

Summary Minutes

**Scientific Advisory Committee on
Alternative Toxicological Methods Meeting
September 5-6, 2018
National Institute of Environmental Health Sciences
Research Triangle Park, NC**

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II. Location of Background Materials and Presentations

Background materials and presentations for the 2018 Scientific Advisory Committee on Alternative Toxicological Methods meeting are available on the National Toxicology Program All Past Events page (<https://ntp.niehs.nih.gov/go/meeting>, select Event Type “SACATM”)

III. Frequently Used Abbreviations

AOP	adverse outcome pathway
CRO	contract research organization
DoD	U.S. Department of Defense
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
GIVIMP	good <i>in vitro</i> methods practices
GLP	Good Laboratory Practice
HSI	Humane Society International
HSUS	Humane Society of the United States
ICATM	International Cooperation on Alternative Test Methods
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ICE	Integrated Chemical Environment
ILS	Integrated Laboratory Systems, Inc.
IP	intellectual property
MPS	microphysiological systems
NAMs	new approach methodologies
NCATS	National Center for Advancing Translational Sciences (NIH)
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NIEHS	National Institute of Environmental Health Sciences (NIH)
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NTP	National Toxicology Program

OECD	Organisation for Economic Co-operation and Development
PCRM	Physicians Committee for Responsible Medicine
PISC	PETA International Science Consortium
QSAR	quantitative structure-activity relationship
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
TTC	threshold of toxicological concern

IV. Attendance

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) met on September 5 and 6, 2018, at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina. The following individuals attended the meeting:

SACATM Members

Michael Bolger, PhD, Simulations Plus, Inc.
Kelly Coleman, PhD, DABT, RAC, Medtronic PLC
Hisham Hamadeh, PhD, DABT, MBA, Amgen, Inc.
William Janzen, Epizyme, Inc.
Lawrence Milchak, PhD, DABT, 3M
Pamela Spencer, PhD, DABT, ANGUS Chemical Company (chair)
ClarLynda Williams-Devane, PhD, North Carolina Central University
Wei Xu, PhD, University of Wisconsin at Madison
Hao Zhu, PhD, Rutgers University at Camden

SACATM Ad Hoc Members

Joseph Charest, PhD, The Charles Stark Draper Laboratory, Inc.
Amy Clippinger, PhD, PETA International Science Consortium, Ltd.
Nadira De Abrew, PhD, The Procter & Gamble Company
Sean Gehen, PhD, DABT, Corteva Agriscience, Agriculture Division of DowDuPont

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Principal Representatives

John Gordon, PhD, Consumer Product Safety Commission
Bert Hakkinen, PhD, National Library of Medicine
Anna Lowit, PhD, U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs, ICCVAM Co-chair
Moiz Mumtaz, PhD, Agency for Toxic Substances and Disease Registry
Barnett Rattner, PhD, U.S. Department of the Interior

*Summary Minutes from the September 5-6, 2018, SACATM Meeting
NIEHS, Research Triangle Park, North Carolina*

Emily Reinke, PhD, U.S. Department of Defense (acting principal agency representative), ICCVAM Co-chair

Daniel Shaughnessy, PhD, National Institute of Environmental Health Sciences (NIEHS)

Other ICCVAM Representatives

Warren Casey, PhD, DABT, NIEHS

Nicole Kleinstreuer, PhD, NIEHS

Geoff Patton, PhD, U.S. Food and Drug Administration

Elijah Petersen, PhD, National Institute of Standards and Technology

Louis (Gino) Scarano, PhD, EPA Office of Pollution Prevention and Toxics

International Cooperation on Alternative Test Methods Representatives

Charu Chandrasekara, PhD, Canadian Centre for the Validation of Alternative Methods

Tae Sung Kim, PhD, Korean Center for Validation of Alternative Methods

Octavio Presgrave, MS, Brazilian Center for the Validation of Alternative Methods

National Institute of Environmental Health Sciences Staff

Brian Berridge, DVM, PhD, DACVP

Linda Birnbaum, PhD, DABT, ATS

Juanita Campbell

Michael DeVito, PhD

Christine Flowers, MA

Virginia Guidry, PhD

Robbin Guy

Allison Harrill, PhD

Madelyn Huang, PhD

Kelly Lenox, MFA

Elizabeth Maull, PhD

Barry McIntyre, PhD

Alex Merrick, PhD

Rick Paules, PhD

Lingamanaidu Ravichandran, PhD

Marianna Rosentsvit, PhD

Kristen Ryan, PhD

Diane Spencer, MS

Amy Wang, PhD

Kristine Witt, MS

Mary Wolfe, PhD

Atlee Watson, PhD

Integrated Laboratory Systems, Inc. (NICEATM support contractor) Staff

David Allen, PhD

Shannon Bell, PhD

Xiaoqing Chang, PhD

Neepa Choksi, PhD

Ella Darden

Kamel Mansouri, PhD

Steven Morefield, MD

Catherine Sprankle, MS

Judy Strickland, PhD, DABT

Public

Richard Becker, PhD, American Chemistry Council

Michael Dzierlenga, PhD, ScitoVation

Anne Gourmelon, MS, Organisation for Economic Co-operation and Development

Esther Haugabrooks, PhD, Physicians Committee for Responsible Medicine

Gina Hilton, PhD, People for the Ethical Treatment of Animals

Sue Leary, MS, Alternatives Research and Development Foundation

Sandra McBride, PhD, Social and Scientific Systems, Inc.

Marjory Moreau, PhD, ScitoVation

Clive Roper, PhD, CSci, CBiol, Charles River Laboratories

Marjolein Smith, PhD, Social and Scientific Systems, Inc.

Raymond Tice, PhD, RTice Consulting

Aaron Weisz, 60 Minutes

Catherine Willett, PhD, Humane Society of the United States/Humane Society
International (by phone)

Miyoung Yoon, PhD, ToxStrategies, Inc.

September 5, 2018

V. Welcome and Opening Remarks

Dr. Pamela Spencer, ANGUS Chemical Company, chair of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), called the meeting to order at 9:14 a.m. on September 5. Attendees introduced themselves. Dr. Elizabeth Maull, the SACATM Designated Federal Officer, read the conflict of interest statement and reviewed meeting logistics.

In her welcoming remarks, Dr. Linda Birnbaum, National Institute of Environmental Health Sciences (NIEHS) and National Toxicology Program (NTP) Director, reviewed the development of the Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States. She

emphasized the inclusivity of the Strategic Roadmap development process, noting the public meetings at which input was invited. The Strategic Roadmap has been a springboard for development of similar documents by the U.S. Environmental Protection Agency (EPA), the U.S Food and Drug Administration (FDA), and the U.S. Department of Defense (DoD). In response to stakeholder interest, the Strategic Roadmap has been translated into five languages. The goals of the Strategic Roadmap are reflected in recent federal agency activities; SACATM feedback and input is critical to success of these efforts. Dr. Birnbaum acknowledged international attendees. She thanked SACATM members whose terms ended in 2017 who agreed to return this year, and Dr. Spencer for chairing the committee. She introduced nominated members of SACATM who are currently serving as ad hoc members.

Dr. Brian Berridge, NTP Associate Director, and ICCVAM co-chair Dr. Emily Reinke, DoD, each welcomed the committee and thanked them for their attendance.

VI. Overview of US Strategic Roadmap and Goal: Connect End-users with the Developers of New Approach Methodologies

Dr. Warren Casey, Director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), reviewed the participants and relationships involved in ICCVAM, ICCVAM's history, and the membership of SACATM. In theory, ICCVAM members represent the heads of their agencies. In practice that is not the case, which has some advantages and disadvantages.

Because ICCVAM has no authority or budget, its effectiveness depends on coordination and participation by the right people. Much of what ICCVAM accomplishes is done through its workgroups. Dr. Casey listed the eight active ICCVAM workgroups and reviewed how they are established and given direction. NICEATM support of ICCVAM and the workgroups is critical, and Integrated Laboratory Systems, Inc. (ILS) contractors play a major role. The NICEATM website, the annual ICCVAM Public Forum, and ICCVAM Biennial Report are important avenues through which information is available about Strategic Roadmap implementation activities.

Describing the International Cooperation on Alternative Test Methods (ICATM), Dr. Casey noted that this voluntary effort towards harmonizing validation studies has no regulatory aspects or authority, and centers around coordination. Another international activity that ICCVAM participates in is the Organisation for Economic Co-operation and Development (OECD). Unlike ICATM, OECD receives financial support, and its Mutual Acceptance of Data provisions have regulatory impact for participating countries.

Dr. Casey explained the acronym NAM, defined as new approach methodologies, recently derived to refer to any new testing or non-testing approach that replaces, reduces, or refines animal use in testing.

The three-year development process for the Strategic Roadmap involved many groups and was a great opportunity to discuss the bigger picture of what ICCVAM does. The old approach to validation was a linear process that assumed development would lead to validation which in turn would lead to acceptance. However, compartmentalization of method development led to lengthy validation efforts and failure to consider that test

methods are used differently by different agencies and even different offices within agencies. The new approach envisioned by the Strategic Roadmap circularizes the development and validation process to connect the end-user with the developer and allows implementation to begin before every agency accepts a new method for every purpose. The faster a method gets adopted by somebody, the more data are generated, which increases confidence. The Strategic Roadmap also recognizes that incentive and motivation are required for institutional change.

Referring to the first goal of the Strategic Roadmap, Dr. Casey stated that the first aspect of connecting end-users with developers is anticipating testing requirements. This encompasses technologies (e.g., microphysiological systems [MPS]), approaches (e.g., read-across), and endpoints (e.g, cancer). Other aspects are establishing grant review criteria tailored to the development of NAMs and improving communication between end-users and developers. ICCVAM currently supports communication through three annual public meetings.

Clarifying questions and comments: In response to a question from Dr. Kelly Coleman, Medtronic PLC, Dr. Casey stated that he gave 38 presentations last year about the Strategic Roadmap, and publicity efforts and conversations will continue. The Strategic Roadmap will be a focus of the SACATM meeting for a while, and ICCVAM is open to input.

Public Comments

Two written public comments were submitted for this section, on behalf of the Humane Society of the United States (HSUS) and the Physicians Committee for Responsible Medicine (PCRM).¹

Oral Public Comments

Dr. Esther Haugabrooks, representing PCRM, expressed concerns that while development of MPS is progressing rapidly, their use in regulatory applications has been limited. Dr. Birnbaum responded that NIEHS will support development of animal-based microphysiological systems (MPS) to relate *in vitro* systems to *in vivo* data; grants will be funded early next year.

Dr. Charu Chandrasekara, Canadian Centre for the Validation of Alternative Methods, asked about revising grant review criteria to encourage alternatives use in basic research. Dr. Casey responded that ICCVAM is not currently focused on that, but there is the potential for NIEHS to fund this research. Once these methods demonstrate their usefulness, investment in them will increase because they are more human-relevant. Dr. Birnbaum added that the National Institutes of Health (NIH) R21 grant program funds *in vitro* or computational approaches, and Dr. Anna Lowit, EPA, described a current EPA Science to Achieve Results grant that supports development of replacements for guideline studies. Dr. Wei Xu, University of Wisconsin at Madison, asked if the National Cancer Institute is encouraging alternative methods for cancer research. Dr. Casey responded that neither ICCVAM nor NICEATM is actively involved in developing methods for cancer research but are still identifying the key stakeholders. Dr. Lowit added that an agricultural chemical sector stakeholder group is looking at how to waive

¹ Written public comments for all topics are available at <https://ntp.niehs.nih.gov/go/meeting>; select Event Type "SACATM" and click on "Meeting Materials."

cancer studies by using mode-of action, read-across, and other *in silico* approaches.

Dr. Catherine Willett², representing HSUS and Humane Society International (HSI), praised NIEHS leadership for supporting the evolution of ICCVAM and SACATM and the collaborative approach that has emerged. It is important in the development of NAMs to understand what information regulatory agencies need to make safety determinations. Key to this understanding are surveys of existing data requirements, as NICEATM has done for acute endpoints. However, new technologies support the generation of new kinds of information, which should be considered as NAMs are being developed. Adverse outcome pathways (AOPs) will inform the development of NAMs that will be more useful for the regulators. HSUS/HSI would like to see grants supporting development of this pathway-based information and of methods mapped to these pathways.

Comments from Designated SACATM Discussants

Dr. Michael Bolger, Simulations Plus, Inc., first discussant, addressed transparency in development of *in silico* technologies. While disclosing all the inputs is important, there are intellectual property (IP) issues involved in developing curated data sets. The emphasis placed on developing tools using open sources and open models may result in loss of the opportunity for a for-profit company to develop a higher-quality model. One opportunity for communication between NAM developers and consumers is through educational outreach; another opportunity is through user groups.

Dr. Hao Zhu, Rutgers University at Camden, second discussant, praised the move toward considering alternative methods development in grant reviews, and asked specifically that R01 grants be developed to support development of NAMs. He noted the inclusion of predictive toxicology and data science in the recently published NIEHS strategic plan. Developers funded by government agencies should be asked to contribute in a specific way toward making end-users aware of their methods, for example by participating in workshops or writing papers and book chapters. He cited NICEATM's Integrated Chemical Environment (ICE) as a good example of how to make high-quality data publicly available.

Dr. Nadira De Abrew, The Procter & Gamble Company, third discussant, expressed concern that the tendency to evaluate NAMs according to standards developed for animal studies is an impediment to their adoption.

Additional SACATM Comments

Dr. William Janzen, Epizyme, Inc., agreed that for-profit companies can play an important role in the advancement of alternative methods. An example is the reduction of animal use realized by pharmaceutical companies by using p450 enzyme-based *in vitro* assays to study liver metabolism.

Dr. ClarLynda Williams-Devane, North Carolina Central University, noted that changing the grant review process needs to start in graduate schools. Availability of training grants supporting use of alternative methods gives the principal investigators incentive to use them. This in turn helps familiarize graduate students with new methods, which will encourage broader acceptance when they are the ones reviewing grant applications.

² Dr. Willett delivered her comments by telephone.

Dr. Amy Clippinger, PETA International Science Consortium (PISC), praised NICEATM, EPA's National Center for Computational Toxicology, and the ICCVAM workgroups for this year's project to develop predictive models of acute oral toxicity. This was an excellent example of how to effectively involve end-users. She asked representatives of regulatory agencies how test method developers should interact with them to help meet the regulators' needs. Dr. Reinke responded that while developers regularly speak to ICCVAM workgroups, it might help if workgroups were to frame these interactions as discussions around needs. Dr. Lowit added that individual agencies are also open to interactions with method developers.

Dr. Xu thanked Drs. Casey and Lowit for presenting at the Midwest Society of Toxicology. This presentation raised awareness of activities around alternative methods development with students and faculty and informed students about job opportunities within regulatory agencies. She encouraged representatives of regulatory agencies to consider increasing interactions with training programs.

Dr. Hisham Hamadeh, Amgen, Inc., stated that regulators should support development of appropriate NAMs through small business grants and training grants. Incentives for regulated industry could include exclusivity extensions, special designations, or accelerated review for assets developed using these breakthrough platforms. These would encourage companies to go beyond using these technologies for internal decision-making and use them for regulatory filings.

Dr. Coleman asked about sources of information about endpoints addressed by alternative methods. Drs. Clippinger and Casey responded that this information is available on the NICEATM website.

Dr. Nicole Kleinstreuer, Deputy Director of NICEATM, stated that ICCVAM is currently revising its operating procedures to allow external stakeholders to participate on ICCVAM workgroups. This is a new venue through which connections between end-users and developers of NAMs could be made.

Dr. Clive Roper, Charles River Laboratories, reiterated that new technologies may require us to think differently about how to implement a NAM, noting that these are generally not going to be one-to-one replacements of animal tests. He stated that Charles River is increasingly running *in vivo* and *in vitro* tests in parallel, which doesn't make sense financially. They would like to stop having to do the animal tests. Several commenters responded that running *in vivo* and *in vitro* tests in parallel is likely to happen if information needs aren't considered up front.

Summarizing the discussion, Dr. Spencer stated that the commenters agreed that ICCVAM and the agencies are moving in the right direction, and the partnerships that are being developed are helping to accelerate the adoption of NAMs. The Strategic Roadmap has been welcomed as a good resource and guide. Challenges include IP issues and how to develop public-private partnerships that protect the developers' investments. Regarding grants, ICCVAM may need to think differently about developing funding resources and make sure funding supports students' understanding of new methods. The acute oral toxicity project was a success and an example of how stakeholders can work together. She closed by noting it is important to recognize that tools are used differently across industries as well as across agencies.

VII. Anticipated Science and Technology – Microphysiological Systems

Dr. Berridge discussed MPS as an example of encouraging end-user engagement in a novel technology. Building confidence in a new technology is different from validation of a new technology in that building confidence is more about addressing human elements. He described his experiences with the pharmaceutical industry IQ Consortium's working group on MPS, envisioned as a safety assessment technology to reduce drug attrition rates. Formation of the IQ Consortium's working group was instigated by the National Center for Advancing Translational Sciences (NCATS) to engage stakeholders as they developed this technology.

Dr. Berridge reviewed the relationship among biological complexity, human relevance, throughput, and progression of development; current approaches trade human *in vivo* relevance for throughput and analytical clarity. To be confident in making *in vivo*-relevant decisions, we must have confidence in the *in vivo* relevance of a novel test system, otherwise we will default to the animal system. MPS can provide that confidence.

Dr. Berridge presented an overview of a proposed process for acceptance of MPS³. A key to achieving acceptance is framing the new technology as filling a testing gap, in this context the gap that precedes the animal studies. This requires identifying a discrete scientific question and recognizing that decisions made from an *in vitro* system are going to be different from decisions made from an animal test. It also requires understanding the biology you want to represent. To illustrate this, Dr. Berridge presented an AOP for breast cancer resulting from estrogen receptor activation. An ability to model *in vitro* the inflection point that leads to pathobiology *in vivo* might allow identification of a toxic chemical without having to reproduce breast cancer in animals. This requires assays to measure events leading to that inflection point.

In comparing *in vitro* to animal systems, Dr. Berridge described an animal system as a black box comprised of processes that would require thousands of assays to replicate, including those with the potential to answer questions we don't know to ask. Qualification of a novel test or modeling system requires an understanding of three things: how the new system compares to the traditional system; how the pathobiology of interest manifests in the species of interest; and how the pathobiology of interest manifests in the traditional model species. Animal studies done in the near term should be viewed as opportunities to better define the questions we are trying to answer.

Summarizing his presentation, Dr. Berridge stated that engaging end-users is key to adoption of new approaches, and end-users have a responsibility to guide developers of novel systems. We need to distinguish regulatory end-users from industry end-users who use tests in both regulatory and non-regulatory contexts. New technologies are easier to implement in non-regulatory contexts, which provide opportunities to build confidence towards applying these technologies to regulatory endpoints. Finally, acceptance of a novel approach requires a clear line of sight from a problem to a strategy for enabling confidence.

Clarifying questions and comments: Dr. Lawrence Milchak, 3M, asked if customization required by a specific end-user for a specific application poses the risk of

³ Described in Ewart et al. 2017. *Experimental Biology and Medicine* 242:1579-1585.

the resulting technology not being transferrable. Dr. Berridge responded that this relates to context of use. That problem might be more likely if MPS are used to answer mechanistic questions than if they used to address problem such as attrition, where a discrete number of targets are involved. Similarly, in the environmental sphere, there are toxicities of interest that provide opportunities to focus on specific platforms, which would become commercially viable. Success will depend on defining those areas of interest and developing platforms for those areas that support some customization.

Public Comments

Two written public comments were submitted for this section, on behalf of HSUS and PCRM.

Oral Public Comments

Dr. Willett, representing HSUS/HSI, described the IQ Consortium as a good example of collaboration to engage the end-user. She was pleased that Dr. Berridge stressed the importance of understanding the underlying biology. Incorporating human biomarkers and AOPs will support both this understanding and qualification. Qualification will also depend on public-private partnerships, such as the partnership Emulate has with FDA.

Comments from Designated SACATM Discussants

Dr. Hamadeh, first discussant, noted that Dr. Berridge's presentation raised the dilemma about whether *in vitro* systems should model human or animal outcomes. This needs to be considered in developing a strategy for use. Predicting adverse effects from emerging macromolecule therapeutics is challenging and may represent an unmet need that could be filled by MPS. Constructing MPS as fit-for-purpose models might be the way forward, but they need to be transferrable as well. Animal studies have multiple endpoints, and it is unlikely that MPS are going to be able to replace all those endpoints. In closing, Dr. Hamadeh reiterated his previous point about the importance of incentivizing and providing assurances to companies that use new technologies.

Dr. Xu, second discussant, noted that while development of MPS has broadened to include multiple cell and tissue types, their ability to model human physiology is still limited. The true utility of MPS might be realized by developing animal tissue chips to better characterize basic physiology, support *in vitro* to *in vivo* extrapolation, and identify biological processes that are conserved between animals and humans. Citing human variation in drug metabolism in humans as an example, she encouraged consideration of how development of MPS could support personalized medicine.

Dr. Charest, third discussant, stated that building confidence in new methods must involve both regulatory and commercial end-users. He agreed that alternative approaches that answer a new question or fill an identified gap will prove easier to adopt than those displacing a current technology, describing immune endpoints as such a potential gap. Characterizing the AOP is critical. The method developer needs to demonstrate that the new technology answers the same question as the old technology, and the end-user needs to define the question appropriately. There are also opportunities to look at new questions, which could be developed with input from physicians. He welcomed the current interest in building animal-based MPS to build confidence in predictivity of MPS. In contrast, some endpoints monitored in humans might lend themselves to monitoring on an MPS, which might be an approach for

qualification of human-based MPS.

Additional SACATM Comments

Dr. Casey pointed out that validation and qualification mean different things to different people, noting FDA and OECD as examples, and clarity is needed in using these terms. Dr. Berridge clarified that in the NCATS tissue chip program, validation is defined as a confidence-building effort that precedes qualification.

Dr. Milchak stated that regulators need training on how to use data from MPS. Dr. Berridge noted that NCATS has engaged with regulators to address this and advocated for sponsors to include data from MPS in submissions. On the other hand, NTP can accomplish things that can't easily be done in a regulated community, and thus has a responsibility to help potential users gain confidence in new technologies.

Dr. Sean Gehen, Corteva Agriscience, stated that we need to consider how to make data that companies have generated for internal decision-making accessible, as these data could be used to support building confidence in new methods.

VIII. US Strategic Roadmap Goal: Foster the Use of Efficient, Flexible, and Robust Practices to Establish Confidence in New Methods

Dr. Reinke described the failure to consider the ultimate context of use as one of the most frequently cited reasons for lack of agency and industry adoption of NAMs. To address this, agencies must clearly communicate their information needs in the context of both the existing animal test and the NAM. ICCVAM members and coauthors have published papers describing regulatory information needs for inhalation toxicity, skin sensitization, and acute systemic toxicity.

Confidence in new approaches can be built through developing a better understanding of the biological basis of toxicity and then publicizing examples of how new methods measure relevant endpoints. Dr. Reinke described current and recent ICCVAM and NICEATM activities relevant to this objective in the areas of skin sensitization, acute oral toxicity, and eye and skin irritation. She reviewed the charges of four new ICCVAM workgroups that have been established in the areas of read-across, *in vivo* to *in vitro* extrapolation, developmental and reproductive toxicity, and ecotoxicology. The latter two groups will comprise both government and nongovernment scientists.

Dr. Reinke described public-private partnerships being pursued to solicit data from industry. These data are being made available through ICE to support evaluations of non-animal approaches for acute toxicity testing. Meetings are being held regularly with stakeholders to ensure that these data are being made available in a useful manner.

Clarifying questions and comments: Dr. Bolger asked how the consensus models from the recent acute oral toxicity predictive models project are being made available. Dr. Kleinstreuer responded they will be available this fall via the EPA Chemistry Dashboard and as stand-alone software that users can download and run locally.

Presentation: Update on ICCVAM Guidelines for Validation

Dr. John Gordon, U.S. Consumer Product Safety Commission, stated that the need to

update the ICCVAM Guidelines for Validation was made apparent by issues that emerged during the validation of the electrophilic allergen screening assay. This prompted a review of recent guidances on assay validation issued by OECD, FDA, and other entities. Dr. Gordon has been revising the Guidelines, which have not been modified since 1997, to include current best practices and clarify what ICCVAM needs from submitters before a test can be evaluated. A draft revision is ready for a small group to review and refine; this revision will then be reviewed by the full ICCVAM committee.

Presentation: OECD Perspective of Test Method Validation

Ms. Anne Gourmelon, Principal Administrator of the OECD Test Guidelines Programme, described OECD's role in coordinating alternative test method validation. The Mutual Acceptance of Data agreement states that data produced using accepted test guidelines under Good Laboratory Practice (GLP) can be accepted by other countries for similar uses. OECD views validation as a means to build confidence in and reach acceptance of a method for a particular purpose.

For traditional animal methods, human biological relevance was assumed. As more subtle measurements were derived, subjectivity became an issue and relevance started to be questioned. The OECD approach to validation is meant to be modular and flexible, a way to minimize bias and increase reproducibility and relevance. Validation of standardized guidelines at OECD involves transparent, open reviews that emphasize transferability and analysis of existing data.

OECD validation activities occur in a regulatory context, with the 2013 European Union ban on animal testing for cosmetics being a key driver. Ms. Gourmelon reviewed progress of international adoption of non-animal methods and defined approaches for skin and eye irritation and skin sensitization since the 2013 ban. She discussed commonalities among validation studies that failed to lead to adopted test guidelines. An iterative approach to validation allows the application of lessons learned from failures. New issues that have emerged include IP rights, needs for reference data and reference chemicals, and how to gain acceptance of negative outcomes. While factors have been identified that slow the validation process down, these can be countered by a sense of urgency on the regulatory side. However, factors other than validation can hinder acceptance of alternative methods.

Activities needed for validation of alternative methods for complex endpoints include building human-relevant AOPs and identifying testable key events that can support development of integrated approaches to testing and assessment and defined approaches. Success here will depend on clear problem formulation.

IP issues stem from a philosophy that technology should be accessible to competent labs, which led to the development of concepts such as performance standards. OECD is developing guidance for good licensing practices for methods including proprietary elements. A series of webinars scheduled for next year will discuss possible future solutions for targeted hazard endpoints.

In conclusion, the main issues in encouraging evolution of the validation process include addressing complex endpoints, access to relevant data, and identification of reference chemicals, collaboration, and recognizing which principles in the current validation paradigm are still relevant.

Clarifying questions and comments: Dr. Milchak stated that applying GLP to new methods can be challenging because GLP criteria were developed for animal studies, and asked if OECD is addressing this. Ms. Gourmelon replied that this is the goal of the recent OECD guidance document on good *in vitro* methods practices (GIVIMP). OECD is also considering how to apply GLP principles to *in silico* models and defined approaches. Dr. Gordon added that FDA has issued guidance for analytical model development. Dr. Roper noted that key aspects of GLP are to identify the test system, clearly describe how it is being used, and have defined SOPs and protocols. In response to a question from Dr. Coleman, Ms. Gourmelon responded that OECD does not object to use of patented assays. The issue is user access. Prior to initiating test guideline development, the test method developer or IP owner needs to consider how to make protected elements available to users via vehicles such as licensing agreements, cell banks, or material transfer agreements.

Public Comments

One written public comment was submitted for this section, on behalf of HSUS.

Oral Public Comments

Dr. Willett, representing HSUS/HSI, emphasized the importance of developing case studies that illustrate fit-for-purpose application. HSUS would be glad to facilitate sharing case studies by developing materials and coordinating meetings. She asked how the revised ICCVAM Guidelines will expand on the GIVIMP document. Dr. Gordon responded that the revised ICCVAM document will address areas that aren't covered by the GIVIMP document, including transparency on the part of developers to ICCVAM. However, ICCVAM may decide to simply adopt the GIVIMP document. If the ICCVAM Guidelines document is updated, procedures should be established to ensure it is updated regularly in the future.

Comments from Designated SACATM Discussants

Dr. Coleman, first discussant, recounted his experience with a recently concluded international effort to replace the rabbit skin irritation test for medical devices. The key to success was bringing all the important stakeholders together: regulators in different countries, contract research organizations (CROs), tissue producers, and academic laboratories, who all donated their efforts because the project had no budget. A major roadblock was creating irritant polymers to use in the study.

Dr. Milchak, second discussant, agreed that Dr. Coleman's example illustrated both the importance of broad participation and the need for appropriate test substances. Approaches to validation need to accommodate the fact that in some cases, companies need to keep the composition of test substances private. Participants need to feel that findings of a study are not going to be used punitively by regulatory agencies. It would also help development of public-private partnerships if industry stakeholders understand how regulators are going to use data from new methods in an overall risk evaluation. Proactive action by agencies could address the uncertainty around that issue. He reiterated that incentives such as expedited review could be useful in promoting new methods. Dr. Coleman described the FDA's Center for Devices and Radiological Health process for submitting data from new methods as a model for this.

Dr. Gehen, third discussant, stated that there's a lot of positive momentum in this area in

the agricultural chemicals sector, driven by interest and engagement by stakeholders. When seeking to validate a new method, it's important to define up front what metrics, such as specificity or sensitivity, would characterize a successful outcome. Other considerations include defining the regulatory need and whether that can be filled by a one-to-one replacement or a defined approach. Defining the regulatory information need is also important. For eye irritation, it may just require a decision about whether eye protection is needed rather than determination of a hazard classification. For cases in which human reference data are not available, processes are needed to ensure that the animal data are high-quality and well-curated. Predicting low toxicity with high confidence is an important goal. Identifying NAMs that could replace animal use for complex endpoints such as developmental and reproductive toxicity is important but is going to be a longer-term process. Identifying safe use scenarios might be a more tractable goal than predicting hazard.

Additional SACATM Comments

Dr. Clippinger noted that a current NIEHS Small Business Innovation Research grant asks for a list of chemicals to be tested in a study of inhalation methods. She asked if that approach would be used in the future, and whether the resulting lists would be made public. Dr. Casey responded that the lists would be made public to help build confidence in the new methods. Dr. Berridge added that the IQ Consortium Microphysiological Systems Working Group is preparing manuscripts with test chemical information relevant to a number of organ systems.

Dr. Elijah Petersen, National Institute of Standards and Technology (NIST), asked if all OECD test guidelines have been validated using the process Ms. Gourmelon described. She responded that animal method guidelines issued before 2005 were not subjected to as rigorous an evaluation. OECD Guidance Document 34 was issued in 2005 and describes the current process. Dr. Roper added those seeking to validate an *in vitro* model as a replacement for an animal model have to choose between comparing the new method to animal data, which might not be entirely relevant to human biology, or comparing the new method to human data, which might not be readily available. In some cases, for example for skin sensitization, both approaches are being used.

Concluding the discussion, Dr. Spencer stated that validation practices are evolving. Past practices or principles should not be discarded just because they don't completely fit with current needs. Important elements of past practices that support acceptance of new methods need to be retained. Establishment of a safe space will be important in bringing industry to the table. We should also be thinking beyond hazard outcomes and towards safe-use scenarios.

IX. Moving Beyond Animal Data as the Gold Standard

Dr. Kleinstreuer described reproducibility of animal data as a widespread and major problem facing the effort to validate NAMs. This underscores the importance of curating reference data, which involves evaluating studies for their adherence to protocols described in accepted guidelines. NICEATM undertook such an evaluation to validate a defined approach for assessing androgen pathway effects. Another such evaluation was conducted on rat oral LD50 data. The rat oral LD50 is the basis of numerous regulatory classification schemes. To approach replacing this test with an *in silico* prediction,

NICEATM and EPA collected and curated a large amount of *in vivo* data. Once transcription errors were eliminated, the resulting data reflected the inherent variability of the animal test. Bootstrapping methods were used to derive a 95% confidence interval of about 0.3 log. The ICCVAM Acute Toxicity Workgroup identified the median of the lower quantile of this interval as a representative value that they would be comfortable with using for validation of new methods.

Dr. Kleinstreuer provided examples of how data variability can affect classification. Examinations of variability across a range of animal study types suggest that animal study reproducibility ranges from about 70-85% for hazard classification and may decrease even further for potency classification. This calls into question how animal models should be used as benchmarks for NAMs. One approach to accounting for animal data variability could be to have the reproducibility threshold for a NAM be no higher than the reproducibility of the analogous animal model.

In a perfect world, the best benchmark for alternative models would be human data. Dr. Kleinstreuer described a collaboration between NICEATM and Cosmetics Europe that evaluated defined approaches based on an established AOP for skin sensitization against human data. The analysis revealed that the defined approaches outperform the murine local lymph node assay for predicting both human hazard and potency classification. Case studies like this that demonstrate applications and benefits of predictive, mechanism-based approaches could be used to build confidence in NAMs for chemical safety testing. Using eye irritation testing as an example, Dr. Kleinstreuer asserted that if the relevant biology is well represented by an *in vitro* system, the animal data become irrelevant, especially if the reproducibility of the animal test is not good.

To address more complicated endpoints such as developmental toxicity or cancer, Dr. Kleinstreuer described an approach that maps high-throughput assays to hallmarks of disease development. Another approach is to define characteristics of chemicals known to cause these diseases. NICEATM is developing models that incorporate these definitions to generate a probability that a chemical may have these activities.

In summary, Dr. Kleinstreuer stated that risk can be addressed using a probabilistic framework that starts with what is already known and then adds human-relevant mechanistic information, exposure data, and population genetics to yield a more realistic risk assessment. The scientific challenges posed by this approach include how to incorporate population variability and metabolic competence, model complex systems, and efficiently assemble reference data. Non-scientific challenges include raising awareness of the limitations of animal data, cross-sector communication, and funding for research and education on human-centric approaches.

Clarifying questions and comments: Dr. Williams-Devane asked how NICEATM derives metrics for determining study quality. Dr. Kleinstreuer responded that if available, OECD test guidelines are used to define metrics such as animal numbers, dosing schedule, timing of necropsy, and so on. Dr. Zhu asked how NICEATM will address the fact that the models submitted for the acute oral toxicity project use different algorithms and descriptors, with some using proprietary software. In her answer, Dr. Kleinstreuer briefly described how the models were developed. Predictions on the full prediction set of 50,000 chemicals were used to develop a generalized model. The generalized model uses an open-source molecular descriptor library and a k-nearest-neighbor prediction algorithm to reproduce predictions that had a high level of

consensus among the submitted models.

Public Comments

Two written public comments were submitted for this section, on behalf of HSUS and PCRM.

Oral Public Comments

Dr. Willett, representing HSUS/HSI, noted that use of NAMs can potentially improve the risk assessment process, but using animal models to validate NAMs makes it difficult to improve on the animal models. ICCVAM agencies could provide recommendations for NIH for grants to develop better understanding of human biology and human pathways.

Dr. Haugabrooks, representing PCRM, commented on how these examples show how alternative methods can outperform animal tests. Statements such as that made by EPA through its interim science policy on skin sensitization should be made by other agencies. Going further, regulatory bodies should require *in vitro* data instead of animal data to provide the sense of urgency needed to change existing practices. Agencies could also advocate for stand-alone, scientifically rigorous methods that do not rely on animals. Integrated approaches to testing and assessment can often incorporate broader data streams and more human-relevant data than animal tests. To address non-scientific challenges, PCRM and other nongovernmental organizations are bridging the education gap with events such as an upcoming training session in Research Triangle Park, webinars, and support of organizations such as the American Society for Cellular and Computational Toxicology.

Other Comments from Public

Dr. Chandrasekara asked if anything could be learned from examining how animal tests were originally validated. Dr. Casey answered that these were not validated to the same standards described in, for example, OECD Guidance Document 34. Dr. Birnbaum added that the basis of animal test validation was a feeling that animals are like people. On the other hand, the level of proof needed to predict toxicity is going to vary for different endpoints. If *in vitro* or computational assays can be related to what is known from *in vivo* studies, that might provide confidence that the NAM is going to predict the human toxicity. Dr. Berridge noted that comfort with animal methods is based on history, a recognition of the complexity of biology, and our fear of the unknown. One way to address this is use what we know about pathobiology to build informative systems such as those described in the presentation.

Comments from Designated SACATM Discussants

Dr. Williams-Devane, first discussant, stated that we need to consider how to improve on the animal data we have. Those who curate data and publish data sets should get credit for that and the subsequent use of the data. NIH is moving towards this. Most programs that teach analytics and informatics don't teach how to clean data. Teaching these skills to students would be helpful. Another consideration is how to use human data; in places where we have human data available, we need to relate that to animal data to see what kind of conclusions we can make.

Mr. Janzen, second discussant, described how FDA requiring the hERG receptor assay as an indicator of cardiotoxicity promoted its broad use. Trends in attrition in the

pharmaceutical industry show how *in vitro* models can support a better understanding of biology. While these are not yet 100% reliable, as models become more and more predictive, this will improve. He noted that quantitative structure-activity relationship (QSAR) models are more successful in predicting positives than negatives, often due to the limitations of the training sets. He cautioned that using reproducibility of animal data as a benchmark might undermine the goal of modeling human data.

Dr. Clippinger, third discussant, commented that if protecting human health or the environment is the goal, we need to look beyond reproducing animal tests, especially if we know that the animal test has inherent limitations. That said, where human data are not available, the variability evaluation of the animal data can provide a realistic benchmark. Characterizing the limitations of the animal models may provide an incentive to develop new models.

Additional SACATM Comments

Dr. Hamadeh stressed the importance of clearly defining the purpose of a gold standard. The standard used may vary according to context, and in some situations a reasonable standard may not exist. Dr. Spencer noted that animal models are genetically standardized to increase reproducibility, but humans are more genetically variable, and we need to protect the most sensitive individuals. We need to be cautious about considering human relevance to be the same as reproducibility. A different validation paradigm will be needed to incorporate more human-relevant data. Dr. Birnbaum noted that the limitation of using both inbred animals and human cell lines is the applicability of conclusions drawn from those systems to other systems. This can be addressed by using outbred animal strains, and NIEHS is also considering human variability in some studies. She agreed with Dr. Hamadeh that standards need to be contextualized.

Dr. Lowit emphasized that most toxicity endpoints don't have as much human data available as skin sensitization, making the idea of human data as the gold standard unrealistic. We need ways to build confidence that can work in the absence of human data, and also consider those applications where we don't have a good animal model. Dr. Kleinstreuer clarified that rather than relying on human data as the gold standard, we should be pursuing a better understanding of human biology, with the goal of developing testing strategies that model human biology to start screening chemicals for human-relevant risk. Variability of human response can be addressed using probabilistic risk assessment models that draws on different information sources. Regarding QSAR models, she stated that these are inherently as good as the data that are used to train them. The data set used in the NICEATM acute oral toxicity modeling project had a lot of nontoxic chemicals. NICEATM is working on extrapolating from *in vitro* data to *in vivo* results, and an *in vitro* to *in vivo* extrapolation workflow will soon be available in ICE.

Dr. Zhu commented that computers are better at identifying toxic chemicals than non-toxic chemicals because they can be trained to recognize the potential for a chemical to induce specific toxic activities.

Dr. Roper noted the availability of humanized animal models and outbred models that incorporate variability. He also commented that preclinical testing of new immune-based therapies is conducted in human-based *in vitro* models because animal models are not relevant.

Dr. Birnbaum stated that NIEHS sponsors training grants that might be able to address

the need for training mentioned in this discussion. Dr. Williams-Devane responded that the problem is that the needs haven't been clearly identified and people that need to be involved in the conversation have not been.

Dr. Bolger commented that there are differences in the quality of descriptors generated by different programs, and these differences can affect accuracy. He also noted that categorization models can be tuned to favor sensitivity vs. specificity, depending on the user's goal. Dr. Kleinstreuer responded that in the acute oral toxicity modeling project, the predictions from the proprietary models were used to validate the open-source consensus models. The predictions from all the models were then used to generate consensus predictions, which were in turn used to develop the consensus models. However, the proprietary descriptor calculations cannot be incorporated into the consensus models because of NICEATM's mandate to use open-source elements.

Dr. Casey emphasized that in those cases in which the animal data are serving the intended purpose, modeling the animal data is good enough. Dr. Berridge encouraged efforts to obtain human data from the pharmaceutical sector.

In summary, Dr. Spencer stated that while animal data have been generally useful, whether they are the best benchmark for validating a NAM depends on the goals of the validation and whether the animal model adequately models human biology.

Drs. Birnbaum, Berridge, and Lowit made brief closing remarks thanking the group for its engagement. Dr. Casey added that removing the timeline from eliminating animal testing can allow us to focus on where we can make progress.

Dr. Spencer adjourned the meeting for the day at 4:31 p.m.

September 6, 2018

Dr. Spencer called the second day of the meeting to order at 9:04 a.m. Participants introduced themselves and Dr. Maull reviewed meeting logistics and read the conflict of interest statement.

X. US Strategic Roadmap Goal: Encourage the Use and Adoption of New Methods and Approaches by Federal Agencies and Regulated Industry

Dr. Lowit described the EPA interim science policy on skin sensitization as an example of how agencies can clearly state what types of alternative methods will be accepted. She emphasized the importance of international harmonization in reducing animal use, because if any countries continue to require animal tests, no reduction of animal use will be realized. The October 2016 ICATM workshop on skin sensitization supported this goal. This workshop led to the EPA science policy and a proposal for an OECD test guideline on defined approaches for skin sensitization. Beginning this year, an ICCVAM member will provide technical support to the U.S. National Coordinator and inform discussions around alternatives. The ICCVAM representative to these meetings will be chosen each year based on expertise needed for that year's discussion.

Dr. Lowit stated ICCVAM welcomes SACATM input on promoting and incentivizing use

of NAMs. Upcoming educational events in which ICCVAM and NICEATM are participating include the PCRMsponsored training in Research Triangle Park. Other educational resources include PISC webinars on inhalation, which include the 2016 webinar series they co-organized with NICEATM. Inhalation is going to be a sector to watch this year. Measuring progress is important but is continuing to be a challenge. The EPA Hazard and Science Policy Council was established in 2011 to identify the potential for waiving studies to reduce animal use for pesticide testing. The milestone of 1000 studies waived was recently achieved, representing a total estimated cost savings of about \$200 million. The U.S. Department of Agriculture is also taking steps to reduce numbers of hamsters needed for leptospirosis vaccine testing. They are close to reaching their 30% stated goal for this.

Clarifying questions and comments: In response to a question from Dr. Coleman, Dr. Lowit stated that data to support EPA waiver evaluations come from multiple sources. Aspects considered include physicochemical properties, exposure, and mode-of-action of the AOP.

Public Comments

One written public comment was submitted for this section, on behalf of HSUS.

Oral Public Comments

Dr. Richard Becker, representing the American Chemistry Council, described the concept of threshold of toxicological concern (TTC). This is a conservative reference value for accumulated lifetime exposure, which is set by setting a 5% lower confidence limit on the no-effect level and adding a safety factor. TTCs have been developed for different classes of chemicals, with the intent to be very health-protective. TTCs can be used to calculate a margin of safety in the context of exposure estimates. Dr. Becker noted that TTC has been used in various contexts by regulatory agencies around the world. A recent study⁴ used exposure data and TTCs to develop risk evaluations for a set of over 7000 chemicals. These evaluations could be used for risk-based priority setting. This is a computational approach that can be done with no animal testing. TTCs can also fill toxicity data needs. In summarizing his recommendations, Dr. Becker noted that TTC was included in the EPA Office of Pollution Prevention and Toxics draft strategic plan but left out of the final, though EPA responses to comments on the drafts described TTC as “an important possible avenue for making some [decisions relevant to the Toxic Substances Control Act].” He asked that TTC be considered in future NICEATM and ICCVAM activities.

Comments from Designated SACATM Discussants

Dr. Coleman, first discussant, stated that the key to implementing alternative methods for the medical device sector has been to work collaboratively through the relevant ISO technical committee. The FDA Medical Device Development Tools program has helped advance these methods, and this approach might apply to other federal agencies.

Dr. Hamadeh, second discussant, noted that if a NAM is providing new and valuable insights and decision-enabling data, it will be easily accepted. However, acceptance will be more difficult if a NAM is replacing something that people are used to and is not

⁴ Study is described in Patlewicz et al. 2018. Computational Toxicology 7:58-67.

enabling clear decisions. A NAM needs to improve the science as well as reduce animal use. The culture of innovation within an institution will also affect acceptance, as well as use of the innovation within the context of new projects and whether the innovation has the potential to change the outcome of the projects. Animal and money savings are valid metrics. We can also measure scientific superiority by looking at citations in literature, use in submissions to regulatory agencies, and the ability of NAMs to resolve questions. A third type of metric might involve improving speed to market, which can benefit both companies and patients. Publicity of success stories is important to encouraging use. Incentives could include special designations; it might be worth investigating whether people would care about knowing if drugs were developed without animal testing. Exclusivity and accelerated review are also important incentives.

Mr. Janzen, third discussant, noted that in his experience cost has been the primary driver for implementation of NAMs. If NAMs are accepted by regulatory agencies and are less expensive people will use them. Companies comparing experiences of how NAMs can save money and improve time to market could encourage broader use.

Dr. Milchak, fourth discussant, stated that challenges 3M has experienced in implementing NAMs include having methods that can test mixtures and insoluble chemicals. Another challenge is regulatory acceptability, particularly on the international level. A third challenge is gaining internal confidence that NAMs are assuring the safety of the products, which can be achieved through working with the assays in the laboratory. There isn't really a one-to-one relationship to reducing animal testing with NAMs. If the NAMs are informative, the amount of testing done with them might increase. Agencies need to help companies become more comfortable with NAMs. Companies are apprehensive about bringing new types of data forward, and agencies could take steps to ease that apprehension. Public recognition of companies by agencies would be a good incentive, as would expedited review.

Dr. Spencer, fifth discussant, noted that large companies can afford to be early adopters in a way that smaller companies can't. The hurdle toward adopting methods is very high for regulatory application but lower for internal decision-making. Therefore, we should be encouraging use of NAMs throughout the product life cycle for assessing safety. NAMs allow assessment of safety by looking at structures, which can add value from an innovation and business perspective. We need to think about how to reach smaller companies if we want to achieve broad use of these methods. Engagement will require a different type of interaction involving early, up-front discussions with the companies.

Dr. Charest, sixth discussant, stated that agencies have to clarify their support for NAMs and assure companies that there will be no penalty for using them. End-users could facilitate adoption by designating superusers to develop expertise with specific technologies. Resources and funding are always in short supply, so developers need to demonstrate utility and value based on end-user needs. Metrics for use of NAMs could include driving down costs or reduced attrition. Better data are also an important metric. Acceptance will need to happen within validation and characterization frameworks that include definitions of context of use. Agencies could help build consortia to define those validation and characterization frameworks. He welcomed earlier discussions of the limits of animal methods, which sets the bar for NAMs a little bit lower. Clean datasets are important for developers and also for a validation framework.

Dr. De Abrew, seventh discussant, noted that data from NAMs are going to be used

differently for classification and labeling than for risk assessment, and that international harmonization is particularly important for large companies.

Additional SACATM Comments

Dr. Gordon asserted that it is the responsibility of the federal agencies to clearly communicate acceptability and limits of use for new methods. He asked if a list of testing labs that perform approved methods could be compiled. Dr. Casey responded that that has been discussed but there is a risk of presenting the appearance of endorsing certain labs. Regarding communication from agencies, he noted that technical validation must precede qualification for a particular context of use. Dr. Gordon responded that the agencies need to work with experts to clarify limits of use. The challenge for CPSC is that mixtures and products aren't usually tested in validation studies. Dr. Lowit noted that companies with internal laboratories are experienced with these methods, and we need a safe space to encourage them to share this information.

Dr. Casey asked the committee for ideas on how ICCVAM should assess progress toward replacement of animal use, and specifically about tracking of animal numbers within companies. Dr. Berridge responded that GlaxoSmithKline tracks animal use and has shared relative animal use data internally and to some extent externally. Dr. Gehen stated that his company has specific corporate goals to reduce animal use and could probably be more transparent about sharing that information. Dr. De Abrew stated that Procter & Gamble doesn't track animal use but does track time and cost spent on alternatives to animal use. Dr. Spencer noted that having a standard format for reporting would help correct for variations such as annual changes in the number of registrations. Dr. Hamadeh agreed that portfolio composition can affect animal use and makes it difficult to assess implementation of NAMs. Dr. Roper noted companies are transitioning from doing in-house testing to using CROs, which can make in-house numbers misleading. Dr. Gehen added that use of NAMs for internal decision-making and increasing confidence in compounds under development could lower animal use by reducing late-stage attrition. Dr. Clippinger noted that Shell and Novo Nordisk publicize their animal numbers and it would be interesting to see how they report. Dr. Coleman stated that Medtronic has an internal database to track testing, although they have never compiled that information. Most of their preclinical testing is done by CROs, who are reluctant to publicize those numbers for business reasons. A better approach might be to work with FDA's Center for Devices and Radiological Health and track submissions: agencies could report the numbers of tests submitted and use of animal and *in vitro* methods submitted. Dr. Hamadeh wondered whether smaller companies would take more risk if they could take advantage of special designations. Dr. Janzen added that small companies may find it easier for them to use a CRO to run new methods.

Dr. Berridge commented that this meeting has highlighted the increased uptake of NAMs. Companies are naturally conservative but still seek to innovate. For example, GlaxoSmithKline used alternative methods in a strategy to accelerate development of cancer drugs. Opportunities like this create spaces where we can build confidence.

Dr. Casey noted that the past validation model used by ICCVAM required complete transferability of methods. This is not a realistic goal, and we need to focus on the performance of the methods in the hands of the CROs that are experts at running them. He asked Dr. Coleman, in reference to the skin irritation methods study, whether having

the regulator involved helped or hindered the process. Dr. Coleman responded that regulators saw the value of this project. Establishing the collaboration early and having a realistic timeline was important, as was having suppliers that were willing to provide free or discounted supplies and training and participants' willingness to donate their time.

Dr. Petersen commented that validation depends on context, both for traditional models and NAMs. Agencies need to decide what is good enough. One advantage of NAMs is that there are no ethical issues around doing repeat testing, which is what is needed to build confidence in them for a particular application.

Dr. Roper noted that for any new technology, there is always going to be a training step. Training by the innovators is very important, because they know all the nuances that sometimes don't get recorded in the protocol.

Dr. Bolger described the drug industry's Accelerating Therapeutics for Opportunities in Medicine consortium, which has a goal of moving new drugs from target to patient-ready in one year, mostly using *in silico* approaches. The consortium is building a computational platform combining proprietary and open-source software. It will be provided free of charge but will require the user to pay licensing to companies that developed the components.

XI. Future Directions

Dr. Casey noted that access to high-quality data has been a recurring theme throughout the meeting. ICE is a source of such data. NICEATM is providing continual support for ICE in response to feedback from stakeholders and continues to accept high-quality data. However, their current approach to data curation is very time-consuming and not sustainable. Therefore, NICEATM is exploring establishment of a "next-gen" toxicology database containing a large quantity of high-quality data available in a standardized reporting format that is computer-readable and continuously updated. NICEATM is looking to CROs such as Charles River as sources of this data, because they have experience and expertise in this area.

Dr. Roper opened his presentation by stating that existing animal data can be useful for development of computational models and identification of new medicines. A study⁵ using an industry-wide nonclinical to clinical database confirmed the utility of these data in developing computational toxicology models. However, the usefulness of these models depends on the quality of the data used to build them. Obstacles to assembling the needed data include IP issues, competition, confidentiality, costs, and time constraints. There are procedures in place to address the first three of these, as demonstrated by the fact that companies are already sharing data.

Turning to the question of how to define high-quality data, Dr. Roper suggested that one approach is to specify that the data are generated under GLP. Approaches to standardizing animal data include using recognized test guidelines, inbred animals, standardized protocols and standard operating procedures, and independent quality auditing. He presented several examples of databases that have been assembled and used to develop models. He described in detail the FDA SEND database, which enables datamining of study reports, reviewed study types, and endpoints. The key to the utility

⁵ Study is described in Monticello et al. 2017. *Toxicology and Applied Pharmacology* 334:100-109.

of this database is implementation of ontologies. In summary, the benefits and opportunities of sharing animal data outweigh the barriers, and solutions such as SEND exist. Cost and time are obstacles but could be overcome given the right approach.

Clarifying questions and comments: Dr. Hamadeh noted that for many years, data were accumulated with no intent towards integration or optimizing for large-scale analytics. He asked if there have been lessons learned with regards to resourcing infrastructure. Dr. Roper responded that there have been. Such infrastructure development will require the same level of investment of time and effort as developing a new method. The major issues are identifying the data and IP. We should also utilize data from compounds that never came to market. Dr. Casey asked about the proportion of drugs tested by Charles River compared to general chemicals. Dr. Roper replied that they mostly test drugs, but do test agricultural and other chemicals. Dr. Williams-Devane asked whether Dr. Roper's remarks referred to public or industry data, and how the metadata from older studies were being captured. Dr. Roper answered he was referring to data produced by Charles River's toxicology studies. Availability of metadata depends on the procedures used by the specific companies. Other things to consider for older studies include changes in quality processes, ontologies, guidelines, and so on. Dr. Coleman asked who the custodian of the proposed next-gen database will be. Dr. Casey answered that it's currently envisioned that NTP would maintain it.

Public Comments

There were no written public comments submitted for this section. There were no designated SACATM discussants and no specific discussion questions assigned.

SACATM Comments

Responding to a question from Dr. Williams-Devane, Dr. Roper stated that SEND data are confidential; only FDA can access them. He didn't know when or if FDA makes them publicly available. Dr. Berridge noted that challenges presented by SEND include the proprietary nature of the data and the fact that structures will not likely be available. Any analyses done with these data will have to depend on bioactivity, and QSAR modeling would not be possible. Dr. Roper characterized the SEND database as an example of how data sharing can be done given the existence of a clear legal framework between the sharing groups. Dr. Casey agreed that the technical challenges of addressing the IP questions are surmountable, but political and legal issues around access and benefits are going to be challenging. He asked if data for chemicals other than drugs could be put into SEND format. Dr. Roper responded that they could, as well as data from *in vitro* tests. Dr. Hamadeh commented that looking beyond the chemical structure is important, especially for macromolecules.

Dr. Petersen asked if Charles River has much data from repeatedly testing the same chemical over time. Dr. Roper answered no, because they are obliged not to test a chemical they have tested before. The idea behind REACH was to avoid generating data that already exists. Dr. Petersen noted that it is difficult to characterize sources of variability without repeat data. Dr. Roper agreed but added that proficiency testing specified in OECD test guidelines for *in vitro* tests can't be done in *in vivo* tests, at least in Europe. Dr. Mumtaz asked what kind of data are available for mixtures. Dr. Roper answered that such data are increasingly available, as the current trend is to consider actual formulations and relevant exposure scenarios when designing tests.

Dr. Birnbaum encouraged the meeting participants to consider how to address issues of data access and data sharing. We may be able to take some lessons from the controls placed on clinical and epidemiology data. Dr. Roper responded that pressure to make this happen is needed. Dr. Hamadeh noted in addition to IP issues, the logistical issues around compiling historic data are formidable. Dr. Williams-Devane asked if a standardized ontology was used for their data, and Dr. Hamadeh answered that it was. Dr. Williams-Devane then asked whether the ontologies are being used in public resources such as CEBS are linked at all to the ontologies used in SEND. Dr. Berridge replied that there are ongoing efforts to align public and pharmaceutical industry resources. Dr. Kleinstreuer added that there is still some inconsistency among ontologies used in CEBS, SEND, and the pharmaceutical industry. There needs to be a coordinated effort to develop a mapping technology to translate among different controlled vocabularies. Dr. Roper noted that Charles River data originates in Provantis, and the terminology used in Provantis can't be changed. Dr. Hamadeh added that free text in data capture systems will always be a source of variability. New datamining tools that can apply natural language processing to physician's notes might help address this. Dr. Kleinstreuer noted that NICEATM, NTP, and collaborators are working on a project to use natural language processing to help identify high-quality studies in the literature and eventually to extract results. Dr. Mary Wolfe, NTP, added that they are also using this technology to facilitate semi-automation of systematic reviews. A current project focuses on extracting information from the methods section of published articles and building relationships between identified terms, e.g., animal and species. The project is still ongoing and results will be presented at the NIST Text Analysis Conference on November 13-14.

Dr. Spencer summarized the discussion by noting that while there are barriers to gaining access to big data, there has been progress. The pharmaceutical sector appears to be ahead of the chemical sector in this area but the work at NIST and NTP is encouraging.

XII. Adjournment

Dr. Spencer thanked everyone for their participation, especially for the thoughtful discussions around using legacy data.

Dr. Birnbaum appreciated the vibrant discussions from all participants. While these issues are difficult they are not insurmountable.

Dr. Berridge described the Strategic Roadmap as an inflection point that will drive progress forward. He hoped that the community will embrace the idea that animal studies don't need to be discounted in order to move towards alternatives. Dr. Casey noted that while the Strategic Roadmap is a great accomplishment, it means nothing without buy-in from agencies and stakeholders, and expressed appreciation for the progress toward this. On behalf of ICCVAM, Dr. Lowit thanked Drs. Casey and Kleinstreuer for their leadership and the contributions of the ILS staff under Dr. David Allen's leadership.

The meeting adjourned at 12:12 p.m.

*Summary Minutes from the September 5-6, 2018, SACATM Meeting
NIEHS, Research Triangle Park, North Carolina*

These summary minutes have been read and approved by the Chair of the Scientific Advisory Committee on Alternative Toxicological Methods as certified below.

Date: December 10, 2018



Dr. Pamela J. Spencer
Chair of SACATM