

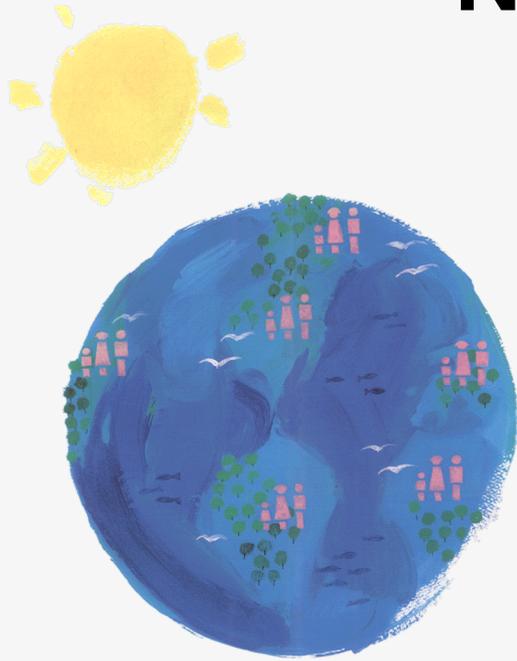
NICEATM

*National Toxicology Program
Interagency Center for the Evaluation of
Alternative Toxicological Methods*

ICCVAM

*Interagency Coordinating Committee on
the Validation of Alternative Methods*

NICEATM-ICCVAM 5-Year Plan



William Stokes, D.V.M., DACLAM

**Rear Admiral, U.S. Public Health Service
Director, NICEATM
Executive Director, ICCVAM**

**Meeting of the NTP Board of Scientific
Counselors**

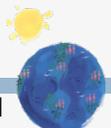
**June 22, 2007
NIEHS**

Research Triangle Park, NC



Outline

- NICEATM and ICCVAM
- Congressional Mandate
- Plan Development Process
- Overview of the Draft Plan
- Public and SACATM Comments



What is ICCVAM ?

Interagency Coordinating Committee on the Validation of Alternative Methods

A permanent interagency committee composed of members designated by the heads of 15 federal agencies.



ICCVAM Member Agencies

Regulatory Agencies

- Consumer Product Safety Commission
- Department of Agriculture
- Department of the Interior
- Department of Transportation
- Environmental Protection Agency
- Food and Drug Administration
- Occupational Safety and Health Administration

Research Agencies

- Agency for Toxic Substances and Disease Registry
- Department of Defense
- Department of Energy
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Institute for Occupational Safety and Health
- National Library of Medicine
- National Institutes of Health, Office of the Director



What is NICEATM?

National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods

- A component of the NIEHS, NIH, DHHS
 - Research Triangle Park, North Carolina
- Functions:
 - Administer ICCVAM
 - Provide scientific and operational support for ICCVAM
 - Convene test method peer reviews, expert panel meetings, and workshops
 - Communicate and partner with stakeholders
 - Conduct independent validation studies
- <http://iccvam.niehs.nih.gov>

ICCVAM's Mission¹

- To *facilitate* development, validation and regulatory acceptance of new and revised regulatory test methods that
 - reduce, refine, and replace (3R's) the use of animals in testing
 - while maintaining and promoting scientific quality and the protection of human health, animal health, and the environment

¹Adopted by ICCVAM February 2004

All of ICCVAM's activities are grounded in the U.S. Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training

<http://grants.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples>



What are ICCVAM's Duties?¹

- To consider petitions from the public for review and evaluation of validated test methods
- To review and evaluate new, revised, and alternative test methods
- To submit test method recommendations to U.S. Federal agencies and make agency responses (due within 180 days) available to the public
- To facilitate and provide guidance on:
 - test method development
 - validation criteria and processes
- To facilitate:
 - acceptance of scientifically valid test methods
 - interagency and international harmonization

¹ICCVAM Authorization Act of 2000, 42 U.S.C. 285I-3

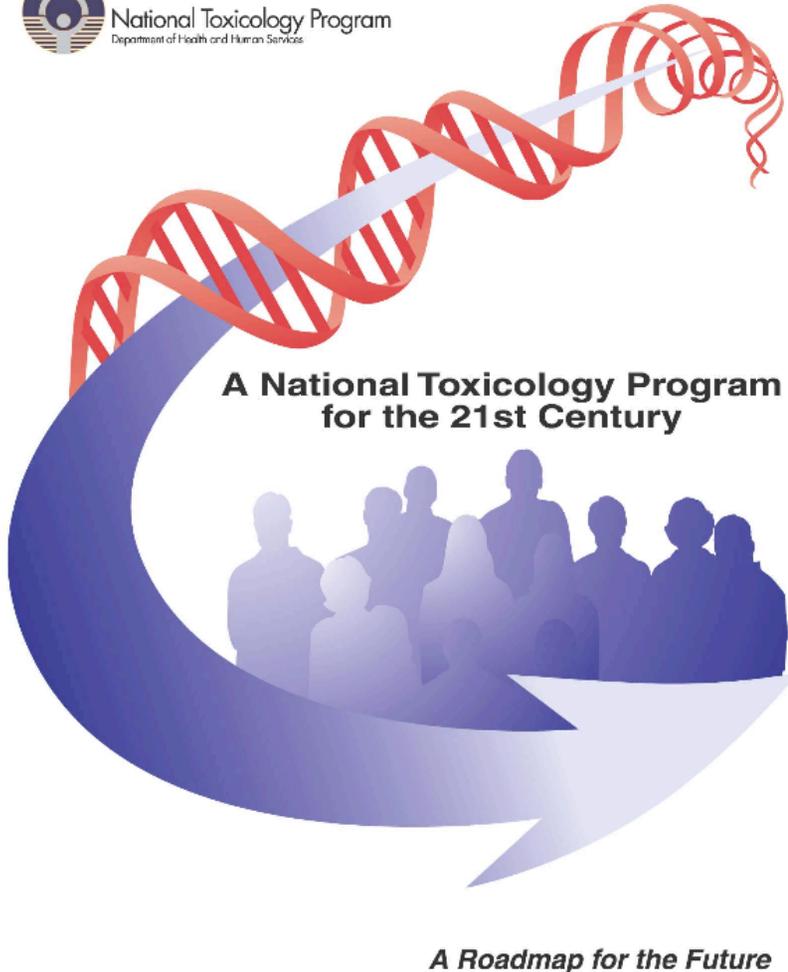
NICEATM-ICCVAM Progress

- Over 150 test methods evaluated since 1997
- Impact
 - Alternative methods recommended and/or adopted internationally for the four most common product safety tests
 - Recommendations provided for R&D, translation, and validation activities to advance alternative methods
 - Performance standards provided to expedite validation studies and regulatory acceptance
 - Guidance provided for validation and regulatory acceptance of new, revised, and alternative methods

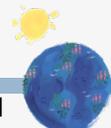
U.S. House and Senate Appropriations Committees: FY07 Requests

- **Request NICEATM/ICCVAM, in partnership with relevant federal agency program offices, to build on the NTP Roadmap to create a five-year plan to:**
 - **Research, Develop, Translate, and Validate** new and revised non-animal and other alternative assays for integration of relevant and reliable methods into the Federal agency testing programs.
 - Identify areas of high priority for new and revised non-animal and alternative assays or batteries of those assays to create a path forward for the 3Rs, when this is scientifically valid and appropriate.

Building on NTP Roadmap



- Goal 2 of the Roadmap:
 - *“Develop and validate improved testing methods and, where feasible, ensure that they reduce, refine, or replace the use of animals.”*
- From page 7:
 - *“Activities and assays developed under the NTP Roadmap will be done in cooperation and consultation with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) to maximize their value to regulatory agencies.”*



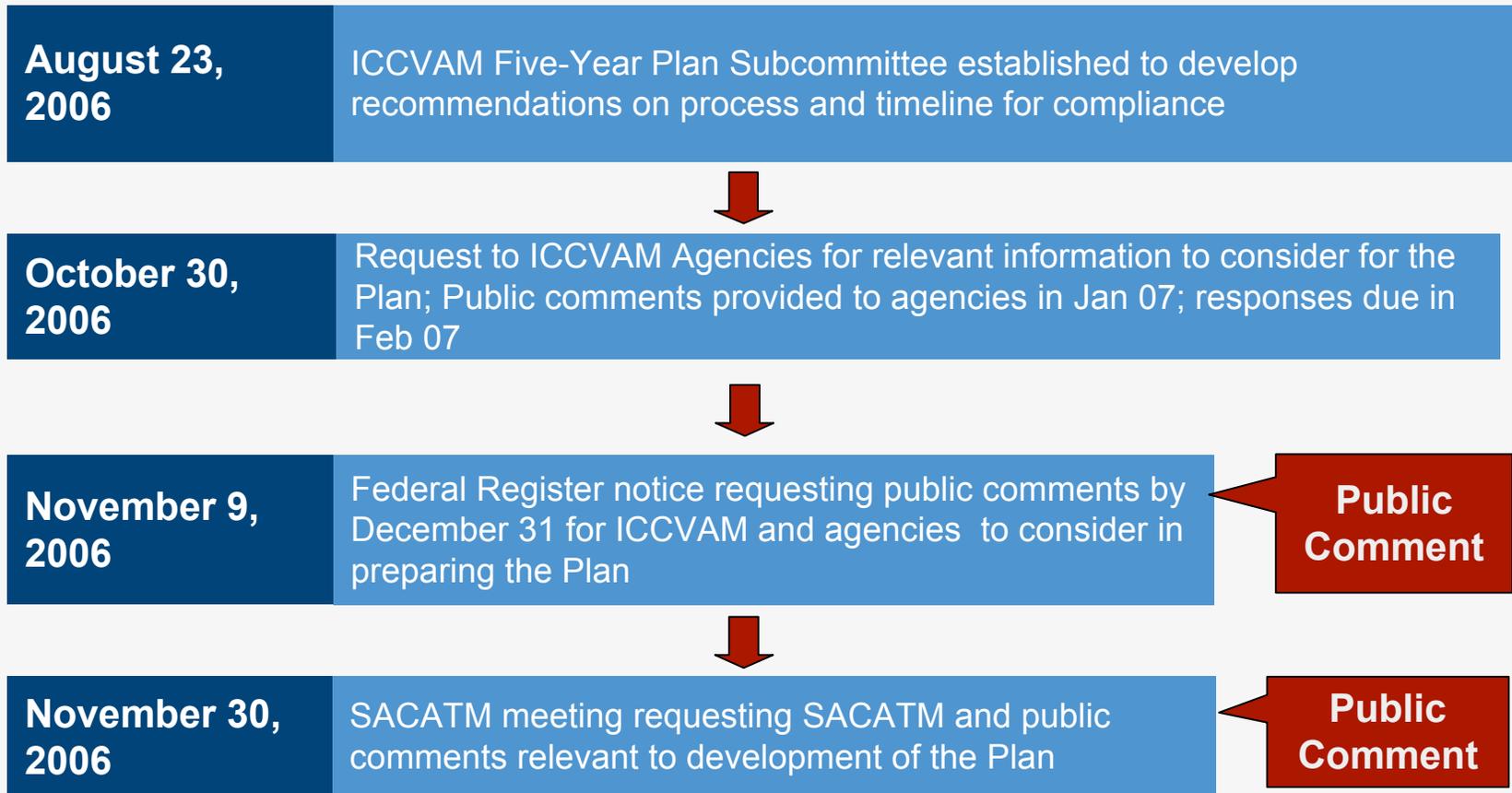
NIEHS Guidance to NICEATM and ICCVAM

for development of the Congressional Appropriations Committee Report (5-Year Plan)

- Report should be aimed at an audience of policymakers (Congress Members and staff)
- Body of report should be limited to no more than 20 pages
- Report must be submitted to NIEHS Budget Office by September 15, 2007 in order to complete clearance by congressional deadline of November 15, 2007

NICEATM-ICCVAM 5-Year Plan Process

Phase I - Gather Information



NICEATM-ICCVAM 5-Year Plan Process

Phase II - Develop Initial Draft and obtain comments



NICEATM-ICCVAM 5-Year Plan Process

Phase III - Prepare and Submit Final Plan

**June 13, 2007 -
August 8, 2007**

ICCVAM considers public, SACATM, and BSC comments and prepares and approves Final Plan



**Aug. 15-
Sept 15, 2007**

Concurrence and clearance approval from ICCVAM agencies on the Final NICEATM-ICCVAM Five-Year Plan



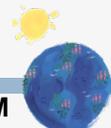
**Sep. 24, 2007-
Nov 15, 2007**

NIEHS forwards Plan to NIH; NIH/HHS forwards Final NICEATM-ICCVAM Plan to House and Senate Appropriations Committees



**December
2007**

Expected Public Release of final Five-Year Plan



Draft NICEATM-ICCVAM Five-Year Plan¹

The NICEATM-ICCVAM Five-Year Plan (2008-2012)

Draft: May 4, 2007



Prepared by the
Interagency Coordinating Committee on the
Validation of Alternative Methods (ICCVAM)
and the
National Toxicology Program (NTP) Interagency Center for the
Evaluation of Alternative Toxicological Methods (NICEATM)

National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Public Health Service
Department of Health and Human Services

- *Federal Register* Notice published May 1, 2007 (Vol. 72, No. 83, pp. 23832-23833)
 - Announced availability of the draft Plan
 - Requested public comments on the draft Plan

¹Available at <http://iccvam.niehs.nih.gov/docs/5yearplan.htm>

Plan Overview

- Introduction
- Chapters 1-4: Four Key Challenges
 1. *Identify priority areas and conduct and facilitate activities in these areas*
 2. *Identify research initiatives that are expected to support the future development of innovative alternative test methods*
 3. *Foster acceptance and appropriate use of alternative test methods through outreach and communication*
 4. *Develop partnerships and strengthen interactions with stakeholders in order to facilitate meaningful progress*
- References and Information Resources
- Glossary of Terms
- Acronyms and Abbreviations
- Appendices

5-Year Plan: Introduction

- **Agencies have mandates to protect human and animal health and the environment (See Appendix A)**
 - In order to fulfill these mandates agencies must ensure that substances are safe, or properly labeled if hazardous
 - Current test methods and strategies involve the use of laboratory animals, *in vitro* methods, and/or *in silico* methods

- **Agencies must determine if alternative test methods can provide equal or better protection of human and animal health and the environment before their adoption or endorsement**
 - The ICCVAM Authorization Act of 2000 requires that new, revised, and alternative test methods must be determined to be valid before agencies can adopt them for regulatory purposes (See Appendix E)

¹ICCVAM Authorization Act of 2000, 42 U.S.C. 285I-3

5-Year Plan Introduction: Current U.S. Laws

- **U.S. laws (42 USC 289d, 7 USC 2131 et. seq.) require consideration of alternatives *prior to* the use of animals for research and testing that may¹:**
 - **Reduce** the number of animals
 - **Refine** procedures to lessen or eliminate pain and distress
 - **Replace** animals with non-animal systems or with phylogenetically lower animal species

¹all of ICCVAM's activities are grounded in the *U.S. Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training*

<http://grants.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples>

5-Year Plan Introduction: Roles of ICCVAM and NICEATM

- **NICEATM and ICCVAM work with stakeholders to facilitate research, development, translation, and validation activities**
 - Depend on stakeholders to conduct and achieve successful test method research, development, translation, and validation
 - ICCVAM reviews submissions from stakeholders to determine the validation status and usefulness and limitations of new and revised test methods
- **Federal agencies with statutory authority to conduct research, development, translation, and/or validation activities (11):**
 - Department of Agriculture
 - Department of Defense
 - Department of Energy
 - Department of the Interior
 - Environmental Protection Agency
 - DHHS
 - ATSDR
 - Food and Drug Administration
 - NIEHS/NTP
 - NIOSH
 - NIH
 - National Cancer Institute

Challenge 1: Identify priority areas and conduct and facilitate activities in these areas

- Addressed in Chapter 1
 - *Current and Planned Activities for Priority Test Methods to Reduce, Refine, and Replace Animals in Regulatory Testing*
- ICCVAM test method prioritization criteria
 1. Potential impact on reducing, refining, or replacing animals for testing
 2. Potential to improve prediction of adverse health or environmental effects
 3. Applicability to multiple agencies
- Priorities may vary across Agencies
- Priorities may change
 - Need to be flexible so we can take advantage of advances in science and technology and availability of new methods

Chapter 1: Current priority areas¹

- Ocular Toxicity Testing
- Acute Toxicity Testing
- Biologics/Vaccines Testing
- Dermal Toxicity Testing
- Immunotoxicity Testing
- Endocrine Disruptor Testing
- Pyrogen Testing
- Chronic Toxicity/Carcinogenicity Testing

¹These priorities are likely to evolve in response to new testing needs and advances



Current Priorities: Ocular Toxicity Testing

(as an example; see Chapter 1 for others)

■ Basis for High Priority:

- Multiple regulatory agencies require that ocular hazards be identified to warn consumers and workers
- Potential for significant pain and distress to test animals

■ Planned activities include:

- Improve non-animal methods to detect permanent eye damage
- Assess non-animal methods to detect reversible eye damage
- Collect reference data to facilitate validation studies
- Evaluate new methods or combinations/batteries of *in vitro* methods
- Review routine use of topical anesthetics and systemic analgesics for reducing pain and distress



Other Toxicity Areas of Interest

- Neurotoxicity testing
- Reproductive and developmental toxicity testing
- Planned activities include:
 - Stay abreast of ongoing research activities
 - Identify the most useful tests
 - Facilitate their development and validation
 - Formally evaluate validation status for regulatory testing



Challenge 2: Identify research that may lead to future innovative alternative test methods

- Addressed in Chapter 2 – *Advances in Science and Technology*
- Eleven agencies have research and development programs
 - ICCVAM will monitor these for potential methods for use in regulatory testing
- Agency programs currently identified as potentially applicable
 - High Throughput Screening
 - Other Animal Systems (Lower Species)
 - Computational Approaches
 - Biomarkers of Toxicity
 - Nanomaterials Testing Strategies
 - Toxicology Databases
- Most of these areas will require several years of development
- ICCVAM and NICEATM will continuously monitor federal agency and other stakeholders' research activities for additional areas of interest

Challenge 3: Foster Acceptance and Appropriate use of Alternative Test Methods

- Addressed in Chapter 3
- Why is this important?
 - New and revised methods must be both accepted *and used* in order to meaningfully impact the 3Rs
- How will ICCVAM foster acceptance and use of alternative test methods?
 - Provide guidance on adequate validation study design
 - Carry out high-quality transparent and public independent peer reviews
 - Provide comprehensive test method evaluations to regulatory agencies
 - Arrange implementation workshops for accepted methods

Challenge 4: Develop partnerships and strengthen interactions with ICCVAM stakeholders

- Addressed in Chapter 4
- Effective interactions are needed to stimulate alternative test method research, development, translation, and validation by stakeholders
- Partnerships will:
 - Best utilize existing resources
 - Maximize efficiency and minimize duplication of evaluation efforts
 - Ensure an early exchange of information
 - Facilitate national and international recognition, acceptance, and implementation of scientifically valid test methods

NICEATM-ICCVAM Town Meeting Summary

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) announce a

Town Meeting

To receive public comments on a draft NICEATM/ICCVAM Five-Year Plan

Monday, June 11, 2007 1:00 to 5:00 P.M.

Agenda

- 1:00 P.M. Welcome and Introductions
- Introductory Remarks
- Process for Developing the NICEATM-ICCVAM Five-Year Plan
- Presentation of the Draft Five-Year Plan
- Public Comments
- Closing Remarks
- 5:00 P.M. Adjournment

National Institutes of Health
William H. Natcher Conference Center
Conference Room E
Bethesda, Maryland

For more information, please contact NICEATM:

Phone: 919-541-2384

Email: niceatm@niehs.nih.gov

ICCVAM Agencies: Consumer Product Safety Commission, Department of Agriculture, Department of Defense, Department of Energy, Food and Drug Administration, National Cancer Institute, Department of Transportation, National Institute for Occupational Safety and Health, National Institute of Environmental Health Sciences, NIH Office of the Director, National Library of Medicine, Department of the Interior, Occupational Safety and Health Administration, Environmental Protection Agency



- Moderator, Dr. Robert Scala
- Presentations
 - Process for Developing the Plan - Dr. Stokes
 - Presentation of the Plan - Dr. Wind
- Public Comments
 - Received Oral Comments from representatives of 4 organizations and 1 independent consultant
 - PETA, PCRM, IIVS, ARDF
- Total Attendance: >94
 - Over 60 members of the public
 - 25 members of ICCVAM and respective Program Offices
 - 9 members of SACATM



Town Meeting Comments -1

- Support expressed for existing efforts by ICCVAM/NICEATM, but need to expand efforts
- Plan should have deliverables with timelines
- Focus should be on replacement alternatives and not so much on reduction and refinement
- ICCVAM and its peer review panels need to recognize the urgent need for alternatives
- Stakeholders prefer a detailed document that could be used as a blueprint for moving forward
- ICCVAM should assume a greater leadership role in the development and validation of new alternative test methods

Note: Please also see submitted written comments on the ICCVAM-NICEATM website

Town Meeting Comments - 2

- Describe analysis leading to priorities
 - Priority setting should be more quantitative
- Consider written comments offered previously
- ICCVAM should devise a plan to address the challenges of a lengthy R&D process
- NICEATM/ICCVAM should be more pro-active (and do more than just facilitate) by developing ways to help prioritize funding within agencies
- Regarding proposed collaborations with ECVAM and JaCVAM
 - ICCVAM peer review of ESAC-endorsed test methods considered duplicative
 - 12 ESAC-endorsed methods not considered by ICCVAM, or if reviewed, recommendations may differ
 - ESAC endorsements do not lead to quicker ICCVAM approval

Why does ICCVAM not consider or automatically endorse all ESAC-endorsed methods?

- **ICCVAM is charged with evaluating test methods applicable to regulatory testing requirements**
 - Several ESAC methods cannot be used to meet regulatory testing requirements (e.g. embryotoxicity), or are not test methods (e.g. in vitro monoclonal antibody methods)
- **ECVAM protocols may only be applicable for EU classification system, not U.S. or international systems (e.g., 2006 in vitro dermal irritation study)**
 - Requires additional analyses of raw data, and may require new decision criteria
- **The ICCVAM evaluation process requires transparency and opportunity for public and stakeholder involvement:**
 - All review materials (BRD) available to the public
 - Opportunity for public comment
 - Public Independent peer review meeting
 - Peer review report available to the public
 - ESAC reviews do not currently include such transparency
 - ICCVAM BRDs and evaluation reports have facilitated rapid ESAC reviews
- **Basis for validity may differ, e.g. as a complete replacement**
 - Will use of the alternative test method provide equal or greater protection of human or animal health or the environment, compared to use of the traditional method?
 - Consider false negative rates, esp. for permanent damage (dermal, eye corrosion)
 - Requires clear delineation of both the usefulness and limitations of alternative test methods



Town Meeting Comments - 3

- ICCVAM should encourage/facilitate funding of alternatives research
- There is tremendous interest by researchers for alternative methods funding
- The plan should revisit the evaluation process to determine if it meets the needs of stakeholders
- A web-based scorecard could be used as an ongoing mechanism for tracking progress
- ICCVAM should become involved in the process of reviewing USDA draft notices for vaccine potency testing.

SACATM: Comments and Recommendations - 1

- Identify 2-3 high priority areas and provide a detailed plan for each
- Delineate roles and responsibilities of ICCVAM, NICEATM, and individual agencies
- Identify gaps and barriers along the method-development, validation, and adoption pathway
- Plan appears weighted toward R&D, but there are gaps in planning for validation activities for these methods
- Include a table of past methods reviewed by ICCVAM and agencies' actions

SACATM: Comments and Recommendations - 2

- Recognize the extensive outreach efforts by NICEATM/ICCVAM to obtain comment and input on the Five-Year Plan
 - Recommend outreach and stakeholder engagement on an ongoing basis
- Incumbent upon the ICCVAM agencies themselves – as critical stakeholders – to fully embrace the 3Rs and exert the leadership needed to assure that the validated methods delivered by the efforts of NICEATM and ICCVAM are actualized into regulatory testing frameworks as soon as practicable.

What Do NICEATM and ICCVAM Hope To Achieve?

- Further reduction and replacement of animal use where scientifically feasible
- Further reduction or elimination of pain and distress where animals must still be used
- Continued protection of public health, animal health, and the environment

Thank you for your participation as we develop this Plan!

Acknowledgements: ICCVAM Agency Representatives

Agency for Toxic Substances and Disease Registry

- Moiz Mumtaz, Ph.D.

Consumer Product Safety Commission

- Marilyn L. Wind, Ph.D. (Chair)
- * Patricia Bittner, M.S.
- * Kristina Hatlelid, Ph.D.

Department of Agriculture

- Jodie Kulpa-Eddy, D.V.M. (Vice Chair)
- ◇ Elizabeth Goldentyer, D.V.M.

Department of Defense

- Robert E. Foster, Ph.D.
- ◇ Patty Decot
- * Harry Salem, Ph.D.

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- ◇ Marvin Stodolsky, Ph.D.

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- ◇ Sarah Gerould, Ph.D.

Department of Transportation

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- ◇ Steve Hwang, Ph.D.

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- Office of Research and Development*

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- * Suzanne McMaster, Ph.D.

OECD Test Guidelines Program

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Office of Pesticides Programs

- * Amy Rispin, Ph.D.
- * Deborah McCall

Food and Drug Administration

Office of Science and Health Coordination

- Suzanne Fitzpatrick, Ph.D., D.A.B.T.
- Center for Drug Evaluation and Research*

Center for Devices and Radiological Health

- Melvin E. Stratmeyer, Ph.D.

Center for Biologics Evaluation and Research

- Richard McFarland, Ph.D., M.D.
- * Ying Huang, Ph.D.

Center for Food Safety and Nutrition

- * David G. Hattan, Ph.D.
- * Robert L. Bronaugh, Ph.D.

Center for Veterinary Medicine

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- * William T. Allaben, Ph.D.

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- ◇ T. Kevin Howcroft, Ph.D.

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- Surender Ahir, Ph.D.

- Principal Agency Representative
- ◇ Alternate Principal Agency Representative
- * Other Designated Agency Representatives



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- SACATM members
 - Richard A. Becker, Ph.D.
 - Mary Jane Cunningham, Ph.D.
 - Helen E. Diggs, D.V.M., DACLAM
- Ad hoc members
 - A. Wallace Hayes, Ph.D., DABT
 - Martin L. Stephens, Ph.D.

■ NICEATM

NIEHS

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| - William S. Stokes, D.V.M., DACLAM | Director; Project Officer |
| - Raymond Tice, Ph.D. | Deputy Director |
| - Debbie McCarley | Special Assistant; Asst. Project Officer |

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| - David Allen, Ph.D. | Principal Investigator |
| - Douglas Winters, M.S. | Project Manager |

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■ ICCVAM Five-Year Plan Subcommittee

- Dr. Alan Poland, Subcommittee Chair
- Dr. Suzanne Fitzpatrick
- Dr. David Hattan
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- Dr. Jodie Kulpa-Eddy, ICCVAM Vice Chair
- Dr. Amy Rispin
- Dr. Margaret Snyder
- Dr. William Stokes
- Dr. Marilyn Wind, ICCVAM Chair
- Dr. Sheila Newton, NIEHS Liaison, Planning Office

■ Agency Program Offices and ad hoc Working Groups

■ Stakeholders