Summary Minutes

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) Meeting

September 27, 2016

National Institute of Environmental Health Sciences, Research Triangle Park, NC

Summary Minutes from the September 27, 2016 SACATM Meeting
NIEHS, Research Triangle Park, NC

Contents

I. Location of Background Materials/Presentations and Frequently Used Abbreviations

Background materials and presentations for the 2016 SACATM meeting are available on the SACATM meeting website (*http://ntp.niehs.nih.gov/go/8202*).

3Rs	replacement, reduction, or refinement (causing less pain and distress) in the use of animals for toxicological testing
ARDF	Alternatives Research and Development Foundation
CPSC	Consumer Product Safety Commission
CFI	Cruelty Free International
CRS	Center for Responsible Science
DABT	Diplomate of the American Board of Toxicology
DoD	Department of Defense
IATA	integrated approaches for testing and assessment
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.
IVIVE	in vitro to in vivo extrapolation
JaCVAM	Japanese Center for the Validation of Alternative Methods
KoCVAM	Korean Center for the Validation of Alternative Methods
LLNA	local lymph node assay
NAS	National Academy of Sciences
NC3Rs	National Centre for the Replacement Refinement & Reduction of Animals in Research
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NRC	National Research Council
NTP	National Toxicology Program
OECD	Organisation for Economic Cooperation and Development
OPP	Office of Pesticide Programs
PCRM	Physicians Committee for Responsible Medicine
PETA	People for the Ethical Treatment of Animals
QSAR	quantitative structure-activity relationship
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
SBIR	Small Business Innovative Research
SSWG	Skin Sensitization Working Group
TSCA	Toxic Substances Control Act

II. Attendance

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) met on September 27, 2016, at the National Institute of Environmental Health Science (NIEHS) in Research Triangle Park, North Carolina. The following individuals attended the meeting:

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)
Brian Berridge, DVM, PhD, DACVP, GlaxoSmithKline
Lauren Black, PhD, Charles River Laboratories
Hisham Hamadeh, PhD, DABT, MBA, Amgen, Inc.
William Janzen, Epizyme, Inc. (chair)
Lawrence Milchak, PhD, DABT, 3M
Pamela Spencer, PhD, DABT, The Dow Chemical Company
Catherine Willett, PhD, The Humane Society of the United States
Wei Xu, PhD, University of Wisconsin at Madison
Hao Zhu, PhD, Rutgers University

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Principal Representatives
Surender Ahir, PhD, Occupational Safety and Health Administration (OSHA, by telephone)
John Elliott, PhD, National Institute of Standards and Technology (NIST)
Bert Hakkinen, PhD, National Library of Medicine (NLM)
Steve Hwang, PhD, Department of Transportation (DOT)
Abigail Jacobs, PhD, U.S. Food and Drug Administration (FDA), ICCVAM Co-Chair
Anna Lowit, PhD, U.S. Environmental Protection Agency (EPA), ICCVAM Co-Chair
Joanna Matheson, PhD, Consumer Product Safety Commission (CPSC)
Moiz Mumtaz, PhD, Agency for Toxic Substances and Disease Registry (ATSDR)
Barnett Rattner, PhD, Department of the Interior (DOI, by telephone)
Karen Taylor, DVM, National Institute for Occupational Safety and Health (NIOSH)
Nigel Walker, PhD, DABT, NIEHS

Other ICCVAM Representatives
Stephanie Padilla, PhD, EPA

International Cooperation on Alternative Test Methods (ICATM) Representatives
Hajime Kojima, Japanese Center for Validation of Alternative Methods (JaCVAM)
Tae Sung Kim, Korean Center for Validation of Alternative Methods (KoCVAM)

NIEHS/NIH Staff
Linda Birnbaum, PhD, DABT, ATS
John Bucher, PhD, DABT
Warren Casey, PhD, DABT
Michael DeVito, PhD
Dori Germolec, PhD
Robbin Guy
William Gwinn, PhD
Ron Herbert, DVM, PhD
Michelle Hooth, PhD
Angela King-Herbert, DVM
Nicole Kleinstreuer, PhD
Kelly Lenox

Robin Mackar
Scott Masten, PhD
Elizabeth Maull, PhD
Richard Paules, PhD
Robert Sills, DVM, PhD
Lori White, PhD
Mary Wolfe, PhD

Bridport Services, LLC
Ernie Hood, MA

Integrated Laboratory Systems, Inc. (ILS, NICEATM support contractor) Staff
David Allen, PhD
Shannon Bell, PhD
Kyathanahalli Janardhan, PhD
Steven Morefield, MD
Catherine Sprankle
Judy Strickland, PhD, DABT

Public
Elizabeth Baker, Esq., Physicians Committee for Responsible Medicine (PCRM)
Ellen Berg, PhD, BioSeek
Gary Burleson, PhD, Burleson Research Technologies, Inc.
Amy Clippinger, PhD, People for the Ethical Treatment of Animals (PETA)
Lowry Curley, PhD, AxoSim (by telephone)
Rodger Curren, PhD, Institute for *In Vitro* Sciences
Tamara Drake, Center for Responsible Science (CRS)
Katherine Groff, PETA
Esther Haugabrooks, PhD, PCRM
Erin Hill, Institute for *In Vitro* Sciences
Gina Hilton, North Carolina State University
Sue Leary, Alternatives Research & Development Foundation (ARDF)
Paul Locke, DrPH, Johns Hopkins Bloomberg School of Public Health
Timothy Malloy, JD, UCLA School of Law/School of Public Health
Anki Malmborg, PhD, SenzaGen, Inc.
Laura Rego, PhD, Cruelty Free International (CFI, by telephone)
Marjo Smith, Social and Scientific Systems
Tom Steinbach, DVM, Experimental Pathology Laboratories
Kristie Sullivan, MPH, PCRM
Mary Ann Vasbinder, DVM, DACLAM, GlaxoSmithKline
Neil Wilcox, DVM, MPH, CRS (by telephone)

III. Welcome and Opening Remarks

SACATM met on September 27, 2016, at NIEHS in Research Triangle Park, North Carolina. Mr. William Janzen, SACATM chair, called the meeting to order at 8:30 AM. All in attendance introduced themselves. Mr. Janzen welcomed the new SACATM members, Drs. Brian Berridge, Hisham Hamadeh, Lawrence Milchak, Pamela Spencer, and Hao Zhu. Dr. Lori White, SACATM Designated Federal Officer, read the conflict of interest statement.

Dr. Linda Birnbaum, NIEHS and National Toxicology Program (NTP) Director, welcomed everyone to the meeting, and recognized the two members in attendance from the International Cooperation on Alternative Test Methods (ICATM), Dr. Hajime Kojima, JaCVAM, and Dr. Tae Sung Kim, KoCVAM. She noted that the National Institute of Standards and Technology (NIST) will soon be joining ICCVAM, and she previewed the various agenda items for the meeting.

Dr. Birnbaum acknowledged retiring SACATM members Drs. Lauren Black and Safdar Kahn for their four years of service on SACATM.

Dr. Warren Casey, NICEATM Director, welcomed everyone to the meeting, and noted that the SACATM meeting would focus on strategy and feedback.

IV. Report on ICCVAM and NICEATM Activities

Dr. Nicole Kleinstreuer, NICEATM Deputy Director, presented an update of the major ICCVAM and NICEATM activities over the past year, which included (1) release of the ICCVAM Biennial Progress Report for 2014-2015; (2) the Communities of Practice Webinar, which focused on quantitative structure-activity relationship (QSAR) and read-across techniques in predictive toxicology; (3) the ICCVAM Public Forum; (4) the Alternative Approaches for Identifying Acute Systemic Toxicity Workshop; (5) the *In Vitro* to *In Vivo* Extrapolation (IVIVE) for High Throughput Prioritization and Decision Making Workshop; and (6) the Alternative Approaches for Acute Inhalation Toxicity Testing to Address Global Regulatory and Non-regulatory Data Requirements Workshop.

Dr. Kleinstreuer explained the new model for workshops adopted in 2016, which uses pre-workshop webinars to encourage consistent engagement and maximize productive participation.

Dr. Kate Willett, SACATM liaison to the acute systemic toxicity and acute inhalation toxicity workshops, was supportive of the pre-workshop webinars, which allowed more time for focused discussions at the workshops.

Dr. Berridge, SACATM liaison to the IVIVE workshop, supported the new workshop format and appreciated the multidisciplinary approach to the complex themes at the workshop.

Dr. Spencer, SACATM liaison to the ICCVAM Public Forum, was impressed with the many efforts at ICCVAM agencies to develop the new tools and technologies to move away from animal testing. She said the time is right for introduction of a roadmap for implementation.

Dr. Lauren Black, SACATM liaison to the Communities of Practice webinar, said she learned that databases accumulated to date had never been subjected to the level of rigor and quantitative accuracy needed today. She noted the need to curate the legacy databases for accuracy and predictive applications.

V. Toxicology Testing: Perspective on How We Got Here

Dr. John Bucher, NTP Associate Director, provided a presentation titled *Toxicology Testing: Perspective on How We Got Here (NTP Centric View)*. He said the NTP rodent cancer bioassay evolved from a screening assay to a tool for risk assessment. Attempts to replace it have been unsuccessful. He noted that the genetic background of the animals used has a large influence on study outcomes and that the increasing use of diversity outbred mice has led to improved accuracy. He said, moving forward, it is important to take into consideration all aspects of the value of both *in vivo* and *in vitro* assays.

Dr. Bucher described the many assays that ICCVAM and NICEATM have evaluated since the ICCVAM Authorization Act of 2000. The 2004 NTP Roadmap, which reviewed and refined traditional toxicology systems, led, in part, to the 2007 National Academy of Science report, *Toxicity Testing in the 21st Century: A Vision and Strategy*. This set the stage for later initiatives such as Tox21, which continues in its Phase III to develop more physiologically relevant *in vitro* models and assays. He said it is important to identify not only the scientific and technical issues regarding implementation of Tox21, but other obstacles to the use and utility of these methods.

Dr. Birnbaum noted the tremendous variability seen with the diversity outbred mouse model, and said genetic variability needs to be kept in mind when using human models such as organ-on-a-chip methods. She noted the other sources of variability beyond genetics, including life stages and mixtures.

VI. U.S Strategy for Implementing the Vision for Regulatory Toxicity Testing in the 21st Century

Dr. Casey presented the *U.S. Strategy for Implementing the Vision for Regulatory Toxicity Testing in the 21st Century*, noting that implementing the strategy will result in a true paradigm shift in how toxicology is done. International collaboration is critical, but the central focus should be getting U.S. agencies to agree on a strategy. He said focusing on the “one R” (replacement) strategy communicated the wrong message. The goal is to be more human predictive; if that is achieved, doing away with animal tests will be a byproduct.

Dr. Casey noted that three high-level drivers move the efforts: ethics, efficiency, and public health (human relevance). Most of the European efforts appear to be driven by ethics, whereas efforts in the United States are likely more driven by the latter two. It would be necessary to clearly define the objective and maintain focus. He doubted that animal testing could be replaced in 10 years by tissue chips and iPS cells, due to the current regulatory framework. He said it is difficult for evolving institutional practices to keep pace with revolutionary advances in science and technology.

Dr. Casey said there is no shortage of ideas, but effective strategies on how to move forward lag behind. He noted that there is a need for parallel efforts, rather than testing sequentially. Also, the infrastructure is lacking to allow regulatory toxicology to take full advantage of rapidly emerging new technologies such as clustered regularly interspaced short palindromic repeats, or CRISPR. He said the new technologies are not self-implementing and obstacles are not self-resolving.

Challenges include consideration of animal models as the gold standard, institutional resistance, and the issue of harmonization.

ICCVAM is developing a short-term strategy to replace, within three years, the six most commonly used acute toxicity tests (the "EPA 6-pack," acute oral, acute dermal, acute inhalation, primary eye irritation, primary dermal irritation, dermal sensitization). Implementing a more holistic, human-relevant approach for toxicity testing in the 21st century will require significant changes in policy, practice, and regulation. Dr. Casey noted that it would be important to know where industrial/agricultural chemicals and pharmaceutics diverge in the roadmap.

Dr. Milchak, first discussant, agreed that there must be a focus on the United States in moving forward, but he emphasized the importance of global efforts, particularly regarding regulatory testing and classification. He said the science of alternative methods has advanced, but there are still significant gaps and impediments, particularly when alternative methods do not apply to unique products and mixtures. Dr. Casey agreed that international harmonization is an important consideration.

Dr. Berridge, second discussant, said there is conceptual alignment between the pharmaceutical and industrial/agricultural chemicals sectors. It is important to replicate human biology, but there remains a significant reliance on animals in testing strategies, driven by a fundamental belief in conservation in mammalian biology. Technology is becoming much less of a limitation than it has been in the past; there is an opportunity at present to start to conduct testing in a way that is more clinically predictive, less animal dependent, and more mechanistically informative. He felt the biggest limitation is an inability to gain confidence in a different way of doing the testing.

Dr. Wei Xu, third discussant, said there is urgency to promote adoption of new testing methods. She called for a better funding mechanism to encourage the development of non-animal testing methods and for more effort to identify adverse outcome pathways.

Dr. Willett felt that just reducing the use of animals is not a sufficient driver for advancement in the United States. She said reduction of animal use can be a driver, depending on the sector, e.g., cosmetics. She noted the success in the update of the Toxic Substances Control Act (TSCA), which addresses reduction in vertebrate animal use. She said the possibility of replacing animal testing in 10 years depended on leadership and will.

Dr. Spencer agreed that the focus should be on predicting human health outcomes, noting that the change would be made during a transition period. During that period, there should be integration of data from the newer methods with the older data from traditional methods to reach a point of confidence in predictivity, ultimately resulting in an animal-free testing paradigm.

Dr. Hamadeh said the technology involved in alternative methods, especially *in silico* and organ-on a chip, are very complex and agreed that genetics plays a significant role; current generic platforms do not take individual variability into account. He felt testing would be much improved in a number of years, with many of the technological hurdles having been surpassed. Funding would continue to be a major issue, and a wide variety of stakeholders would need to be involved in a national initiative. Dr. John Elliott concurred with the importance of funding validation studies.

He said the challenge is that validation studies are expensive and more pedestrian than developing the new technologies themselves. An appreciation of the challenges of validation would be helpful to achieving the shift in toxicity testing.

Mr. Janzen observed that much of the data being collected on toxicity where genetic variability is known to be a factor as shown from biomedical research.

A. Update on ICCVAM's Vision and Strategy

Dr. Anna Lowit, EPA, ICCVAM co-chair, said ICCVAM is developing a strategy and roadmap to establish alternative methods for the 6-pack and a more comprehensive U.S. strategy and roadmap to implement the use of more human-predictive approaches for assessing complex biological processes such as developmental toxicity and carcinogenicity. The EPA Office of Pesticide Programs (OPP) is actively seeking to significantly reduce the use of animals in acute effects testing for pesticide active ingredient registration programs, resulting in potentially enormous animal savings.

Dr. Lowit described the general approach ICCVAM used for each 6-pack test. A database of complete 6-pack studies from approximately 900 pesticide products has been established. EPA, collaborating with NICEATM, has released a draft waiver guidance for fundamentally eliminating the acute dermal toxicity test, which saves approximately 300 animal studies per year. For acute oral and inhalation toxicity testing, integrated approaches for testing and assessment (IATAs) and harmonization have been discussed. For skin sensitization testing, ICCVAM has published IATAs, and ICATM has held a workshop. For skin and eye irritation testing, there has been an effort to catalog and curate existing industry data.

B. ICCVAM Roadmap for Skin Sensitization Testing

Dr. Joanna Matheson, Consumer Product Safety Commission (CPSC), provided an update on the activities of the ICCVAM Skin Sensitization Working Group (SSWG). She noted the challenges of incorporating alternative testing methods that include varying and ambiguous data requirements, limited coverage of chemical space, and regulatory and institutional inertia. The SSWG was charged with develop testing strategies to replace the commonly used animal method for skin sensitization testing, the local lymph node assay (LLNA), as well as older tests such as the Buehler assay and the guinea pig maximization test. The SSWG's key strategic activities include (1) design and evaluation of integrated approaches to testing and assessment of data using validated alternative methods, (2) validation of the NIOSH Electrophilic Allergen Screening Assay, (3) increase in the number of chemicals tested *in vitro* to expand the coverage of chemical space, and (4) international harmonization.

Dr. Matheson said NTP is compiling chemical nominations from ICCVAM agencies, and has procured 48 chemicals for the initial testing phase which begins in late 2016 and continues with additional testing in 2017.

Dr. Milchak praised the SSWG's significant progress and asked about 3D human tissue cultures with more metabolic capacity and how to deal with mixtures and chemicals with unique physical

properties. Dr. Matheson said the SSWG had not done any 3D work, but that evaluating mixtures is a goal of the new NTP study.

Dr. Spencer asked about the limited metabolic capacity, the ability to identify prohaptens of some of the new methods, and whether some of the new assays are designed to address those issues. She said without the appropriate metabolic capacity, an assay might miss some sensitizers that could be prohaptens. Dr. Matheson said there are some next-stage assays under development, adding that commercial availability is an issue.

Dr. Willett asked if the initiative to expand the chemical space would focus on some chemicals for which there are human data. Dr. Nigel Walker said human data would be limited. Dr. Kleinstreuer said most of the chemicals with human data are cosmetics ingredients and almost all of them have previously been tested with *in vitro* methods. The goal is to expand their use into industrial chemicals, pesticides, and herbicide formulations, which have not yet been covered.

1. Oral Public Comments

Dr. Neil Wilcox, representing Center for Responsible Science (CRS), said he was pleased with the direction being taken by NICEATM and that it is essential to develop a more concrete strategy to get tests validated and approved. He praised Dr. Casey's leadership in guiding NICEATM in new directions. He noted Dr. Abigail Jacobs' remarks at the ICCVAM Public Forum regarding FDA's willingness to accept alternative skin sensitization testing if there were a Good Laboratory Practices laboratory to conduct the testing. He said he hoped progress had been made in finding such a laboratory and that guidance would be issued in the near future.

Ms. Kristie Sullivan, representing Physicians Committee for Responsible Medicine (PCRM), noted the many public commenters at the meeting, which she attributed to the new direction being pursued by ICCVAM and NICEATM. PCRM supports the approach NICEATM is taking in skin sensitization testing and recognizes the importance of implementation. She recommended that all groups push beyond their comfort zone to adopt alternative methods. She said ICCVAM and NICEATM should look at the tests actually being conducted by industry and not simply at the regulatory guidelines themselves.

Dr. Anki Malmborg, representing SenzaGen, Inc., felt it was important for SACATM to hear from a method developer. She noted the need to gain consensus on acceptance of alternatives to animals for skin sensitization and pointed out that *in vivo* methods are actually less sensitive than *in vitro* methods. She said the LLNA and guinea pig assays should be discontinued, due to high cost to society and inferior predictions. Industry is reluctant to use the *in vitro* assays, as they are not specified in the guidance from regulatory agencies. She cited validation of new methods as another major challenge.

2. SACATM Discussion

Dr. Willett, first discussant, said she was happy with the approach NICEATM is taking on acute toxicity, particularly the strong coordination with EPA. She felt communication had improved considerably, but there is room for improvement in terms of ICCVAM understanding the agencies'

priorities. She said NICEATM is doing a good job in beginning a discussion about how to do validation in new ways. Dr. Willett encouraged ICCVAM and NICEATM to continue their participation in international activities.

Dr. Xu, second discussant, said skin sensitization testing is a big success due to two factors (1) nine agencies are willing to cooperate and share a large amount of human data and (2) the integrated testing strategy developed by NICEATM and ICCVAM has contributed to advancing the methods. She noted that there is a bill before Congress proposing to phase out animal cosmetic testing. Dr. Xu said that could contribute to development of new methods to test complex compounds such as mixtures.

C. Moving Away from Animal Models for Toxicity Testing

Dr. Casey presented strategies for moving away from animal models for toxicity testing, noting that the ultimate goal is to understand human physiology, which will allow the use of pathway-based approaches. He said until alternative methods actually are predictive, animal models will continue to play a role, but the question is how to move away from the animal models when there is a better alternative test. The paradox is the need to validate human-based approaches against animal models that are not predictive of human outcomes, e.g., using rodent-based approaches to predict rodent toxicity, when they are not necessarily predictive of human outcomes.

Dr. Casey said there are some steps to begin moving away from animal data in the near term. He noted that concordance between *in vitro*/computational approaches is increased by using high-quality data, so ensuring high-quality animal data is important at this stage, particularly in acute toxicity. He noted that variability in animal testing should allow regulators to more readily accept *in vitro* tests. Ultimately, a comparison to human data will be needed, with access to large amounts of high-quality human toxicological data. He said little human, non-pharmaceutical data are currently available.

1. Oral Public Comments

Dr. Wilcox, representing CRS, said a simple first step to help the process of moving away from animal models for toxicity testing would be to amend FDA regulations to reflect current policy. The current regulations actually require animal testing, which discourages the use of non-animal methods, despite the fact that they may be more predictive of human response. Dr. Wilcox said CRS and 13 additional groups have petitioned the FDA to update 29 of its regulations to allow the use of pre-clinical test methods most predictive of human response.

Dr. Lowry Curley, representing AxoSim, said his comments would be from the perspective of a company pioneering organ-on-a-chip technology. He noted that the burden of validation is falling on the development companies, which are, as a result, put at risk. The majority of pharmaceutical companies are taking a wait-and-see approach; they are not yet incentivized to work together with the smaller development companies. Access to data among the various stakeholders is critical, as much of the data are currently siloed. He questioned what happens when human test data do not align with animal data.

Ms. Laura Rego, representing Cruelty Free International (CFI), said her organization wished to raise an issue regarding 10 tests, identified by CFI, that are of limited value in determining safety or efficacy of chemicals or pharmaceuticals. She said ICCVAM can play an important role in ensuring that these tests, which use many animals annually, are eliminated, both federally and internationally. She asked ICCVAM to help determine which animal tests currently in use may be redundant, resulting in unnecessary animal usage.

Ms. Elizabeth Baker, representing PCRM, said her group strongly supports having the Office of Science and Technology Policy charge a high-level workgroup with drafting a roadmap for implementing the National Research Council's (NRC) Vision for Toxicity Testing in the 21st Century, and having the National Academy of Sciences (NAS) convene a series of workshops that identify the impediments and enablers of progress. The roadmap and workshops should focus on replacement of animal tests, with consideration given to reduction opportunities. Efforts should be coordinated by the President, as they represent an unfulfilled need across many federal agencies. PCRM commends ICCVAM and NICEATM on previous validation work and encourages continued assistance and funding opportunities in that area. PCRM suggests using human-based methods as models in a disease research context and further developing adverse outcome pathways. PCRM approves of ICCVAM's communication with external stakeholders, but calls for improved communication among ICCVAM agencies.

Ms. Sue Leary, representing the Alternatives Research and Development Foundation (ARDF), felt the efforts of SACATM, ICCVAM, and NICEATM had become particularly fruitful, with measurable progress toward their goals. She noted the need to acknowledge that animal tests are not the gold standard. She suggested not only moving away from animal tests, but moving toward a new way of doing science. She encouraged more extramural funding for development of alternative methods and validation studies.

2. SACATM Discussion

Dr. Berridge, first discussant, addressed enabling the next generation of pharmaceutical safety assessment, which has key components of motive, opportunity, strategy, and partnership. He said although the use of animals in toxicity testing has had positive benefits through the years, there is an opportunity to change the paradigm and significantly reduce the use of animals. The cost of developing a new drug has continued to increase and more and more compounds are failing for safety reasons, at great expense. With new technologies, such as computational drug discovery and systems-on-a-chip, there are significant new opportunities in discovery and development, offering more predictivity and less animal use. He noted several possibilities for leveraging the new opportunities, including a collective willingness to accept managed risk and freedom to operate. In drug development, the clearest opportunity to apply novel methods is during molecular design, but the strategy has challenges. He described the emerging partnership to examine and validate the role of tissue chips in safety testing, where a roadmap to evolve confidence and capability has been developed. The ultimate value proposition includes improved predictive validity of the early preclinical models, decreased cycle time, early risk/benefit integration, decreased animal use, lower development costs, and more efficient and impactful innovation efforts in the near term. He advocated for a single-species, incentive-driven holistic

strategy, the value of which would increase dramatically through a deliberate, organized effort involving partnerships.

Dr. Hamadeh, second discussant, said there needs to be a national strategy and campaign, sponsored at the highest levels of the U.S. government, because so much is at stake. The push for new methods has the potential to fundamentally change the economics of drug, chemical, and consumer product development. The effort should be amplified to include more unlikely or non-traditional stakeholders. He called for a roadmap for alternative methods, but warned that it should not be too proscriptive, as it is not possible to forecast what the solutions will ultimately be. He favored prioritization and consideration of impact versus feasibility and he approved of an incentive-driven approach. He said animal models today are the practical gold standard, and recognized the efforts to establish a new human-based gold standard, which is crucial to inform validation. He noted the importance of establishing the connection between *in vitro* models and human health. In some cases, he suggested using a hybrid approach, e.g., reproductive studies, where use of human models is limited. Dr. Hamadeh noted the risk involved in validation, which may require the use of safe harbors (i.e., provisions that specify that a certain conduct will be deemed to not violate given rules) and waivers, when necessary.

Dr. Spencer, third discussant, noted that many of the concepts presented by Dr. Berridge regarding the pharmaceutical industry are also relevant to the chemical industry, but with some distinct differences. While animal tests have done a good job of predicting human health outcomes, they have also created challenges for the chemical industry, which does not have the benefit of drawing from human clinical data. Human relevance studies can lead to increased animal use; the need for extrapolation of animal results to humans is a driver for industry to move forward with alternatives. She said new test methods have been in development for more than a decade and it will be important to put the new methods into a chemical safety framework or chemicals management program. She called for a consideration of how to accomplish the creation of a new framework. Dr. Spencer noted that many companies are already using the new methods early in product development, potentially presenting an opportunity to capitalize on the information being generated.

Dr. Milchak, fourth discussant, said 3M is using many of the new technologies because they work in targeted ways. There is not an assumption that all animal testing will be eliminated, but 3M looks for specific opportunities to reduce or replace animal testing. He said using a targeted approach and looking at specific endpoints will lead to success in 3Rs efforts.

Dr. Black said the pharmaceutical industry has not always been able to predict animal toxicity, even when using the most modern *in vitro* and pathway-based methods. Companies need better *in vitro* tools - ones that are physiological more complex and integrated - because they need to avoid putting time, energy, and funds into developing a drug that will prove to be toxic. She cited Astra Zeneca's publication on their drug development programs from 2005-2010, in which 38 of 142 programs were discontinued due to unacceptable toxicity. She said it would be important to determine why toxicities were not discovered earlier in the pipeline and why *in vitro* tools missed these liabilities. Mr. Janzen noted that the large number of discontinued programs indicates that better tests are needed.

Dr. Spencer said in the chemical industry, the chemicals typically being screened for public health effects are not designed to be highly bioactive, but are intended for a certain function or performance. Early in the process, the focus is to discover chemicals that may have profound carcinogenic, reproductive, or developmental toxicities. She observed that it will be necessary to have both the alternative methods and the animal methods, informing one another moving forward. Regarding discrepancies between human cell line tests and animal tests, Dow was using a combination of both approaches. Dr. Berridge said there has been a debate about whether to develop human-based or rat-based chips. He said that for building confidence, there is value in having species-specific extrapolations. Dr. Casey pointed out that NIEHS will be funding a Small Business Innovative Research (SBIR) to adapt some of the platforms that have been developed for the human chip to rodent cell lines.

Dr. Hamadeh said the ultimate assessment of risk in drug development happens in clinical trials. Animal-based systems are important to protect eventual human volunteers. He supported having human-based platforms take the lead in preclinical systems.

Dr. Willett did not support having adverse outcome testing recreated on animal or human chips. She suggested assessing global toxicity first, and then more specific toxicity later, as warranted, as opposed to the 1-to-1 replacement approach. She said when systems biology approaches are employed, the validation role will be supported by internal consistency. Dr. Casey agreed that 1-to-1 replacement is not possible. He noted that the goal for pharmaceutical companies is to develop confidence in a compound to move into Phase I testing, but that agricultural and industrial chemicals take a different approach; their compounds are not tested directly in humans, which is an important difference in the sectors.

Mr. Janzen noted that in the pharmaceutical industry, compounds move from a bias toward false positives to a bias toward false negatives. When evaluating potential new drugs, many false positives are acceptable in order to capture as many potential drug candidates as possible, leading up to preclinical studies. As toxicity later becomes the focus, then it is necessary to identify toxicity in the drugs.

D. Implementing the Vision for Toxicity Testing in the 21st Century

Mr. Timothy Malloy, from the University of California-Los Angeles School of Law/Fielding School of Public health, briefed SACATM on the results of an international survey his group had conducted among 1300 toxicologists and related professionals. The survey gathered opinions about alternative methods and applications, socio-legal barriers to adoption, and socio-legal drivers of adoption. The survey asked about six methods and seven applications, resulting in a matrix of 42 distinct scenarios. The major barriers identified were regulatory acceptance, lack of standardization, slow validation process, and resistance to change.

The most important drivers were the need for toxicological data to review thousands of chemicals, the need for reduced testing costs, demand by regulatory agencies, ethical concerns, desire to advance science, and the need to improve *in vivo* testing. Mr. Malloy said the survey showed that adoption of alternative methods is not purely a scientific pursuit, and that beyond technological

advancement, there is a need to create legal and institutional environments where the new methods will flourish. He said policy makers and regulators will need to be directly involved.

1. SACATM Discussion

Dr. Willett, first discussant, noted that impediments exist at several different levels, including legal and regulatory. There are non-scientific barriers of language, communication, and support. The language barriers exist at the regulatory and legal levels. She discussed an agency's guidance as it relates to language and communication barriers, and considered a guidance as a communication tool to legitimize the use of alternative methods. She said NICEATM and ICCVAM could help improve those communications and help coordinate training in alternative methods within the regulatory agencies. She said support at the leadership level within the agencies is needed and cited EPA's OPP as an example of successful leadership at the highest levels. She felt NIEHS has done a great deal to fund alternatives research, but thought NIH could do much more in terms of funding such research at the other institutes.

Dr. Milchak, second discussant, said 3M has already made a commitment to using non-animal testing wherever possible. The impediments typically fall into three categories: regulatory acceptance, technical feasibility, and rarely, cost. The vast majority of the testing 3M conducts is to meet regulatory requirements, which often eliminates the possibility of using an alternative method. He said if there is a technically feasible assay without a requirement for an animal test, 3M will use it, but the reality is that the testing frequently involves chemical mixtures, often precluding the use of alternative methods.

E. Coordinating Activities between the Federal Government and Stakeholders and Promoting Adoption of Alternative Testing Strategies

Dr. Kleinstreuer addressed the need to coordinate activities between the federal government and stakeholders, while promoting adoption of alternative testing strategies.

The 2007 NAS report stated the need (1) for development of an infrastructure for data sharing, (2) for high-level coordination of research efforts, and (3) for the federal government to drive the efforts while ensuring participation by industry and public interest groups. Vital elements include collaboration, communication, and data sharing. She noted the importance of adequate funding, SBIR initiatives, and effectively combining resources among all groups.

She described the necessity for international collaboration and harmonization, through such programs as the Organisation for Economic Cooperation and Development (OECD) Test Guidelines and ICATM. She noted the Acute Toxicity Workgroup formed by OPP as an example of an effective partnership with stakeholders. To promote adoption of alternative test methods, there must be a commitment to education and training programs, clear guidance from regulatory authorities on acceptance of alternative methods, understanding and addressing impediments to adoption, and coordination with OECD, ICATM, and other international partners.

Dr. Kleinstreuer described a new NICEATM web resource called the Integrated Chemical Environment (ICE), which is slated for roll out in early 2017. ICE will have three major components: data integration and availability of data, workflows (e.g., IVIVE and QSAR), and educational tutorials.

Mr. Janzen asked about response rate for data from stakeholders and the potential for safe harbor. Dr. Kleinstreuer replied that the response is moderate. Dr. Lowit said 1-to-1 engagement with companies allows for answering questions and enhances responses. In some situations, safe harbor is not possible; however, a process document was recently finalized that creates a public process to work with stakeholders to create the time and space to conduct collaborative efforts before the legal reporting requirements start.

1. Oral Public Comments

Dr. Wilcox, CRS, was pleased with ICCVAM's focused strategy and clearly defined outcomes. Regarding impediments, he noted that several current FDA regulations require traditional animal testing and promote the status quo, creating an unreceptive environment that fails to encourage innovation and development of more predictive test methods. A solution would be to modify regulatory language to encourage sponsors to use modern test methods, along with generation of specific guidance documents to educate sponsors about specific test methods. He recommended (1) adoption of "pragmatic validation," as developed by the Safer Medicines Trust, (2) improved continuing education for agency reviewers, (3) development of uniform acceptance criteria, and (4) frequent well-organized communication among all stakeholders. He said the institutionalized use of animal-based methods is preventing more human-predictive methods from being developed and adopted by federal agencies and industry.

Dr. Curley, AxoSim, said education and training are key issues. He noted that access to data needs to be improved, especially historical data, which could be blinded. He advocated the need for a strong coalition.

Ms. Rego, CFI, said the time scale from validation to adoption and replacement of new methods has been in excess of 10 years, due in part to the failure of regulatory authorities to take responsibility for identifying new methods, assessing their feasibility for their sector, and notifying industry of their decision. She described four steps for regulatory acceptance of new methods and replacement of animal tests: assessment, decision, acceptance, and policing. She added that transparency is important once an alternative method has been accepted.

Ms. Sullivan, PCRM, was gratified to see EPA leadership interacting with the stakeholder community. She called for better information about how many animals are used in toxicity testing and in what contexts, with better metrics contributing to a clear strategy for how to move away from the current paradigm. She noted the importance of effective communication within agencies.

Dr. Paul Locke, said his group at Johns Hopkins University has extensively studied the implications of the 2007 NAS report and discussed how to move the 3Rs process forward. He predicted that ICCVAM, NICEATM, and NIEHS should be and likely would be very involved in the implementation of the new TSCA law, which includes a section on developing a strategy to

reduce vertebrate animal testing. He suggested they should actively participate in the NIH Precision Medicine Initiative and the cancer moonshot. He said NIEHS should adopt a replacement-first approach in its research and testing, favoring *in vitro* science in its solicitations. He called for building a bridge between old data and new data and suggested it may be a good source for research projects for students.

Sue Leary, ARDF, stressed the value of collaboration with groups working together on shared goals, which would build trust. She agreed with Dr. Malloy's statement that adoption is not purely a scientific matter. She endorsed the idea of an innovation competition. She said it is important that agencies issue clear guidance to result in immediate reductions in animal use.

Katherine Groff, representing People for the Ethical Treatment of Animals (PETA), said PETA has been encouraged by the development of non-animal test methods, but that development is far outpacing adoption by regulatory agencies. She called for agencies to rapidly adopt clear guidance on the acceptance and/or preference for non-animal methods and to incentivize companies to use the methods by implementing a system of expedited review of data submissions using non-animal methods. She encouraged SACATM to work with ICCVAM and member agencies to track implementation of non-animal methods. She noted the importance of increasing access to existing data and providing training for agency reviewers on non-animal testing policies, methods, and data interpretation. She offered PETA's assistance in that pursuit. Another strategy to reduce the use of animals in testing would be to conduct periodic reviews of how data from currently required tests are applied. PETA encouraged all ICCVAM member agencies to quantify all types of animals used for specific endpoints. She called for access to USDA Category E justifications, with an ability to search the reports. PETA also suggested establishment of a public-private center dedicated to the 3Rs.

2. SACATM Discussion

Dr. Black, first discussant, said she had no disagreements or suggestions for improvements to Dr. Kleinstreuer's comments. She noted that there are opportunities to increase cooperation and coordination among the stakeholders. She endorsed the idea of funding a specific 3Rs center in the United States. She encouraged SACATM members to look at the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) website, which solicits "bottom-up" suggestions for solutions.

Dr. Zhu, second discussant, stressed the importance of adequate funding. He related his own experiences in acquiring funding. He recommended that reviewers have multi-disciplinary knowledge and advocated for improved access to historical data.

Dr. Hamadeh offered a framework for the path to adoption of alternative methods, comprised of five steps: awareness, access, trial, value assessment, and conversion or adoption.

Dr. Spencer said many smaller companies do not have access to the same resources and expertise as large companies; it is a problem that should be addressed to encourage adoption of alternative methods.

F. Next Steps Toward Developing a Strategy for Implementing the Vision for Toxicity Testing in the 21st Century

Dr. Casey said he was aware of four separate initiatives to establish a 3Rs center. He said much can be accomplished with current resources, but a clear plan needs to be formulated. To take advantage of the current momentum, he and Dr. Bucher planned to address the NAS on September 28, with the goal of engaging the Office of Science and Technology Policy. Dr. Bucher said they would be speaking to the Committee on Emerging Science for Environmental Health Decisions, for which he has served as NTP liaison. The committee, which is sponsored by NIEHS, selects topics for workshops for funding by NIEHS. He said a goal is to hold workshops that would address the obstacles to adoption of alternative methods. Dr. Casey said involvement at the highest levels would be necessary to fundamentally change toxicology testing.

Mr. Janzen asked SACATM to think about the next steps and assess progress at next year's meeting. He said the keys he perceived from this meeting are regulation and approval, differences between the pharmaceutical and chemical industries in terms of alternatives adoption, and the importance of validation.

Dr. Berridge said changes in toxicity testing will be evolutionary. To get the needed stakeholder buy-in, the strategy must be deliberate and concrete. He recommended leveraging the potential shared framework incorporating the agricultural chemical and pharmaceutical industries, despite the divergent challenges facing them. He noted that in the pharmaceutical industry there is motive for change, but little space to take huge risks.

Dr. Willett stressed that, although leadership should drive the effort, it is also important to achieve stakeholder buy-in at all levels. She acknowledged that there are many resources available, but it will be necessary to have a plan of action to attract the resources, particularly funding.

Dr. Spencer recommended concentrating on some of the immediate opportunities that could be capitalized on, such as TSCA reform, where there could be direct impact to influence how the regulation will implement and use alternative methods.

Dr. Casey said there was agreement with NC3Rs that acute toxicity would be a good place to start, and there will be an effort to extend it to the global community through a series of workshops and meetings. There is also a single-species safety initiative, encouraging adoption of a single-species endpoint, versus the currently required two species for pesticide registration. He asked for consideration of a toxicology version of the cancer moonshot.

Dr. Birnbaum said currently there is no funding for the cancer moonshot and no budget for the federal government. She said great information had been shared at the meeting and there is a loud and clear will for people to work together. She was proud of ICCVAM for their efforts to satisfy the needs of regulators. She said there are still many opportunities to advance alternative methods and it must be done because toxicity testing cannot continue as it has been done in the past.

VII. Adjournment

Dr. Bucher thanked everyone for attending the meeting. Mr. Janzen thanked everyone for their participation and adjourned the meeting at 5:00 PM.