

Summary Minutes

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) Meeting

September 2, 2015

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

Table of Contents

| | | |
|-------|----------------------------------------------------------------------------------------|----|
| I. | Location of Background Materials/Presentations and Frequently Used Abbreviations | 2 |
| II. | Attendees..... | 3 |
| III. | Welcome and Opening Remarks..... | 4 |
| IV. | Update on NICEATM Activities..... | 5 |
| V. | Update on ICCVAM Activities..... | 8 |
| VI. | Federal Agency Updates | 10 |
| | A. USDA..... | 10 |
| | B. EPA..... | 10 |
| | C. FDA | 11 |
| | D. NIEHS..... | 12 |
| VII. | International Activities, Opportunities, and Challenges | 14 |
| VIII. | Metrics: Measuring Success in the 3Rs..... | 15 |
| IX. | Creating a 3Rs Roadmap and Strategy for the United States | 19 |
| X. | Adjournment..... | 22 |

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

Background materials and presentations for the meeting are available at <http://ntp.niehs.nih.gov/go/8202>.

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| 3Rs | replacement, reduction, or refinement (causing less pain and distress) in the use of animals for toxicological testing |
| AOP | Adverse Outcome Pathway |
| APHIS | Animal Plant Health Inspection Service |
| CHO | Chinese Hamster Ovary |
| CPSC | Consumer Product Safety Commission |
| CRO | contract research organization |
| CVB | Center for Veterinary Biologics |
| DABT | Diplomate of the American Board of Toxicology |
| DoD | Department of Defense |
| EDSP | Endocrine Disruptor Screening Program |
| ELISA | enzyme-linked immunosorbent assay |
| EPA | U.S. Environmental Protection Agency |
| ER | estrogen receptor |
| ES | embryonic stem cells |
| EU | European Union |
| EURL- ECVAM | The European Union Reference Laboratory for Alternatives To Animal Testing |
| FDA | U.S. Food and Drug Administration |
| GLP | good laboratory practice |
| GST | General Safety Test |
| HHS | U.S. Department of Health and Human Services |
| HIST | murine histamine sensitization test |
| IACUC | Institutional Animal Care and Use Committee |
| ICCVAM | Interagency Coordinating Committee on the Validation of Alternative Methods |
| ICATM | International Cooperation on Alternative Test Methods |
| ILS | Integrated Laboratory Systems, Inc. |
| IND | Investigational New Drug |
| IPS | induced pluripotent stem cells |
| IVIVE | <i>in vitro</i> to <i>in vivo</i> extrapolation |
| LLNA | local lymph node assay |
| NAS | National Academy of Sciences |
| NC3Rs | National Centre for the Replacement Refinement and Reduction of Animals in Research |
| NCATS | National Center for Advancing Translational Sciences |
| NGOs | non-governmental organizations |
| 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 |
| NIH | National Institutes of Health |
| 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 |
| SACATM | Scientific Advisory Committee on Alternative Toxicological Methods |
| SBIR | Small Business Innovative Research |
| STTR | Small Business Technology Transfer |
| UK | United Kingdom |
| USDA | U.S. Department of Agriculture |

II. Attendees*

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)

Lauren Black, PhD, Charles River Laboratories
Tracie Bunton, DVM, PhD, Eicarte LLC
Joan Chapdelaine, PhD, Calvert Laboratories, Inc.
Mark Evans, DVM, PhD, Pfizer
William Janzen, Epizyme, Inc. (chair)
Catherine Willett, PhD, The Humane Society of the United States
Wei Xu, PhD, University of Wisconsin at Madison

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

Principal Representatives

Carol Clarke, DVM, DAACLAM, U.S. Department of Agriculture (USDA; by webcast and telephone)
Bert Hakkinen, PhD, National Library of Medicine
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)
Karen Taylor, DVM, National Institute for Occupational Safety and Health (NIOSH)
Nigel Walker, PhD, DABT, National Institute of Environmental Health Sciences (NIEHS)

Other Federal Attendees

David Dix, PhD, EPA
Richard McFarland, MD, PhD, FDA/Center for Biologics Evaluation & Research
Stephanie Padilla, PhD, EPA

NIEHS/NIH Staff

| | |
|--------------------------------|----------------------|
| Mamta Behl, PhD, DABT | Elizabeth Maull, PhD |
| Linda Birnbaum, PhD, DABT, ATS | Kirsten Mease |
| John Bucher, PhD, DABT | Richard Paules, PhD |
| Warren Casey, PhD, DABT | Kristen Ryan, PhD |
| Robbin Guy | Lori White, PhD, PMP |
| Angela King-Herbert, DVM | Mary Wolfe, PhD |
| Robin Mackar | Rick Woychik, PhD |

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

| | |
|--------------------------|----------------------------|
| David Allen, PhD | Michael Paris |
| Neal Cariello, PhD | Catherine Sprankle |
| Nicole Kleinstreuer, PhD | Judy Strickland, PhD, DABT |
| Steven Morefield, MD | |

Bridport Services, LLC

Ernie Hood, MA

* The meeting was webcast. Individuals who viewed the webcast are not listed, except as noted.

Public

Brian Berridge, DVM, PhD, DACVP, GlaxoSmithKline

Jeffrey Brown, People for the Ethical Treatment of Animals (PETA)

Amy Clippinger, PhD, PETA

Jack Fowle, PhD, DABT, Science To Inform, LLC

Marie Gibbons, North Carolina State University

Katie Paul Friedman, PhD, Bayer CropScience

Kristie Sullivan, MPH, Physicians Committee for Responsible Medicine (PCRM; by webcast and telephone)

Katya Tsaion, PhD, Evidence-Based Toxicology Collaboration (by webcast and telephone)

Mary Ann Vasbinder, DVM, DACLAM, GlaxoSmithKline

Gary Wnorowski, MBA, Product Safety Labs

III. Welcome and Opening Remarks

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) met on September 2, 2015, at NIEHS in Research Triangle Park, North Carolina. SACATM Chair Mr. William Janzen called the meeting to order at 8:30 AM. All in attendance introduced themselves. Designated Federal Officer Dr. Lori White read the conflict of interest statement.

Dr. Linda Birnbaum, NIEHS and National Toxicology Program (NTP) Director, welcomed everyone to the meeting and noted that it had been just over two years since the reinvention of Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). She described the significant progress ICCVAM has made toward meeting the objectives set in 2013 and previewed the various agenda items for the meeting.

Dr. Birnbaum presented certificates and letters of appreciation to outgoing SACATM members, Drs. Tracie Bunton, Joan Chapdelaine, and Mark Evans, and thanked them for their service.

Dr. Warren Casey, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) Director, welcomed everyone to the meeting and highlighted the proposal to develop a national strategy and roadmap for 3Rs efforts within the U.S. He noted that the basic question behind the 3Rs is, "Why do we care?" He said that it has become clear within the pharmaceutical industry that animal models are insufficient to sustain cost-efficient research and development, and often results do not translate to the clinic. He said new methods improving predictivity of human physiology are needed.

IV. Update on NICEATM Activities

A. Presentation/Discussion

Dr. Casey presented an update of NICEATM activities over the past year. He reviewed progress in the four NICEATM focus areas established in the 2013 ICCVAM reinvention: reference data, fit-for-purpose validation, integrated analysis of data, and *in vitro* to *in vivo* extrapolation (IVIVE).

He described the critical importance of reference chemicals in validation studies and discussed the problem of using animal studies as the gold standard, when the purpose of developing new methods is to discontinue using animals for testing. He asked whether the objective of using a non-animal method would be to establish equivalent performance with animal studies currently used in regulatory toxicology testing, or to achieve superior predictivity of toxicity in humans. Dr. Bunton said that although equivalent performance is important, at some point with drugs or chemicals there would be human data that can be tapped into to assess translation into human physiology. Dr. Kate Willett, Dr. Casey, and she discussed the issue of validation to both animal and human standards. Dr. Casey said more human data are needed to develop and validate systems that are more predictive of human toxicity than animal models.

Dr. Casey cited the example of skin sensitization, where reference data from studies in both humans (e.g., clinical studies, case reports) and mice (local lymph node assay [LLNA]) are available. He asked whether the objective is better predicting human skin sensitizers or simply replacing the LLNA. Dr. Abigail Jacobs noted that in pharmaceuticals, predicting human response is the ultimate goal. Mr. Janzen mentioned the current European focus on replacing the animal models, asking whether that would lead to superior prediction in humans.

Regarding reference data, Dr. Casey said there is a need for quality and context. He described NICEATM efforts to develop high-quality reference databases for use in several priority areas. He described in more detail recent work to develop a database of developmental toxicants using systematic review methods.

Dr. Casey reported on recent agency-specific, fit-for-purpose validation activities. With EPA, collaborative work has progressed with the Endocrine Disruptor Screening Program (EDSP) and acute oral/dermal LD₅₀ assays. In some cases, such as skin sensitization, data can be used by multiple agencies including EPA, CPSC, and FDA. Dr. Lauren Black asked why the phasing out of LD₅₀ assays has not been accomplished. Dr. Casey said the test is still being conducted because it is required (by non-drug-development guidelines); the LD₅₀ replacement remains a priority for ICCVAM and the agencies.

Dr. Casey discussed the concept of transferability in validation studies and whether between-lab transferability is absolutely necessary, particularly where that would be difficult or impossible. He said a more flexible model of validation is needed, and the real issue is establishing confidence in the data that are being generated. Mr. Janzen said protocols are transferred constantly between high throughput screening labs, particularly within pharmaceutical companies. Dr. Willett noted that sometimes the transfer involves a battery of assays; movement is away from one test and one endpoint toward a battery or integrated testing strategy. Thus, validation involves a prediction model as opposed to a single assay. Dr. John

Bucher noted that the issue is not so much validation as it is confidence in the outcome. Mr. Janzen said high throughput results could be reproduced in medium or low throughput, as long as the results are equivalent to what was found in the high throughput lab. He said, aside from proprietary reasons, he has never encountered an assay that could not be transferred. Dr. Casey said the question is whether one can establish confidence in the quality of the data in the absence of transferability. Dr. Birnbaum noted that a bigger issue is reproducibility, which is presently at the forefront of the scientific literature. She said results do need to be reproducible, even if by another method or in another setting. Dr. Casey agreed that that is an extremely important distinction. He added that the predictivity of the model should be clearly distinguished from validation of the assays.

Dr. Casey described IVIVE and mentioned a NICEATM-sponsored best practices workshop on this topic to be held in February 2016.

B. Public Comments

Ms. Kristie Sullivan, representing Physicians Committee for Responsible Medicine (PCRM), said she appreciated the work Dr. Casey had described regarding developmental toxicity. She acknowledged that it would be challenging, but would add much to the field by helping develop better models for that endpoint. She expressed support for the IVIVE work and agreed that understanding what is being predicted is an important question. Regarding the question of whether to replace animal tests or protect humans, she said the answer is both, and added that where there are *in vitro* methods available, which are clearly protective of humans, they need to be implemented to reduce animal use as much as possible.

Dr. Amy Clippinger, representing People for the Ethical Treatment of Animals (PETA), expressed appreciation for NICEATM's work. She said the issue of equivalent performance versus human predictivity in validation studies is a recurring one. She noted that FDA prefers tests in human cells and human predictive assays for pharmaceuticals. She asked whether the other regulatory agencies have a public stance on the question, and whether it might be possible for agencies that use the same test to come to consensus on which cell type to use. She said trying to validate against both human and animal cells adds time and expense to an already very time-consuming and expensive process. Dr. Lowit said it should be kept in mind that each federal agency works under a different set of directives from Congress. Even within one agency, there are different directives and statutes guiding processes, so asking agencies to harmonize could be very challenging.

C. SACATM Discussion

Dr. Wei Xu, first discussant, noted that she had viewed several NICEATM posters and presentations at the most recent Society of Toxicology meeting. She had seen improvements over the past year in the use of computational models to predict toxicity, the use of human cells with known activity to metabolize chemicals, the consideration of genetic variation to understand susceptibility, increased focus on the use of embryonic stem cells and induced pluripotent stem cells for toxicity testing, and biological model diversity using *Caenorhabditis elegans* and zebrafish. She suggested a workshop on selection of a model system using the Adverse

Outcome Pathway (AOP) approach. She said work needs to continue on choosing a cell line for IVIVE, as well as in use of human primary cells in organ-on-a-chip-type systems. She also suggested a workshop in computational toxicology to analyze more complex toxicants such as chemical mixtures and low-dose chemicals and nanoparticles. There is a pressing need for rapid adoption of new methods, with clear guidance to industry on their acceptance, and a means to ensure that reviewers understand them. There is also a need for training at the agencies to help implement validated alternative methods. Dr. Xu called for a workshop in acute systemic toxicity, based on the Department of Defense's request for methods for protection against toxic chemical exposures.

Dr. Bunton, second discussant, appreciated Dr. Casey's presentation and the references that had been made available on the website. She noted an abstract regarding an integrative approach to decision-making for skin sensitization, which she said would be key to getting more accurate information regarding predictivity. She noted another abstract that discussed using a combination of approaches, raising a potential issue of specificity, which could generate false positives. She approved of NICEATM's approach of evaluating the literature as a good method to reduce the number of assays needed and thus reduce whole animal use.

Dr. Willett said conducting systematic reviews of existing methods is important, because there has never been a comprehensive look at their overall performance. Having a clear understanding of the reliability of the current system would be necessary before instituting a new system. She added that the Evidence-Based Toxicology Collaboration is also working on a developmental toxicology review, and suggested communication between the two projects. Dr. Casey said NICEATM has identified a list of experts to nominate chemicals for literature review. The list will be made public, and ultimately used to select the chemicals for review.

Dr. Bucher said NTP is currently developing text-mining tools to accelerate literature review and allow answering complicated questions in a targeted fashion.

Regarding validation of animal cell-based assays versus human cell-based assays, Mr. Janzen said FDA still requires a series of animal tests before moving to human cellular models. Dr. Jacobs said acceptability to the FDA of alternatives to animals depends on the question being addressed; in some areas FDA accepts *in vitro* assays and is generally flexible in terms of data submissions. Dr. Black said pharmaceutical companies have needs that differ from FDA's when they are identifying lead candidate drugs, prior to FDA submission. She noted that pharmaceutical companies struggle to screen out ineffective or unsafe compounds early in the development process to avoid late stage attrition and find unique mechanisms that impact disease; later in development, when supplying (good laboratory practice) GLP safety testing data for the IND (Investigational New Drug), the issues are different because the aim of the IND experiments is "hard" data "proving" adequate clinical safe doses. Dr. Black said the predictive safety of rodent toxicology data (to human safety) is roughly 60%, reflecting that there are significant differences between the two.

Dr. Lowit said EPA is a multifaceted organization, and the Office of Pesticide Programs (OPP) is the main group requiring testing. EPA has had considerable success in waiving thousands of animal studies, which has saved tens of thousands of animals and almost \$100 million for the

pesticide industry. Under EPA's statutes and rules, it is challenging or nearly impossible to get human data. Dr. Lowit mentioned the challenge of international requirements, where the "checkbox" approach is still required in many areas. When EPA is able to waive a particular study, it may still be performed because another jurisdiction requires it.

Addressing the issue of the use of human cell lines, Dr. Birnbaum noted a recent study that showed considerable variability among human cell lines. Dr. Black said she makes the same point when counseling pharmaceutical clients in early drug development; well-qualified human cell lines used for screening assays often come from one tumor, or a limited set of individuals. Individual genetic and response variability must be taken into account. Dr. Birnbaum added that a similar wide range of variability in susceptibility has been seen in studies with outbred rodent populations such as the Collaborative Cross. Mr. Janzen said similar diversity is true within cell lines. Dr. Bucher noted that even within inbred rodent studies, there is variability in responses.

V. Update on ICCVAM Activities

A. Presentation/Discussion

Dr. Lowit, ICCVAM co-chair, updated SACATM on ICCVAM activities over the past year. She detailed a variety of developments within the four priority areas identified during the 2013 ICCVAM reinvention: acute toxicity testing, skin sensitization testing, biologics testing, and endocrine disruptors testing. She listed several recent activities in the area of communications, outreach, and information dissemination, another high priority since 2013. She also previewed upcoming meetings and workshops, which include (1) Communities of Practice, January 26, 2016; (2) *IVIVE* for High Throughput Prioritization and Risk Decision Management, February 17-18, 2016; and (3) ICCVAM Public Forum, May 26, 2016.

Dr. Bucher asked about the difficulty of skin sensitization testing of formulations. Dr. Lowit said EPA's OPP had been engaging pesticide companies for several months. The companies have reportedly been running a great many skin sensitization assays to help develop safer products and have both whole animal studies and *in vitro* data on matched products. She said EPA has an interest in collecting data on matched products, which would be of interest at EPA's stakeholder meeting in the fall of 2015.

B. Public Comment

Dr. Clippinger said PETA appreciated the opportunity to work with NICEATM on the February 2015 workshop titled *In Vitro Testing Strategies to Assess the Inhalation Toxicity of Nanomaterials*. The workshop led PETA to fund a lab to develop the model that had been recommended by the workshop participants; a workshop summary report would be submitted by the end of the year. She looked forward to hearing more about ICCVAM's activities related to acute systemic toxicity testing.

C. SACATM Discussion

Mr. Janzen, first discussant, commended ICCVAM on its progress. He felt the acute dermal toxicity and skin sensitization efforts are moving quickly to the point that a data-driven conclusion can be made. In terms of the short to intermediate-term areas for ICCVAM and NICEATM, he recommended the groups maintain their current focus to move projects toward conclusion. He praised the ICCVAM's efforts to communicate with the scientific and industrial stakeholder communities through webinars. He noted that, as alternative methods become more available, there would be a need for communication efforts aimed at different audiences, including broad communication to the general public, commercial vendors, and Small Business Innovative Research (SBIR) programs. Regarding social media, he felt communication with industrial and commercial stakeholders should be more formal, although social media may be an excellent vehicle for communication with the broader public.

Dr. Chapdelaine, second discussant, concurred that ICCVAM has made good progress in the past year, especially in the priority areas articulated in the 2013 ICCVAM reinvention plan. She commended communications efforts, especially the public forums ICCVAM held recently. She recommended more training for regulators and stakeholders regarding non-animal methods and strategies; continued use of websites, webinars, and email newsletters; and development of a LinkedIn presence for additional communication. She agreed that ICCVAM and NICEATM should remain focused on the current priority areas.

Dr. Willett said the target audience and communication goals are important to understand when using social media. She agreed that reaching scientists should be more formal and done through professional channels and noted that it is equally important to reach out to the public and other interested stakeholders.

Dr. Birnbaum said NIEHS has a growing social media presence, including Facebook and Twitter accounts. She said NICEATM works closely with the NIEHS SBIR program, with new approaches being developed through the collaboration.

Dr. Black said there are opportunities for weight-of-evidence approaches that could potentially replace some existing guideline-requirements for whole animal test methods. She asked if there is any outreach by regulatory agencies to communicate flexibility in accepting these new approaches in lieu of existing testing requirements. Dr. Lowit said in OPP, there is flexibility in the statutes; however, only within the last few years has EPA exercised that flexibility. She cited efforts to allow waivers in certain situations, which is now common practice, although it has not been well publicized.

Regarding training, Dr. Joanna Matheson encouraged the creation of a central location for training materials available to everyone, not just for the federal agencies. It would be a state of the science effort, fully listing all of the currently available alternative methods, along with the relevant slide sets.

VI. Federal Agency Updates

A. USDA

Dr. Carol Clarke, USDA, presented an update of 3Rs activities, concentrated on reducing hamster usage in *Leptospiriosis* vaccine potency testing, a requirement under the Virus-Serum-Toxin Act. This is being accomplished by promoting an *in vitro* enzyme-linked immunosorbent assay (ELISA) alternative, which will reduce the number of hamsters required for testing. USDA is using a team approach between two divisions, the Animal Plant Health Inspection Service (APHIS) and the National Agricultural Library (NAL), to accomplish the goal. Dr. Clarke explained the steps in *Leptospiriosis* vaccine potency testing, described the ELISA antigen quantification methods developed and validated by the APHIS Center for Veterinary Biologics (CVB), and showed the number of hamsters used in 2013 and 2014. She said companies are not required to use the ELISA and may apply to CVB for an exemption to the live animal test. The impact of reduction efforts is monitored through the annual reports of facilities listed in the Product Code Book, which are filed with APHIS Animal Care. The NAL Animal Welfare Information Center, which provides training on 3R activities, will post information on the ELISA alternative on its website. Efforts to further reduce hamster usage continue through the exploration of ways to eliminate hamsters needed to maintain virulent challenge strains (maintenance animals) and those needed to determine the LD₅₀ of challenge strains (back titration animals). CVB is exploring the use of cryopreserved strains to eliminate maintenance animals and prepared a notice to eliminate back titration animals for two *Leptospira* serovars. Dr. Clarke said success in these efforts would have a significant impact on reducing animal usage.

B. EPA

Dr. David Dix, EPA, presented an update on activities in partnership with NICEATM, focusing on the use of high throughput assays and predictive models in the EPA's EDSP. He showed that the EDSP has reached a "pivot" point, because at its current pace using the Tier 1 battery of tests, it would take decades to screen all 10,000 chemicals in the EDSP universe. Pivoting to use high throughput assays and computational models will allow much more rapid screening of chemicals for potential bioactivity and exposure. The estrogen receptor (ER) bioactivity model incorporates 18 high throughput assays using a variety of technologies, allowing receptor interaction detection at various points along the signaling pathway. There are plans to eventually replace all of the EDSP Tier 1 battery of assays with high throughput and computational models. The path forward is to (1) determine how well existing models predict intact animal results; (2) use additional computational tools to develop models for estrogen, androgen, and thyroid pathways; (3) expand reference chemicals with defined potencies for performance-based test guidelines incorporating computational tools; and (4) revise integrated bioactivity and exposure rankings for prioritizing and screening chemicals with limited exposure data. These developments should allow resources to be focused on chemicals more likely to have endocrine effects, and greatly decrease the time needed for screening of chemicals.

Dr. Black asked whether the computational model allows for detection of chemicals that have the ability to discern both agonist and antagonist activity, depending on dosage. Dr. Dix said that it does have that capability.

Dr. Xu said she assumed that the high throughput assay described is for ER- α , and asked whether there is a similar assay for ER- β . Dr. Dix said some of the 18 assays are specific for ER- α , others are specific for ER- β , and some are relevant to both.

Dr. Birnbaum noted that there are other potential models and pathways involved. She appreciated the specificity regarding assessment of estrogen, androgen, and thyroid hormone activities, but noted that there are many other forms of endocrine activity. Dr. Dix said once the program is successful in those three hormone pathways, it would be appropriate to consider expanding it to include other pathways within the EDSP.

Dr. Jacobs asked if Dr. Dix could conclude that the rat uterotrophic assay is well predicted by human cells. He replied that he could not, since the model is a combination of mouse, bovine, and human cells among the 18 different assays; there has not been a detailed analysis based only on human cells.

Mr. Janzen asked whether chemicals would continue to be submitted to EPA for testing or if the assays and computational models would be made available to industry partners. Dr. Dix said the path forward is not yet determined. Generally EPA is not expected to generate the data; however, in the case of ToxCast and Tox21, it was a unique opportunity. Mr. Janzen said the decision would have a huge impact on discussion of external validation of the assays.

C. FDA

Dr. Richard McFarland, FDA, provided SACATM with an update on activities toward alternatives to the murine histamine sensitization test (HIST) and the general safety test (GST). The HIST, an animal-based challenge test, is a key safety test performed to detect residual active pertussis toxin prior to vaccine release. It requires large numbers of mice that experience unrelieved pain and distress. Its replacement was identified as one of the highest priorities for human vaccines at the ICCVAM/NICEATM *Vaccine Potency and Safety Testing Workshop* in 2010. Since then, an International Working Group on Alternatives to HIST has been active. A recent workshop held in London concluded that a Chinese Hamster Ovary (CHO) cell-based assay is a suitable alternative to HIST for regulatory purposes.

Dr. McFarland also gave some background information on the GST, which was used to issue monographs, known as *Minimum Requirements* on individual biologics. The federal regulations governing the test were revoked, effective August 3, 2015, because the test regulations are duplicative of requirements in biological license applications.

Dr. Black asked if the HIST vaccine replacement initiative could be applied to other vaccines. Dr. McFarland said one of the challenges is the resistance to validate fit-for-purpose, and what the actual question of the test is. In the case of the HIST test, the *in vitro* CHO test is better and

more sensitive. Dr. McFarland said that another issue that arose with the CHO assay is lab-to-lab transferability.

Dr. Willett asked whether FDA has any plans to monitor implementation of these changes over time. Dr. McFarland said, regarding the HIST, there are relatively few manufacturers using it and the FDA is in discussions regarding implementation of the CHO assay. Regarding the GST, FDA would check on what companies have sent in supplements.

D. NIEHS

Ms. Kirsten Mease, NIEHS, reported to SACATM on a new NIEHS Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) funding opportunity for validation and commercialization of approaches to reduce animal use in toxicology testing. She described the SBIR/STTR program and the solicitation process. For the U44 Request for Application, which will be a cooperative agreement, grantees will work through a steering committee and ICCVAM/NICEATM personnel to address validation steps needed for acceptance of alternative test methods by federal agencies. The first cycle awards will be issued in July 2016, with 2-3 awards per cycle anticipated over the program's three cycles. The high priority areas are ocular toxicity testing, reproductive and developmental toxicity testing, carcinogenicity testing, and acute toxicity testing. The highest priority will be given to standalone alternative test approaches. Ms. Mease reviewed the business and technical eligibility requirements.

Dr. Willett asked how many applications are anticipated. Ms. Mease replied that 12-20 applications are expected in the first round. Dr. Walker noted that, in this instance, the different investigators would be anticipated to come together as a group. He asked if there are any potential conflicts anticipated due to the investigators working in similar areas. Ms. Mease said there is an intention to deal with that issue up front, in consultation with legal representation at NIH. Other institutes have conducted cooperative agreements, so there is knowledge that can be leveraged. She said the situation would depend on the awards that are made. Dr. Bert Hakkinen asked if the intent is to develop a decision support tool, as opposed to an individual alternative method. Ms. Mease said that a decision support tool is part of what is being sought in the initiative.

E. Public Comments

Ms. Kristie Sullivan, representing PCRM, said she was excited about the SBIR/STTR funding opportunities. She praised the fact that the grants are directed specifically to regulatory applicability, and the built-in involvement of ICCVAM and NIEHS staff, and regulatory agency staff. She supported the grant priority areas. She appreciated the update on the EDSP and looks forward to seeing how the approach would integrate with the Other Scientifically Relevant Information program and with Tier 2 assays. She recommended close collaboration with companies and other stakeholders for alternative ways to generate information needed to make Tier 2-reliant regulatory decisions. She encouraged public input and discussion.

Mr. Jeffrey Brown, representing PETA and PCRM, described the organizations' regulatory activities to promote robust, human-relevant, non-animal test methods. The groups recommend

that SACATM assist agencies in instituting plans for rapid adoption of new test methods, with clear, up-to-date guidance. He cited specific examples in skin sensitization, phasing out of the Draize tests, the FDA Center for Food Safety and Applied Nutrition's updates to the Redbook, and EPA's Office of Pollution Prevention and Toxics. He said the groups also recommend that agencies provide regular training opportunities for reviewers and inspectors and maintain an updated list of accepted alternative methods. He added that USDA APHIS inspectors and veterinary medical officers should be up-to-date on available alternative methods so they are able to evaluate the accuracy of claims that there are no alternatives to *in vivo* procedures. He offered his groups' services to help coordinate training sessions. He suggested that FDA and USDA provide routine updates on progress toward meeting the recommendations put forth in ICCVAM-organized workshops so that the information could be shared at SACATM meetings. He asked for an update from FDA about *in vitro* botulinum toxin detection method development.

Dr. Jacobs said the Draize test is done early in the process of drug development as a test for occupational exposure; FDA is not currently requesting the test. Regarding the botulinum toxin, she said the manufacturer of the most widely used pharmaceutical botulinum toxin product developed an *in vitro* assay for potency, which is currently being used.

F. SACATM Discussion

Dr. Willett, first discussant, said NICEATM's recent work with the agencies has been impressive. Regarding the ER-agonist efforts, membrane ERs should be included at some point. She noted that endocrine disruption is a larger problem than is addressed just by the EDSP and EPA, and that some of the tools being developed may also be applicable in other contexts. It would be important to assess the individual assays and determine their effectiveness, and how necessary they may or may not be to the overall screening process. She encouraged EPA to continue to work with the Organisation for Economic Cooperation and Development (OECD) on the development of AOPs. She noted that linkages have been established between molecular initiating events that EPA is using and more downstream events. It would be helpful to have that information integrated in a more organized fashion in the AOP pathway with respect to downstream key events and the eventual adverse outcome. In terms of the models' accuracy, she said she was impressed with how EPA looked at their accuracy versus the *in vivo* reference chemicals and the *in vitro* reference chemicals. She emphasized the importance of understanding the variability of the gold standard studies. She noted that the Browne *et al.* paper included a new concept in what validation means in terms of fit-for-purpose. She encouraged EPA and ICCVAM to continue to work with OECD on that important issue. She lauded the EPA efforts for transparency of the interpretation paradigms for ToxCast and Tox21 and asked how the ToxCast and Tox21 information would be integrated into general chemical assessments. Dr. Willett questioned how the proof of principle that EPA is using for endocrine disruptors might be applied more broadly to other chemicals and other regulatory contexts. She mentioned that the annual agency updates provided to SACATM should give more context and inform SACATM's recommendations, by including 3Rs activity overviews. For example, FDA could include work on other vaccine programs, such as the rabies vaccine. With respect to the DoD and acute toxicity work, she noted that the National Academy of Sciences (NAS) report was very critical and will form a framework for a possible global industry pathway. She was glad

the report stressed collaboration with existing programs and projects, and said ICCVAM could be very helpful in coordinating ongoing acute toxicity efforts by EPA and other areas. She would like to know the status of DoD's other projects in this area. She was very supportive of the NIEHS SBIR/STTR project and said NIH should also consider funding pathways-based approaches. She also asked that NTP provide an overview of its work in other areas.

Dr. Evans, second discussant, applauded the continued improvements to the ICCVAM website. He approved of the idea of putting training materials on line, but cautioned that such a site would need to be thoughtfully composed and maintained if it is to be a central repository for current information in the field. He discussed the importance of paying attention to outlier data. He supported the approach of balancing bioreactivity with exposure as a way to prioritize chemicals for testing. He approved of EPA's path forward in the EDSP and was pleased to hear Dr. McFarland's report, noting that the outcomes on the HIST and GST are very positive. Regarding the SBIR/STTR grants, he recommended site visits to evaluate the facilities that would conduct the research.

VII. International Activities, Opportunities, and Challenges

A. Presentation/Discussion

Dr. Jacobs said international collaboration, along with harmonization and adoption of alternative test methods, are high priorities for ICCVAM. She noted that just as ICCVAM was organized to prevent duplication of efforts among federal agencies, the International Cooperation on Alternative Test Methods (ICATM), was created to prevent similar duplication globally. She described the participation of ICCVAM in workgroups related to OECD test guidelines. ICCVAM continues to work with the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) on a process that will enable U.S. scientists to participate more actively in its test method evaluations. The goal is for U.S. representatives to participate in each of the steps in the evaluation of test methods. Currently, many ICCVAM agency experts participate in international expert working groups and validation management teams. For FY 2016, the goals are to (1) nominate more ICCVAM agency experts to international expert working groups, validation management teams, and organizing committees; (2) serve as a forum to communicate updates to ICCVAM agencies on international 3Rs activities; (3) nominate methods for interlaboratory validation to the EURL-ECVAM network of testing laboratories; (4) continue active participation in ICATM; and (5) work with ECVAM on a process for test method acceptance.

Dr. Casey said the major driver in the pursuit of the 3Rs, aside from ethics and public health, is economics. In a globalized economy, the issue of animal testing affects free trade; the market is bifurcating into countries that require animal testing and those that explicitly prohibit it. The momentum behind the issue is likely to continue beyond animal testing in cosmetics, and it needs to be quickly determined how to harmonize the many different global requirements. Dr. Casey said the issue is larger than ICCVAM could handle alone.

Dr. Lowit said there are issues of global harmonization with pharmaceuticals, pesticides, and toxics. Dr. Casey agreed and noted that it does no good for the U.S. to approve an animal-free test method if another country still requires animal testing of products marketed there.

Dr. Jacobs said there is harmonization in development of pharmaceuticals, and noted that the situation is complicated by some products (e.g., sunscreens are regulated as cosmetics in Europe, but as drug products in the U.S.).

B. Public Comments

Dr. Clippinger, representing PETA, supported the global harmonization of methods. She cited the monocyte activation test as a good example, which is an ELISA-based replacement for the rabbit pyrogen test. She said the inconsistency in requirements across various agencies is often cited as a reason for unsuccessful implementation of the alternative methods. She noted that one way to increase participation might be to encourage attendance at the SACATM meeting or the annual ICCVAM Public Forum. Dr. Clippinger felt it would also be helpful to occasionally include a public forum in conjunction with ICATM meetings.

Dr. Katie Paul Friedman, representing Bayer CropScience, Dow AgroSciences, and Syngenta, said she supports global harmonization of assay acceptance criteria, as well as perspectives on hazard and risk and the data requirements that sometimes mandate *in vivo* testing. She said differences in viewpoint on potency and exposure and their importance in risk assessment would need to be addressed as a component of science-based risk assessment internationally in terms of advancing the 3Rs. She cited several examples of situations where global acceptance of alternative methods is still needed, as *in vivo* studies are still required in many situations. She said continuing work would be needed to find consensus in a science-based approach to acceptance of new alternative testing strategies. She noted that measuring success in the 3Rs might often be a function of international cooperation.

Dr. Bucher asked if there are any international cooperative efforts across sectors that ICCVAM and NICEATM should be aware of in terms of bringing industry or multi-national perspectives. Dr. Jacobs said the OECD working groups cover all the sectors. Dr. Friedman said there are some industry work group efforts ongoing, but industry's need is for a tiered framework for the use of alternative test methods, defining their domains of applicability. She added that another critical need is to push the envelope with other countries in their consideration of exposure potential and potency in the *in vitro* assays.

VIII. Metrics: Measuring Success in the 3Rs

A. Presentation/Discussion

Dr. Lowit briefed SACATM on current ICCVAM activities devoted to developing metrics to determine the impact of the 3Rs in regulatory testing. SACATM and multiple stakeholders have encouraged ICCVAM to develop metrics for quantifying animal use. At the federal level, it may be a challenge to tabulate animal usage, although within individual agencies it may be possible to do a better job of quantifying animal use. Dr. Lowit described the reporting requirements in

the EU, where animal use data, which include all non-human vertebrates (including laboratory mice and rats), are required to be reported every three years. In the UK, the overwhelming majority of animals used in scientific procedures are rodents. In the US, the statute for animal reporting is the Animal Welfare Act, which does not require reporting of rodent use in research. By excluding laboratory mice and rats, counts in the U.S. greatly underrepresent the total number of animals actually used.

Dr. Lowit said that as important as developing a metric is, having a metric that can be interpreted is more important. She noted that each federal agency works under its own set of regulatory mandates, which is a challenge when it comes to attempting a broad metrics system. Also, each agency has differing levels of transparency in terms of making data publicly available. Time schedules can also create a challenge, in that testing performed under regulatory schedules varies. Research and development-related testing within companies may account for substantial animal use, but it may not be submitted to regulatory agencies and thus cannot be quantified. Studies conducted internationally for submission to U.S. regulators also may not be counted, and some studies may be required in other countries and not in the U.S.

Dr. Jacobs said FDA has not been able to quantify animal use, and she noted that drug companies are conducting fewer animal studies because of the use of *in vitro* assays during drug discovery and because harmonization of drug development is increasing. Dr. Birnbaum said statistics at NIH actually point to a doubling in the use of animals in NIH-funded research over the past 10-15 years.

Dr. Lowit noted that it is possible to do some quantification of animal use. In OPP, there is a committee that handles granting waivers; in 2011, they started counting, and it has become part of the process. There is a count of how many studies have been waived and how many animals have been saved as a result. Dr. Casey noted the difficulty in gaining access to data in some instances and praised the EPA's openness in sharing information.

Dr. Evans noted that in some areas, there is increased use of non-human primates. There may be reductions in some areas, but overall, he is not convinced that animal usage has decreased.

Dr. Chapdelaine asked whether there has been an increase in the use of dogs and primates over the past few years. Dr. Black, referring to the 2013 Great Britain report, said it showed fairly constant non-human primate use, despite worldwide economic recovery and also relative growth in the development of biopharmaceuticals (that often require non-human primate models). She made the point that whatever metrics are being employed, consideration of the larger economic situation should be included. She said it should also be recognized that a great many rodents are used in breeding and in vaccine safety testing; biomedical research, by comparison, is relatively small, with safety testing as a subset of that.

Dr. Casey noted that these issues are vitally important to prioritization. He concurred that biologics testing uses far more animals than toxicity testing. He said strategic efforts should be focused on these issues.

B. Public Comments

Ms. Sullivan, representing PCRM, said the situation in which rats and mouse, which are used in the highest numbers, are not counted in the U.S. has been a problem for a very long time. She said it is good that the conversation about the challenges involved in animal use metrics is taking place. She noted that there would ideally be a national tracking system, but until then, it is up to ICCVAM and the federal agencies. She said it is important to be able to count and track animal use to see where and how progress is being made. She agreed that it is also important to know how the animals are being used. She felt that companies might be able to help, since many of them have an estimate of their animal use. She thanked Dr. Lowit for the information about the counting of animals at EPA.

Mr. Brown said PETA was grateful that the conversation on metrics is taking place. He noted that under the Animal Welfare Act, almost 99% of animals used in NIH-funded research are from species not counted under the act, with a 72% increase in the use of those animals from 1997-2012. Thus, although USDA reports show a decrease in the number of animals used, the total number of animals used has actually increased dramatically over the past 15 years. He said PETA encourages ICCVAM to work with NIH, industry, and member agencies to publish the numbers of animals of all species used, as is done in the EU.

Dr. Friedman commended EPA for its efforts to reduce animal usage and promote targeted testing in the EDSP program. She hoped that other agencies would adopt similar weight-of-evidence approaches that incorporate non-animal approaches to screening for both hazard and exposure. She noted the need for harmonization among global regulatory authorities to impact overall animal use. In addition to the acceptance of alternative methods and reduction of animal usage through a more targeted and efficient testing paradigm, she recommended two other efforts: (1) development of a tiered relevance framework for different types of data, and (2) incorporation of potency and exposure considerations to support science-based risk assessment internationally.

C. SACATM Discussion

Dr. Black, first discussant, said it is very important to get accurate numbers of animals in the U.S., but it is difficult given so many different institutions involved. She said that as innovative as this country is, there is still no sense of how much research is done *in vitro* versus *in vivo*, or a good breakdown of the species used in biomedical research at large, or in safety testing research as a subset. The effort to reduce animal use cannot be done in the U.S. alone; it must be part of a coherent international effort, to get rid of the “checkboxes” in regulatory review processes, and put in science-based risk assessment. She cited the continued presence of a checkbox mentality in vaccine testing paradigms, including an example, extra animal testing required by Japan for the pneumococcal pneumonia vaccine. In terms of metrics for impact of the 3Rs, she said there is a different way to tally each of the components, and it would be useful to come up with a series of metrics to measure the effectiveness of efforts in each area. In some instances, a reduction in animal use in one area may cause an increased use in another area. So it would be important to consider metrics in a wide context. She suggested that a group be established to address developing 3Rs metrics incorporating various interconnected subsets of

data, including denominators that would factor out some of the economic factors at work. She agreed that dose/concentration response and compartmental modeling should be built into *in vivo* extrapolations. She felt that distressed animals and refinements deserve more attention. Dr. Black emphasized that the overall objective is to reduce the necessity to use non-rodent models and to use them only – studiously – when needed; simply substituting one large animal model like pigs for another like monkeys is not an ethical solution.

Dr. Bunton, second discussant, said a big problem relating to metrics is that researchers don't know what should be reduced. Indicators show that it is likely that rodent use is increasing. Although there is not an edict to do so, it would be worthwhile to get a general idea of the true usage of mice, rats, and all other animals in the U.S. Dr. Bunton said some rough idea of animal use would be better than none, which is what is currently available. She noted that the objective should always be to reduce whole animal use, as opposed to using them more efficiently. She said there should be ceilings established which would compel organizations to reduce their use of animals. Dr. Bunton felt it would be possible to measure adoption of alternative methods through reductions in use of older methods.

Dr. Evans noted that testing homologs might result in increased animal use, in that homologs are not exactly the same as the drugs under development. He cautioned against trying to get exact counts of animal usage and suggested using the methodology of the U.S. Census, in which a subset of data is analyzed and then extrapolated. He suggested that Institutional Animal Care and Use Committee (IACUC) forms should be double-checked to ensure the accuracy of assertions that alternative methods are not available. Dr. Walker concurred that getting exact animal usage numbers is impossible.

Dr. Karen Taylor, NIOSH representative, noted that librarians could be enlisted to search the literature for alternatives to animal testing. Dr. Chapdelaine said her IACUC is responsible for searching the literature for alternatives. She said her group is required to give an annual count of animal use; all species are reported, including rodents. She speculated that there might be many other organizations that do the same thing, giving a possible starting point for quantification of animal use, although the numbers may not be accurate. Dr. Evans said, based on his knowledge, it is possible that such a count could be relatively accurate.

Mr. Janzen noted that in pharmaceutical companies, a large percentage of studies are now outsourced. Thus, it may be possible to work with contract research organizations (CROs) to gain information about animal use. He noted that a huge number of studies are now done offshore, adding to the challenge of counting U.S. animal use. He said that issue is tied to the issue of harmonization.

Dr. Black said in the United Kingdom (UK), the National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs) has done an excellent job of initiating ways to reduce animal use and gather metrics, which could inform U.S. efforts

Dr. Willett said the animal welfare organizations are quite practiced in extrapolating from foreign data to estimate U.S. use. She felt that having some estimates by sampling would be a good way to start. She added that the numbers to be counted depend on the goal for using the

numbers and doing so would help to determine priorities for problem solving. She said there is a need to get actual numbers in practical situations, and she thought it might be difficult to assess animal use data obtained from CROs.

Dr. Evans questioned whether CROs would provide animal use data. Dr. Chapdelaine said animal numbers are required to be supplied under current regulations. Dr. Bunton wondered whether CROs would provide the number of studies they do, which could perhaps be used as a proxy to estimate animal use. Dr. Chapdelaine said CROs have data on numbers of studies. Mr. Janzen said that might be a good way to acquire the initial numbers for a census.

Dr. Bucher said it was important to determine the number of animals used in any particular test to be able to tell which tests should be targeted for working on a replacement method. He felt that if the goal is to apply pressure to reduce animal use, it would be much more compelling to apply pressure on a financial basis, in showing where use of alternatives would reduce the financial burden of testing.

IX. Creating a 3Rs Roadmap and Strategy for the United States

A. Presentations

Dr. Brian Berridge, GlaxoSmithKline (GSK; not representing GSK), gave a presentation titled *Enabling Optimized Preclinical Modeling: A U.S. National Roadmap and Resource*. GSK is very interested in the 3Rs and decreasing its dependence on animal use. He said contemporary drug development is an unsustainable model, with increasing efficacy challenges late in development. Animal studies have been a significant part of the process, due to their scientific value; however, some believe that the platform is a problem, with issues of translation relevance and methodologic reproducibility. Efforts are underway to address both of those areas. He said, on the other hand, there is much opportunity to incorporate other, more advanced, non-animal capabilities. He noted that there is considerable investment in the U.S. in developing those novel capabilities, from agencies such as NIH and Defense Advanced Research Projects Agency. There is also substantial investment from the pharmaceutical industry.

Dr. Berridge said it is challenging to fully take advantage of those many opportunities without a specific roadmap or strategy. There can be a significant decrease in animal dependency, balanced against an improved predictivity. This could happen in a shorter time frame if there is more integration and improved predictivity of non-clinical modeling strategies. He proposed development of a national, multi-sector strategy for supporting and industrializing innovative, non-animal technologies. It would involve development of incubators to facilitate the integration and industrialization of novel capabilities, while aligning the technologies to real world challenges. He said this would involve pooling public and private resources.

Dr. Casey followed with a presentation titled *Creating a 3Rs Roadmap and Strategy for the U.S.* He noted the number of significant investments being made by the federal government to understanding human health, such as the National Center for Advancing Translational Sciences (NCATS) organ-on-a-chip microphysiological systems and the 21st Century Cures Act. There

has been a clear message from various agencies in recent years regarding the need to understand the effects of chemicals and drugs on human physiology in the interest of public health.

Dr. Casey said animal-based tests have established a baseline, although many may now be irrelevant, providing a false sense of security, or preventing the use of chemicals and drugs that may be beneficial. He cited public health, economics, and ethics as the major drivers behind the need and the effort for a cohesive strategy. The core principle is that development, validation, and adoption of predictive, human-based test methods requires multiple stakeholders all working together with specific intent. He acknowledged challenges that include coordination of effort, the belief that animal studies are the gold standard, institutional inertia that favors animal models, developing a transition plan, and funding. He stressed that there must be a very high-level plan to move away from animal testing, because there will be resistance to banning animal testing. Dr. Casey said the stakeholders in this effort would be U.S. agencies, pharmaceutical companies, non-governmental organizations (NGOs), international partners, and many others.

B. Public Comments

Dr. Clippinger, representing PETA, supported the idea of developing a 3Rs strategy. She envisioned the establishment of a 3Rs center charged with implementation of the roadmap and serving as a focal point for organizing coordination efforts, databases, training and educational opportunities, and harmonization with international activities.

Dr. Katya Tsaion, from Johns Hopkins University and representing the Evidence-Based Toxicology Collaboration (EBTC), noted that mission of the EBTC is promoting the adoption of evidence-based principles by toxicology. It has two active work groups on methodology and systematic review. She discussed the group's communication and outreach activities relative to the roadmap strategy.

C. SACATM Discussion

Dr. Chapdelaine, first discussant, said a national 3Rs strategy and roadmap is definitely an area that must be pursued. There needs to be a more coordinated effort among the various groups working on 3Rs issues. She noted that the National Research Council, in its 2007 report, recommended the creation of a new institute devoted to the new paradigm of toxicity testing. In that context, a 3Rs organization might be exactly what is needed to help establish a roadmap that could be realized. Experts from several different arenas would be necessary. Dr. Chapdelaine said by using well-established alternatives, the field might identify better options than those currently available. However, buy-in from all stakeholders would be important, as would thinking outside the box to arrive at new ways to promote and advance the 3Rs.

Dr. Willett, second discussant, concurred that the national 3Rs strategy and roadmap is necessary and a good way to coordinate information. She cautioned ICCVAM to consider the realities of (1) obtaining funding in the current environment for a center devoted to the 3Rs, and (2) finding practical ways to achieve the stated goals. She noted that it would be very important to connect with the NGOs that would be affected, such as workers groups, environmental

groups, and people concerned with susceptible populations. Within the agencies, there are very focused needs, and their programs are directed at addressing those needs.

Dr. Xu, third discussant, also felt that a national 3Rs strategy and roadmap is needed to allow for improved coordination. She reiterated the steps involved in toxicology decision-making. Dr. Xu approved of the idea of forming a new agency, particularly if its charge were to perform a trial based on existing data, such as data from Tox21.

Mr. Janzen noted that international activities would clearly need to be part of the conversation about a roadmap.

Dr. Bunton said it seemed that some momentum has developed around the idea for a roadmap, perhaps due to the recent changes at ICCVAM and NICEATM. She noted that apparently pharmaceutical companies have reached a limit in terms of the utility of animal models. She said, given the momentum, now it is time to figure out how to create incentives for stakeholders to work together. Dr. Casey agreed that this is a good time to have the discussion, which probably could not have taken place 10 or 15 years ago. He said, at this point, many people are willing to pursue these ideas, particularly given advances in technology. He cited the developments at the NCATS microphysiological systems program, where a high level of progress and collaboration were possible in a very short period of time.

Dr. Casey said ICCVAM's mission is not to validate alternative methods; ICCVAM needs to work with those who validate methods and with pharmaceutical companies. He said a minimum amount of effort in coordination could result in a lot of benefit.

Dr. Taylor said a marketing person might be needed to help advance the successes in alternative methods, to help the public understand the achievements in the field. She cited the potential economic impact of a complete replacement of animal testing, in that it would put many people out of work. She said those workers should receive assistance to train for other careers.

Dr. Casey felt ICCVAM is making excellent progress; however, he saw that there is still a great deal of work to be done. He agreed that marketing would be crucial to continuing efforts, concentrating on the narrative that alternative methods represent a better way to predict human health, with the ethical concerns as a side benefit. Mr. Janzen agreed that a financial incentive would be necessary. Dr. Bucher mentioned an upcoming publication that calls upon the medical field to adopt some of the current concepts from toxicology, such as AOPs. He said the NTP 2004 *Roadmap for the Future* focused on the convergence of financial, ethical, 3Rs, and scientific reasons; such an approach is needed for the current effort.

Dr. Bucher felt that a new bricks-and-mortar institution would not actually be necessary to carry the mission forward, and funding would not be possible. He cited Tox21 as an example of that phenomenon. He said a critical mass of converging pressures is needed to move the idea forward, but without creating buildings or new institutions.

Dr. Jack Fowle, from Science To Inform, LLC, discussed a 2003 effort at EPA to describe new approaches to chemical testing and suggested it might be useful to consult those records. From a historical perspective, he said that over the decades it was recognized that there was a social

contract that stated that animal tests are predictive of human health. The animal-based approaches have informed many laws, regulations, and decisions as a result. Going forward, as that approach is bypassed, there will be several economic, legal, and other factors to be addressed. It must be shown that the new approaches are more informative, more efficient, and more economical than the current approaches. Dr. Fowle said a social science aspect would be needed, along with the other drivers, to bring the roadmap into being more efficiently.

Dr. Berridge noted that he had not referred to the 3Rs in his presentation, because he believes that the effort needs to be based on science, public health, and predictivity. He said the missing element in the effort is leadership, and he agreed that there is a challenge involved in operationalizing a roadmap. He mentioned that in pharmacology testing, more animals are actually used for efficacy testing than for safety testing, so there is a need for platforms in that area. He said he had been advocating a “medicines outcome pathway” process, which he considers a good way to help build confidence in alternative ways of modeling. He said a different way of thinking is as important as building an alternative approach to modeling.

Dr. Mary Ann Vasbinder, a colleague from GSK, said she had visited NC3Rs in London, and they were quite interested in having a collaborative partner in the U.S.

Dr. Friedman said it would be important to further develop AOPs quantitatively, which may actually require more animal experiments to identify the tipping points between key events in a pathway.

Dr. Casey noted that the roadmap under discussion is not a 3Rs strategy; it is focusing on replacement of animal testing. Thus, the focus should be on an “R” roadmap versus a 3Rs roadmap. Dr. Casey said a 3Rs roadmap would require sub-roadmaps, because the people who lead the refinement efforts are not the same people who would be championing replacement.

Dr. Willett agreed that a replacement roadmap might be most important and that refinement involves separate people. She said she is unsure that combining them would be the most helpful approach.

X. Adjournment

Mr. Janzen adjourned the meeting at 4:30 PM, thanking everyone who participated.

Summary Minutes from the September 2, 2015 SACATM Meeting
NIEHS, Research Triangle Park, NC

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

Date: November 30, 2015

Signed

Mr. William P. Janzen

Chair of SACATM