specific accomplishments and highlight opportunities that remain.

IMPROVING DIALOGUE BETWEEN END USERS AND NAM DEVELOPERS

The roadmap describes the need for collaboration between new approach methodology (NAM) developers and end users. We commend NICEATM and ICCVAM for consistently keeping the lines of communication open in an effort to break the silos of communication that previously existed in regulatory testing. We have also been impressed with the National Center for Advancing Translational Sciences (NCATS) Tissue Chips collaboration and the ability of NCATS to bring together regulators, the private sector, and academia to work together at all stages of development to quickly and responsibly advance these technologies. We were pleased to see that the Food and Drug Administration's (FDA) own Predictive Toxicology Roadmap also highlights the need for collaboration.

In the spirit of collaboration and as part of roadmap implementation activities, we would like to explore co-sponsoring a workshop with ICCVAM and FDA to identify overlapping agency and industry priorities for integration of NAMs into the drug development pipeline.

NAM FUNDING

The roadmap identifies that funding of NAMs should begin as early in the research and development process as possible, and that current grant review processes are tailored to reward research involving animals. We appreciate previous and existing opportunities such as the SBIR/STTR NIH grants and NIH's National Eye Institute competition for 3D retina organoids. The more agencies and institutions that sponsor grants tailored to the development of NAMs, the quicker technologies that are fit for regulatory purposes will emerge and mature.

In recent years, we have had many conversations with scientists who received feedback that their grant proposals were denied because animals were not included in their grant submission. To address this problem much more funding should be specifically allocated to NAMs. It would be helpful for the NIH to be transparent in reporting how much funding is awarded to NAMs compared to research involving animals. One suggestion to ensure the funding of NAMs is for NIH to adopt a policy in which all institutes allocate funding specifically for this area.

Another idea to increase the distribution of funding to NAMs is to support systematic literature reviews by the National Academy of Sciences (NAS) highlighting areas of study where NAMs are needed most urgently to ameliorate poorly predictive experimental models using animals. These highly regarded reviews provide rationale for any findings, conclusions, and recommendations that are discussed in the report. The results of these reports often form the basis of public policy for the future. This type of favorable support could be used to justify to Congress the need for an increase in funding for NAMs. Validation from the NAS, along with the backing of NICEATM, ICCVAM, and other supporting organizations could encourage NIH to shift significant funding towards NAMs. The NIH could then take specific NAS recommendations and create targeted requests for applications (RFAs) to address these areas and ensure the increased development of NAMs.

To uphold the value of peer review the current grant review criteria should be revised to place a greater emphasis on the use on NAMs, while removing any explicit reference to or implication of a requirement to include animal experiments. To better support grant applicants using NAMs, review committees should consist of researchers well versed in various methodologies, not solely in research involving animals. We are interested in partnering with ICCVAM on the development of additional review criteria and active training to further reviewer knowledge and consideration of the use of NAMs.

NAM ASSESSMENT

As the roadmap describes, scientific evaluation of new approaches is an important step in confidence building. Confidence will increase as users and regulators begin to see consistent and pertinent examples where NAMs were successfully used. We encourage ICCVAM to continuing sharing these examples, such as the Environmental Protection Agency's (EPA) use of Adverse Outcome Pathways (AOP) and toxicity pathway frameworks in the Endocrine Disruptor Screening Program (EDSP).

Creative incorporation of human data into the assessment process should also be considered. An AOP can bring a biological plausibility approach to the assessment of NAMs, providing an understanding of the context of biology of a NAM or approach and allowing for a weight of evidence consideration of other data streams, including that from human tissues and clinical or epidemiological studies.

Equally important is an assessment of the frequently used in vivo methods. While human data are not always available to discern the true predictive capacity of an in vivo method, they should be used where possible. Where human data is not available, in vivo methods can be assessed for their reproducibility—that is, a method's ability to predict itself. New methods based on human cells and tissues should not be held to a higher standard than that to which existing in vivo methods can perform, particularly since many in vivo methods in use today were never assessed for their predictive capacity.

Finally, we are interested in exploring co-sponsorship with ICCVAM of a workshop aiming to expedite the regulatory acceptance of NAMs already in use in-house by the pharmaceutical and chemical industries.

ADOPTION AND USE OF NAMs BY FEDERAL AGENCIES AND REGULATED INDUSTRIES

Clear language regarding the acceptance of NAMs

The roadmap states that industry stakeholders indicate lack of clear guidance on the status of regulatory acceptance as a significant factor impeding the use of NAMs. This is consistent with industry feedback we have received. While industry has a responsibility to proactively use and submit NAMs wherever possible, clearer guidance and policy documents from agencies will help to facilitate this shared endeavor.

The Frank R. Lautenberg Chemical Safety for the 21st Century Act addressed this to a degree for chemicals and pesticides, and the EPA has done an excellent job so far at implementing this law. Room for improvement remains in transparently outlining test methods which may be accepted alongside traditional in vivo EPA test guidelines (on its web site); however we believe the implementation of the strategic plan still being drafted will help to ameliorate some of this concern.

Industry is reluctant to submit alternative approaches without clear language or specific request by regulators. While we don't agree that agencies should need to specifically request alternative approaches in order for industry to submit data from them, clear

statements about their acceptance are very helpful. We encourage agencies to routinely generate guidance or other documents or statements to industry that clearly outlines acceptance of alternative methods or strategies that could reduce or replace in vivo studies, including exemptions and waivers, and post them on their Web site adjacent to existing toxicology (often in vivo) guidelines. Communication on NAMs that can be used for specific regulatory needs may enable industry on a broader scale to increase their creative incorporation of NAMs into regulatory submissions and avoid testing using animals.

We recently provided the Regulatory Reform Task Force at the FDA with 235 regulations that mandate or prioritize animal data. To clearly communicate FDA's discretion to accept NAMs, these regulations should be broadened to accept data from 'nonclinical approaches' rather than specifically requesting data from 'animals'. This will help build industry confidence in NAMs and ensure the longevity of the regulation despite rapidly advancing nonclinical approaches. We encourage other agencies to consider this approach and "generalize" toxicology language away from specific reference to in vivo tests, methods, or data.

Global harmonization

As the roadmap highlights, international testing requirements influence NAM adoption in the United States because companies test for the requirements of the most conservative country.

We encourage ICCVAM to strengthen engagement with Organisation for Economic Co-operation and Development (OECD) to encourage international harmonization efforts. Currently, the EPA is actively involved in OECD activities. Other agencies, where applicable, should consider joining OECD activities by leading the development of test guidelines, guidance documents, and case studies.

Involvement in other collaborations, such as the International Cooperation on Alternative Test Methods (ICATM) should continue to be encouraged to influence global harmonization.

Reviewer training on NAMs

Consistent with the roadmap, we understand that the successful implementation of NAMs includes building agency confidence through training. In recent years, we have sponsored multiple trainings for EPA reviewers on NAMs such as the OECD QSAR toolbox and to the scientific community on Adverse Outcome Pathways.

We are eager to expand our reviewer trainings to address FDA needs identified in FDA's Predictive Toxicology Roadmap, including NAMs addressing developmental and reproductive toxicity.

Early career scientist involvement
The next generation of scientists will be key to developing, evaluating, and use of NAMs. We encourage ICCVAM to consider ways to involve next generation scientists in ICCVAM activities.

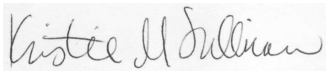
Skin sensitization
Thanks to the work of NICEATM and other scientists, it is now understood that nonanimal testing strategies and methods for skin sensitization are more predictive for human health outcomes than the animal methods traditionally used. We commend NICEATM and ICCVAM for its work leading to adoption of a standalone OECD test guideline for in vitro skin sensitization and EPA's draft Science Policy on skin sensitization.

The Physicians Committee continues to be impressed by NICEATM and ICCVAM's leadership in modernizing safety assessment. We look forward to collaboration over the next year to advance our shared goals.

Because the roadmap is not intended to reflect the policy of the member agencies, we encourage representatives from each member agency to consider working to publish strategic plans for their agencies addressing the use and development of 21st century science.

Thank you for your time and consideration of these comments.

Sincerely,



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