PhysiciansCommittee
for Responsible Medicine
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Sent via email to whiteld@niehs.nih.gov

Dear Dr. White,

The Physicians Committee for Responsible Medicine appreciates the opportunity to comment on Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) related activities. Our comments are divided among the sections outlined for public comment in the preliminary agenda.

ICCVAM Roadmap for Skin Sensitization Testing
We support NICEATM's approach for gaining consensus on the acceptance of alternatives to animals for skin sensitization globally. With the truly robust mechanistic knowledge and suite of alternative test methods currently available, the days of the Local Lymph Node Assay and the guinea pig assays should be numbered. We encourage ICCVAM federal agencies to continue to support this transition and to publish clear guidance for their respective regulated communities and internal staff to ensure that animal tests are not conducted.

Moving Away from Animal Models for Toxicity Testing
We are repeatedly impressed by NICEATM and ICCVAM's progress under Dr. Casey and Dr. Kleinstreuer's leadership. Dr. Casey's recent publication, *A Strategy for Implementing the Vision for Toxicity Testing in the 21st Century*, reflects NICEATM's fervent commitment to advancing science while replacing animal testing.

We strongly support the suggestions that the Office of Science and Technology Policy (OSTP) be engaged to charge a high level workgroup with drafting a roadmap for implementing the National Research Council's vision for Toxicity Testing in the 21st Century, and that the National Academy of Sciences (NAS) convene a series of workshops or panels that identify and address the impediments and enablers of progress. We recommend the roadmap and workshops focus on replacement of animal tests, with consideration give to reduction opportunities. These groups are

well positioned to lead these necessary projects and a single agency should not be expected to coordinate such a large effort. We would like to add that developing a national strategy and roadmap for replacing animal testing is an unfulfilled need that is applicable across federal agencies and therefore, would ideally involve coordination and direction from the President. We recommend SACATM engage the Administration to emphasize the importance of a national strategy and roadmap to advance innovative science and replace animal testing.

We commend NICEATM and ICCVAM on previous validation work and encourage continued assistance and funding opportunities. Also relevant to the publication, we are particularly concerned that modern human-focused technologies are compared to unvalidated animal tests when evaluating their ability to perform. Aside from ethical concerns, a significant reason to advance from using animal tests to using alternatives is the animal tests do not always provide information that is relevant to humans. Therefore, the standard for validation should be a technology's ability to predict known human toxicity, rather than a technology's ability to predict the animal test.

One method which may help us to improve the validation process for human-based methods is to consider what information or experience can be gained from using these models in a disease research context. Human tissue culture or microphysiological models can be used to understand the etiology of human disease and discover or assess the efficacy of new treatments, helping industry and regulators to gain experience with use of such models, making replacement of toxicity assays more likely in the future. We encourage NICEATM to explore potential for this approach with NCATS and other NIH institutes, including how the NIH can exploit extramural research funding projects to gain experience with human-relevant, nonanimal disease models in the context of drug development and testing.

We also suggest that identifying Adverse Outcome Pathways for toxicological endpoints—or even simply gaining more mechanistic insight into toxicological pathways—will help to validate new tools and support their use in specific regulatory contexts by providing information on the relevance of test methods with favorable reproducibility and transferability characteristics.

The publication also addresses the need for and suggestions to increase coordination amongst and between federal agencies. Communication is key to improving scientific efficiency and increasing the use of human-focused alternatives to animal tests. Recently, with additional events such as the Spring ICCVAM public forum, communication with external stakeholders has improved.

However, the communication of new agency policies with NICEATM, among ICCVAM partner agencies, and *within* agencies must improve. In order to increase communication among federal ICCVAM agencies, we suggest SACATM advise NICEATM and ICCVAM to establish a process whereby ICCVAM agencies

communicate with NICEATM when policy changes are made that will replace or reduce the use of animals in testing. NICEATM should then take the lead on communicating such changes to other federal agencies for harmonization and appropriation, where appropriate.

We agree with Dr. Casey's statement in the publication that important non-scientific considerations can impede the adoption and implementation of alternative approaches. In particular, we would like to address legal, policy and training opportunities. Established agency regulations may be reasonably read to require animal tests, or prioritize them over nonanimal alternatives. For example, there are 29 FDA regulations[1] that, on their face, require animal data. We recommend SACATM advise member agencies to ensure their regulations do not discourage the use of alternative test methods by requiring animal data or prioritizing it. Instead, agencies should endeavor to revise their regulations to outline test-neutral safety standards. Such updates could be made through changes to the text of the regulations, and/or by issuing agency guidance to clearly communicate current policy to agency and industry.

Training is another opportunity for improving science and replacing animal tests. It is critical that agency scientists and reviewers are knowledgeable about available and acceptable alternatives, and that less reviewer variability exists regarding acceptance of alternative tests. We can serve as a resource to achieve this, offering both our time in coordinating and implementing trainings, and financial backing. We have experience coordinating training for agencies including California EPA, US EPA, and others.

We thank SACATM for giving close consideration to the need for a national strategy/roadmap and our suggestions toward implementation.

Coordinating Activities Between the Federal Government and Stakeholders
The mission and goals of federal agencies and stakeholders often overlap, offering many opportunities for collaboration. In such cases, stakeholders can serve as additional resources to support federal agencies in furthering mutual goals. We look forward to continued collaboration on training programs with EPA and new opportunities with other agencies such as FDA.

[1] 21 C.F.R. § 310.303, 21 C.F.R. § 312.22(c), 21 C.F.R. § 312.23(a)(3)(iv), 21 C.F.R. § 312.23(a)(5)(ii), 21 C.F.R. § 312.23(a)(5)(iii), 21 C.F.R. § 312.23(a)(8), 21 C.F.R. § 312.23(a)(8)(i), 21 C.F.R. § 312.23(a)(8)(ii), 21 C.F.R. § 312.23(a)(10)(i), 21 C.F.R. § 312.23(a)(10)(ii), 21 C.F.R. § 312.33(a)(6), 21 C.F.R. § 312.82(a), 21 C.F.R. § 312.88, 21 C.F.R. § 312.160, 21 C.F.R. § 314.50(d)(2), 21 C.F.R. § 314.50(d)(2)(iv), 21 C.F.R. § 314.50(d)(5)(i), 21 C.F.R. § 314.50(d)(5)(vi)(a), 21 C.F.R. § 314.50(d)(5)(vi)(b), 21 C.F.R. § 314.93(e)(2), 21 C.F.R. § 315.6(d), C.F.R. § 330.10 (a)(2), 21 C.F.R. § 601.35(d), 21 C.F.R. § 812.2(c), 21 C.F.R. § 812.5(c), 21 C.F.R. § 812.27(a), 21 C.F.R. § 812.35(a)(3)(iii), 21 C.F.R. § 860.5(f), 21 C.F.R. § 860.7(d)(2).

Impediments to Adoption of Alternative Approaches
Communication, training and harmonization are impediments to the adoption of alternative approaches.

A lack of communication is an impediment because the fact that an alternative test is accepted, or that an animal test is not required, may not be properly communicated to agency and industry. For example, the Center for Drug Evaluation and Research (CDER) at the FDA states at ICCVAM meetings that it does not require Draize data for skin or eye irritation testing. In October 2015, CDER issued Guidance stating that in vitro or ex vivo tests should be used in lieu of the in vivo rabbit ocular irritation test, commonly know as the Draize test, for dermal route of administration where a new formulation contains a substance that has not been evaluated for ocular irritation. While we commend CDER for this effort to clearly communicate with stakeholders that Draize data are not required in this limited instance and that in vitro or ex vivo tests should be used, a Guidance with broader applicability is welcome to communicate that Draize data are not required and in vitro or ex vivo tests are accepted. Additionally, to increase the communication among stakeholders, if NICEATM and ICCVAM establish a process whereby ICCVAM agencies communicate with NICEATM when policy changes are made that will replace or reduce animal testing, as suggested above, NICEATM could take the lead on communicating such changes to the broader stakeholder community.

Across the board, communication can be improved by federal agencies issuing guidance on alternative test methods. While Guidance documents are non-binding, they can have the effect of a binding regulation because they are recommendations that reflect an agency's current thinking on a topic and are followed by agency staff and industry. We ask SACATM to advise ICCVAM federal agencies to issue and maintain guidance that describes which traditional tests are no longer required.

Training is an impediment to adoption of alternative approaches because agency reviewers may not recognize when and how an alternative test may be used.

Conflicting international testing requirements can impede the adoption of alternative approaches. Without international agreement regarding the use of alternative tests, animal tests are likely to continue in order to meet international regulations, even where ICCVAM agencies advance alternative methods. As a member of ICCVAM and International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), FDA should establish a process for communicating NICEATM and ICCVAM related activities to the ICH and lead ICH to issue more guidance on alternative methods. At the very least, FDA should work to establish flexibility in ICH Guidance to allow for alternative tests.

Another impediment to the adoption of alternative approaches is the lack of information about how, and how many, animals are used in toxicology in the United States on an annual basis. This information would help to show that efforts by the

government and stakeholders to implement the recommendations of the *National Academies Toxicity Testing in the 21st Century Report* are (or are not) being effective, and help to focus efforts and resources where they are needed most or would have the most effect. We encourage SACATM to consider and discuss this problem, and we encourage ICCVAM agencies to design systems that would allow the capture and reporting of this information regularly. Finally we encourage USDA to explore voluntary programs to collect the numbers of rats, mice, and birds from private research and testing facilities as an add-on to its current collection activities.

Promoting Adoption of Alternative Testing Strategies

We ask SACATM to advise NICEATM and ICCVAM to continue engaging in collaborative work with stakeholders, such as collaborating with the American Society for Cellular and Computational Toxicology (ASCCT) to hold webinars, and continuing to take advantage of Communities of Practice.

As discussed above, improved communication among federal agencies and between agencies and stakeholders, improved validation processes and training opportunities will help promote adoption of alternative tests.

The Physicians Committee looks forward to continued progress and collaboration to improve science, replace and reduce animal testing, and bring safer and more effective medicines to patients.

Best regards,

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