PhysiciansCommittee
for Responsible Medicine PCRM.ORG
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May 27, 2022

Nicole Kleinstreuer
National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)
P.O. Box 12233
Mail Drop K2-16
Durham, N.C. 27709

Re: ICCVAM Public Forum, May 2022

Dear Dr. Kleinstreuer and ICCVAM Committee Members:

The Physicians Committee for Responsible Medicine is an NGO supported by over 175,000 members working for effective, efficient and ethical research and testing. We appreciate the opportunity to provide input on NICEATM and ICCVAM-related activities. Below, we offer input to help meet our shared goals of evaluating and advancing improved approaches to research and testing that focus on human biology while reducing animal testing.

MUTLI-AGENCY COMMENTS

Policy Updates Needed to Accommodate NAMs

Regulatory professionals within companies look to agency policies and communications about policies to understand which methods will be accepted in which circumstances. We appreciate that federal agencies hold the position that NAMs data from companies will be reviewed. However, clear communication from agencies regarding acceptance of NAMs will go a long way towards building industry confidence to do so. Please remember the inertia behind use of animal studies. Regulations, guidance, and guidelines that companies have followed for decades have required or recommended animal use. These communications should be updated to clearly allow for *in vitro* and *in silico* approaches. In cases where specific NAMs are accepted, clear policy communications are needed. Without certainly that an approach will be accepted, many companies will default to the traditionally accepted animal tests. Publishing in the scientific literature is helpful and encouraged, but is not sufficient communication for many companies. There are also instances where written communications are conflicting, or where policies lead to testing that is not useful to the agency. ***We ask all agencies to consistently review and update written policies, to remove requirements for animal data and clearly allow for NAM use, to identify and correct conflicting information, and to communicate when companies submit animal data that could have been avoided or obtained without animal testing.***

Animal Protection Organization Involvement

Animal protection organizations can be a resource to federal agencies, in terms of resources, ideas, and expertise. Many APO staff are experts in their fields and motivated to collaborate on

NAM integration activities. ***We encourage agencies, as part of their NAMs efforts, to host stakeholder meetings with APOs to utilize this resource.***

Metrics

The number of animals used in research and testing in the United States continues to be an enigma. This should not be accepted for multiple reasons. First, science and technology have evolved. A multitude of *in vitro* and *in silico* approaches have been developed and enormous efforts are underway to integrate them, partially to reduce animal use, which is consistently stated as a priority for multiple agencies. Without at least approximate accounting of animal use, there is no way to measure agency progress toward reducing animal use. ***We ask agencies to develop processes for tracking the number of animals submitted by species, test, and endpoint, and to ensure transparency by making metrics publicly available.*** This will help identify where progress is being made and where more attention is needed.

Training

As agencies develop, accept, and implement NAMs for decision-making, changes to policies and procedures need to be communicated effectively to staff, regulated industry, and other non-federal decision-makers. Novel technologies provide different kinds of data; trainings can outline the scientific robustness of NAMs and how to interpret data from them to bridge the gap between current and future decision-making practices and grow trust and confidence. Efforts to provide training on the use of new tools have begun and should be continued and expanded. Partnerships with NGOs can be leveraged here to increase the effectiveness of these efforts.

FOOD AND DRUG ADMINSITRATION

Qualification

We appreciate the FDA's leadership in establishing qualification pathways that accommodate nonanimal tests. These programs have the ability to revolutionize product development by providing a process for methods to be qualified, and therefore, available for confident use by all drug sponsors without the need for additional evaluation work. The FY 2023 Presidential Budget Request included $5 million for a New Alternative Methods Program at FDA to qualify and integrate NAMs. We support this funding request and hope Congress will appropriate the funding so FDA will have staff dedicated to these activities. ***If this funding is provided, we ask for a public workshop to inform NAMP planning, and a public report on activities.***

Data Used for NAM Evaluation

The President's FY 2023 Budget Request also included $7.5 million for the National Center for Toxicological Research (NCTR) for comparative studies to evaluate NAMs to understand their potential. The proposal would fund assessment studies that compare side-by-side the traditional animal tests to NAMs, resulting in new animal studies for NAM evaluation. For NAMs intended for testing human products, this would be a step back with regard to both science and ethics. An inherent advantage of NAMs is they utilized human biology to predict human outcomes. ***We ask FDA to work among its centers and with interagency partners to access human data for use in NAM validation. When NAMs are intended for use in testing animal products, we ask for FDA to utilize data derived from existing animal studies.***

Predictive Toxicology Roadmap
The Predictive Toxicology Roadmap launched as a regulator-driven effort to integrate new methods. ***We appreciated the annual stakeholder updates and ask that they be reinstated. We also ask that the annual report to the Chief Scientists, as outlined in the roadmap, be made publicly available to help with transparency around roadmap activities.***

Pyrogen Testing
Animal testing to detect pyrogens can largely be eliminated by utilization of the Monocyte Activation Test and recombinant Bacterial Endotoxins Tests. These approaches offer many advantages over the traditional rabbit and horseshoe crab-based tests, including improved science, ability to easily scale, and allowing companies to meet 3Rs and sustainability goals. The Microbiology Expert Committee of the United States Pharmacopeia is delaying adoption. ***Please work with the USP on acceptance of these approaches.***

ENVIRONMENTAL PROTECTION AGENCY
New Chemicals Collaboration Research Program
PCRM enthusiastically supports the New Chemicals Collaborative Research Program between the Offices of Pollution Prevention and Toxics and Research and Development. By implementing its next generation blueprint for computational toxicology, EPA will markedly advance the transformation of toxicology from a discipline based on whole-animal testing to one based primarily on nonanimal methods. Importantly, an upcoming Memorandum of Understanding between these Offices and the Division of the National Toxicology Program will extend this collaboration to share DNTP's expertise in scaling down and qualifying NAMs for external use. ***As with the Tox21 MoU, we hope that FDA and other ICCVAM partners will consider joining this MoU to contribute their resources and expertise to the achievement of the Program's widely applicable goals.***

TSCA List of Alternative Methods
The process for adding NAMs to the list is unclear. ***We suggest EPA propose a process, including proposed information fields, for nominating NAMs to the list and request public input on this process.*** Additionally, although the list is not meant to be exhaustive, some companies are interpreting it as so. ***We ask EPA to clearly indicate that the list is not exhaustive and EPA has flexibility to accept additional approaches.*** These facts can be communicated on the list, in communications about the list, and during conversations with submitters. Communications of this nature should also be conducted with EPA staff.

Human Data
The human relevance of NAMs meant to assess the risks of chemicals to humans is an important consideration. Human data isn't always available. However, certain restrictions make it difficult to consider the human relevance of NAMs, even if historical human clinical or occupational data is available. ***We suggest EPA consider strategies to allow the use of some human data to support the evaluation of NAMs wherever possible.***

NATIONAL INSITUTUES OF HEALTH
Animal-free Antibodies
Much technological progress has been made in the creation and production of recombinant

antibodies, which can provide more reproducible tools for testing and research, while avoiding the use of animals as antibody-producing vessels. ***We request the NIH consider revisiting its 1994 decision that the ascites procedures is still needed for antibody production, take steps to transition its intramural researchers away from animal-derived antibodies, and create incentives for extramural grantees to switch away from animal-derived antibodies wherever possible.***

We look forward to continued collaboration over the next year to carry out our specific requests described above. Thank you for all you do to evaluate and integrate NAMs to improve testing outcomes while reducing animal studies.

Sincerely,

(signature redacted)

Elizabeth Baker, JD (and team)
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