THE HUMANE SOCIETY OF THE UNITED STATES

HUMANE SOCIETY LEGISLATIVE FUND™

May 4, 2023

Dr. Steven Morefield
Inotiv Co.

RE: Interagency Coordinating Committee on the Validation of Alternative Methods; Notice of Public Webcast; Request for Public Input (FR Doc. 2023–07700).

Dear Dr. Morefield,

On behalf of the Humane Society of the United States (HSUS), Humane Society Legislative Fund (HSLF), and our members and supporters, we appreciate the opportunity to provide comments in response to the April 6, 2023, notice, "ICCVAM Public Form: May 2023; Notice of Public Meeting; Request for Public Input."

I look forward to sharing our views with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) to advance development and acceptance of test methods and strategies to ultimately replace the use of animals.

Overview of Historical Accomplishments Achieved by ICCVAM

Since the establishment of the ICCVAM Authorization Act of 2000 (H.R. 4281), the organization has progressed in moving toward development, acceptance, and incorporation of alternative approaches to animal testing in drug and chemical safety assessment. With strong leadership at the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), non-animal approaches for toxicity testing continue to be acknowledged through their development, and acceptance in the global toxicology testing arena. Through regular engagement with regulators, industry, and other stakeholders on the latest testing strategies, NICEATM provides valuable information and leadership about modernizing safety assessments and minimizing animal use.

While we are pleased to see that some of the agenda items of the ICCVAM meeting focus on advancing alternatives for regulatory use, I am compelled to share the historical view that while the development and acceptance of new approach methodologies (NAMs) with regulatory agencies and stakeholders has progressed, the rate of progress over the last 2 decades is disappointing, particularly concerning the regulatory acceptance of NAMs.

I have actively participated in the scientific development of alternative toxicological methods from when cell culture methodologies for toxicology testing were in their infancy. Through my role as a former member of SACATM, and President of the *In Vitro* and Alternative Methods (IVAM) specialty section of the U.S. Society of Toxicology, I have witnessed the expansion of scientific developments in the field and the interaction with regulatory, industrial, and public stakeholders. The initial recognition of the scientific validity and acceptance of these methods into the various arenas was challenging and wrought with controversy, as it still is today. Since then, there has been acknowledgement of the science and improvement in acceptance as guidance documents and regulatory frameworks.

However, the current situation in the regulatory status of the models 23 years after establishment of ICCVAM has been disappointing. Although the number of methodologies accepted by the Organization for Economic Development (OECD), as the standard bearer for international guidelines, has increased, the number of protocols and procedures accepted by U.S. Federal agencies has progressed very slowly. Despite the tremendous advancements in computer technology, biomedical, biochemical, genetic, cell biology and physiological sciences, as well as *in silico* methodologies, the recognition of the potential of these methods to accurately assess safety and replace animal testing has been delayed for over 2 decades.

It is our hope that ICCVAM will improve its historical record by assuming a more active role in encouraging formal acceptance of NAMs by regulatory agencies.

Current Novel Science and Technology – Microphysiological Systems (MPS) and NAMs

The partnership between the National Center for Advancing Translational Sciences (NCATS), the Defense Advanced Research Projects Agency (DARPA), and the Food and Drug Administration (FDA) that initiated the *Human Microphysiological Systems: Organs-on-Chips for Drug Safety and Efficacy Testing Program*, has met and even surpassed expectations in the rapid development and commercialization of several organ-on-a-chip systems that are currently in different phases of implementation and commercialization. This type of interagency collaboration should serve as a model for other technology development projects, and for projects that address common information needs. Scientifically, attempts at simulating physiological systems has achieved tremendous success, yet the implementation for toxicological testing has yet to be realized. At the current rate of progress, implementation of NAMs into a battery of testing protocols will not occur for about 15-20 years. There is a tremendous opportunity to accelerate this timeline and for ICCVAM to play a role in this acceleration.

Implementing the Strategic Roadmap: Incorporation of Alternatives and Associated Metrics

HSUS and HSLF encourage participants to focus on metrics during this ICCVAM meeting following release of a 2019 Government Accountability Office report, *Animal use in Research:*

Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives, and a subsequent 2021 report by ICCVAM's metrics workgroup (MWG), particularly since there is no apparent topic on metrics in the meeting agenda. We believe that the MWG report is missing an important opportunity to provide clarity and best practices to agencies regarding metrics.

Accurate metrics are important for:

- ensuring that NAMs are used by regulated industries and are accepted by regulatory agencies;
- identifying areas of priority for development of new methods and areas of concern or overlap among agencies; and,
- demonstrating successful application of new methods.

ICCVAM can play an important role in providing recommendations regarding development of metrics, communicating them to the public, and developing plans to overcome obstacles that prevent full implementation of NAMs.

Validation and Establishing Scientific Confidence in New Approach Methodologies (NAMs)
With the recognition that many of the methods that were endorsed 10-15 years ago were not effectively integrated or accepted by regulatory agencies as approved models for toxicity testing, ICCVAM published the Strategic Roadmap[†] in January 2018 as a new strategy for toxicity testing, in order to expedite the development and use of NAMs that provide information more relevant to human health than existing animal-based methods. Successful development and implementation of these novel and innovative approaches requires coordinated efforts that address three strategic goals: 1. connect end users with the developers of NAMs; 2. foster the use of efficient, flexible, and robust practices to establish confidence in new methods; and, 3. encourage the adoption and use of new methods and approaches by federal agencies and regulated industries.

Recently, van der Zalm *et al*. (2022)[‡] in a publication entitled *A framework for establishing scientific confidence in new approach methodologies,* offer a modern, flexible basis to establish scientific confidence in NAMs for the regulatory assessment of chemicals for human health effects. The authors propose "five essential elements that form the basis of a framework that

[†]A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States, https://ntp.niehs.nih.gov/iccvam/docs/roadmap/iccvam_strategicroadmap_january2018_document_508.pdf

[‡] A.J. van der Zalm, J. Barroso, P. Browne, W. Casey, J. Gordon, T.R. Henry, N.C. Kleinstreuer, A.B. Lowit, M. Perron, A. J. Clippinger, A framework for establishing scientific confidence in new approach methodologies, *Archives of Toxicology*, August 2022. https://doi.org/10.1007/s00204-022-03365-4.

can be applied by regulators or other end users to establish scientific confidence in NAMs used internationally to assess potential chemical effects on humans and provide information needed for regulatory decision making." The plan is intended to promote scientific confidence in any of the NAMs models and establishes a process for determining the adequacy of the NAMs overall performance, together as part of an integrated approach to testing and assessment, or as stand-alone assays. The framework consists of five essential elements: fitness for purpose, human biological relevance, technical characterization, data integrity and transparency, and independent review. This framework, and corresponding five essential elements, bears remarkable resemblance to various historical proposals originally described by Ekwall and Barile (1994),[§] and later categorized in guidance documents by OECD[**]. Some of the corresponding comparable terms and proposed definitions include: relevance, reliability, sensitivity, specificity, standardization, and multilaboratory-multimethod programs, all of which were promoted as part of validation programs for acute oral, dermal, and ocular *in vitro* toxicity testing.

We request that ICCVAM and its member agencies finally embrace this approach, creating the scientific confidence needed to advance NAMS in a tangible way.

Conclusion

To successfully implement the original objectives established with the formation of the organizations, and to further reduce reliance on animal test methods, HSUS and HSLF urge ICCVAM member agencies to focus on coordinating their efforts to ensure NAMs are accepted for regulatory use, while also protecting human and environmental safety.

HSUS and HSLF welcome the opportunity to work with NICEATM or any ICCVAM agency to help achieve the common goal of replacing animals with relevant non-animal test methods and strategies.

Thank you for consideration of our comments.

Sincerely,

(signature redacted)

Frank A. Barile, Ph.D.

[§] B. Ekwall and F.A. Barile, Chapter 11. Standardization and Validation, in: *Introduction to In Vitro Cytotoxicology: Mechanisms and Methods*, CRC Press, Boca Raton, FL 1994. Reissued by CRC Press 2019.

[**] OECD Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment, OECD 2005.

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