

PhysiciansCommittee

for Responsible Medicine

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August 29th, 2018

Dr. Mary Wolfe, SACATM's Designated Federal Official
Dr. Pam Spencer, SACATM's Chair
Rodbell Auditorium
National Institute of Environmental Health Sciences
111 TW Alexander Drive
Research Triangle Park, NC 27709

Dear Drs. Wolfe, Spencer, and SACATM Members,

The Physicians Committee for Responsible Medicine is a national non-profit organization of over 175,000 doctors and laypersons advocating for preventive medicine, good nutrition, and ethical standards in medical research and toxicology testing. We appreciate the opportunity to provide input for the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) meeting in advance of September 5-6, 2018.

US Strategic Roadmap and Goal

The creation of the US Strategic Roadmap by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and even the subsequent translation into other languages is a notable accomplishment. We extend our accolades to specific U.S. agencies, such as the Environmental Protection Agency (EPA) and Food and Drug Administration (FDA) for their internal creation of strategic plans that highlight a way forward concerning the use and implementation of alternative approaches. We still continue to stress the significance of seeing clear language regarding the acceptance of alternative approaches from all US federal agencies. In this manner, it will be 1) transparent how alternative approaches are implemented and 2) possible to identify areas for harmonized language and guidance within the US.

Using the EPA's Strategic Plan as an example with recent developments to date, we would like to outline how SACATM and other agencies can fulfill the Roadmap's goal to connect end-users with developers, establish confidence in new methodology approaches (NAMs), and encourage broad implementation of NAMs.

The EPA's implementation of the amended Toxic Substances Control Act (TSCA) illustrates both the opportunities and challenges of encouraging the adoption of non-animal methods by regulatory agencies and regulated communities.

Despite competing priorities of a diverse group of stakeholders, the EPA met their statutory deadline and delivered a strategic plan which promises, over time, to advance Congressional mandates and the interests of the public it serves. In particular, the EPA's strategic plan promotes the development and timely incorporation of alternative approaches under TSCA. The EPA must also report to Congress on

their implementation progress to reduce and replace the use of vertebrate animals in the testing of chemical substances 5 years after the law was enacted. This level of transparency, although congressional mandated, is an opportunity other agencies can adopt for accountability to the implementation of NAMs.

Unfortunately, EPA's early exercise of its new testing authorities has so far resulted in dramatically increased animal testing requirements. We have documented, in previous comments to the EPA, roughly a ten-fold increase over pre-TSCA reform implementation levels. Moreover, these requirements include tests for skin sensitization and eye irritation for which EPA has already identified acceptable alternatives in its own strategic plan and recent policy initiatives. We hope that implementation of the plan will quickly result in more internal consistency and an increase in the uses, submissions of, and requests for NAMs. This current effort should not only serve as encouragement to other agencies but will demonstrate that US federal agencies should follow this approach.

TSCA requires EPA to describe how available information was used to inform its decision and to explain the basis for decisions that require the use of vertebrate animals. Here is another critical opportunity for all Agencies, as end users, to implement an effort to connect with developers when requiring the development of new information.

In addition, TSCA requires those developing information on a voluntary basis to first attempt to develop the information by means of alternative test methods or strategies. It is important for the EPA to make available their reviews of voluntary submissions with NAMs. Providing examples of the successful regulatory use of NAMs will thereby establish confidence in the methods. A commitment from EPA and other agencies to transparently review whether alternatives were considered would encourage awareness and acceptance of alternatives by industry.

PCRM remains committed to working with EPA and other agencies to fully implement TSCA's non-animal testing provisions through education in all forms (workshops, targeted training, academic presentations, etc.). We acknowledge EPA's commitment to transparency by providing ample commenting opportunities and stakeholder engagement. Thus we encourage other US agencies to follow EPA's collaborative lead when implementing NAMs.

Anticipated Science and Technology of Microphysiological Systems

Microphysiological Systems (MPS) have advanced rapidly through the efforts of academic and regulatory researchers. Research has shown promise for MPS to mimic biological complexity¹, predict human hazards², and customize disease models^{3, 4, 5, 6, 7}. However, it is difficult to find their use in regulatory

¹ Marx et al. (2016) Biology-inspired Microphysiological System Approaches to Solve the Prediction Dilemma of Substance Testing. *ALTEX*. 33(3): 272–321.

² Jackson et al. (2018) The use of human tissue in safety assessment. *Journal of Pharmacological and Toxicological Methods*, In press.

³ Guimaraes et al. (2018) Generation of iPSC-derived human peripheral sensory neurons releasing substance P elicited by TRPV1 agonists. *Front Mol Neurosci*. 11:277.

⁴ Watson et al. (2016) Fitting tissue chips and microphysiological systems into the grand scheme of medicine, biology, pharmacology, and toxicology. *Exp Biol Med* (Maywood). 242(16): 1559–1572.

⁵ Benam, et al. (2016) Small airway-on-a-chip enables analysis of human lung inflammation and drug responses in vitro. *Nat. Methods*. 13:151-157.

⁶ Raasch et al. (2018) Microphysiological systems meet hiPSC technology – New tools for disease modeling of liver infections in basic research and drug development. *Advanced Drug Delivery Reviews*, In press.

⁷ Esch et al. (2015) Organs-on-chips at the frontiers of drug discovery. *Nat Rev Drug Discov*. 14: 248-260.

decisions. In fact, our own internal review of New Drug Applications through June of 2018 failed to find any instances of MPS use. We are excited to see a dedicated discussion to pinpoint what areas can be actively targeted to push MPS into a regulatory spotlight within the US.

Moving Beyond Animal Data as the Gold Standard

In 2018 it can still be heard countless times at any scientific meeting for chemical safety testing that animal data are the 'gold standard'. NICEATM and the International Cooperation on Alternative Testing Methods (ICATM) are positioned to take a bold stance challenging this impulsive default thinking. Through the work of NICETAM and the EPA, we already have practical examples where alternative approaches through scientific technology and data have proven to **be** the gold standard when addressing human safety. As more of these methodologies become available, statements like the EPA's Science Policy on Skin Sensitization should be made by agencies and the associated methodologies should be required in lieu of in vivo data. Another way to make a bold statement to disrupt the perception that animal data are the gold standard is to heavily advocate for standalone scientifically rigorous methodologies that do not rely on animals. Confidence will increase when regulators, industry, and interested stakeholders see prominent placement of alternative approaches consistently implemented across US federal agencies.

Thank you for your consideration of these comments.

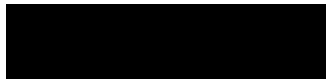
Warm regards,



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