Establishment of the International Cooperation on Alternative Test Methods (ICATM) and Its Role in the Validation and Regulatory Acceptance of Globally Harmonized Safety Assessment Methods

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Abstract

Several countries have established national validation organizations to promote the validation, evaluation, and regulatory acceptance of alternative safety testing methods that may reduce, refine, and replace the use of animals while maintaining adequate protection of human and animal health and the environment. On April 27, 2009, Canada, the European Union, Japan, and the U.S. signed a Memorandum of Cooperation (MoC) on International Cooperation on Alternative Test Methods (ICATM) to promote enhanced cooperation, collaboration, and communication among their respective validation organizations. The initial participating validation organizations are the Environmental Health Science and Research Bureau within Health Canada, ECVAM, JaCVAM, and NICEATM–ICCVAM. The organizations developed an initial framework to promote harmonization of scientific recommendations on alternative toxicity testing methods in response to a charge from the International Cooperation on Cosmetics Regulation. The ICATM MoC implements this framework and lays out processes for cooperation across three critical areas: design and conduct of validation studies, independent scientific peer review, and development of harmonized test method recommendations for regulatory consideration. This agreement is providing greater efficiency and effectiveness for the participating validation organizations by avoiding duplication of effort and leveraging of resources for recently initiated international validation studies. The increased cooperation and collaboration is expected to support more rapid international adoption of scientifically valid test methods by organizations such as the OECD that will protect people, animals, and the environment while reducing, refining, and replacing animal use where scientifically feasible.

Introduction

On April 27, 2009, representatives from four international agencies signed a Memorandum of Cooperation (MoC) establishing the International Cooperation on Alternative Test Methods (ICATM). The agreement promotes enhanced international cooperation and coordination on the scientific validation of non- and reduced-animal toxicity testing methods. The test methods evaluated under this agreement are expected to be more readily accepted by regulatory agencies by assuring international agreement on the scientific information demonstrating that the methods are reproducible and able to accurately identify product related health hazards. This poster describes the development of the MoC and the three major areas of cooperation covered by the agreement.

ICATM Validation Organization

ICATM is a voluntary international cooperation of four validation organizations from the United States, Japan, the European Union, and Canada.

- Japanese Center for the Validation of Alternative Methods (JaCVAM)
  Dr. Hajime Kojima, Director
- European Centre for the Validation of Alternative Methods (ECVAM)
  Dr. Joachim Kreysa, ECVAM Head
  Dr. Elke Anklam, Director, Institute of Health and Consumer Protection
- U.S. Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)
  Dr. Marilyn Wind, Chairman, ICCVAM
  Dr. William Stokes, Director, NICEATM and Executive Director, ICCVAM
- Health Canada
  Dr. David Blakey, Director, Environmental Health Sciences and Research Bureau

The inclusion of other participants and their appropriate status can be decided by consensus by current participants.

Figure 1: The ICATM Memorandum of Cooperation was signed at the National Institutes of Health on April 27, 2009, by (seated, left to right):

- Linda S. Birnbaum, Ph.D., DABT, ATS, Director, National Toxicology Program (NTP) and National Institute of Environmental Health Sciences (NIEHS);

- David H. Blakey, D.Phil., Director, Environmental Health Science and Research Bureau, Health Canada;
- Elke Anklam, Ph.D., Director, Institute for Health and Consumer Protection, European Commission of the European Union; and
- Hajime Kojima, Ph.D., Director, Japanese Center for the Validation of Alternative Methods.

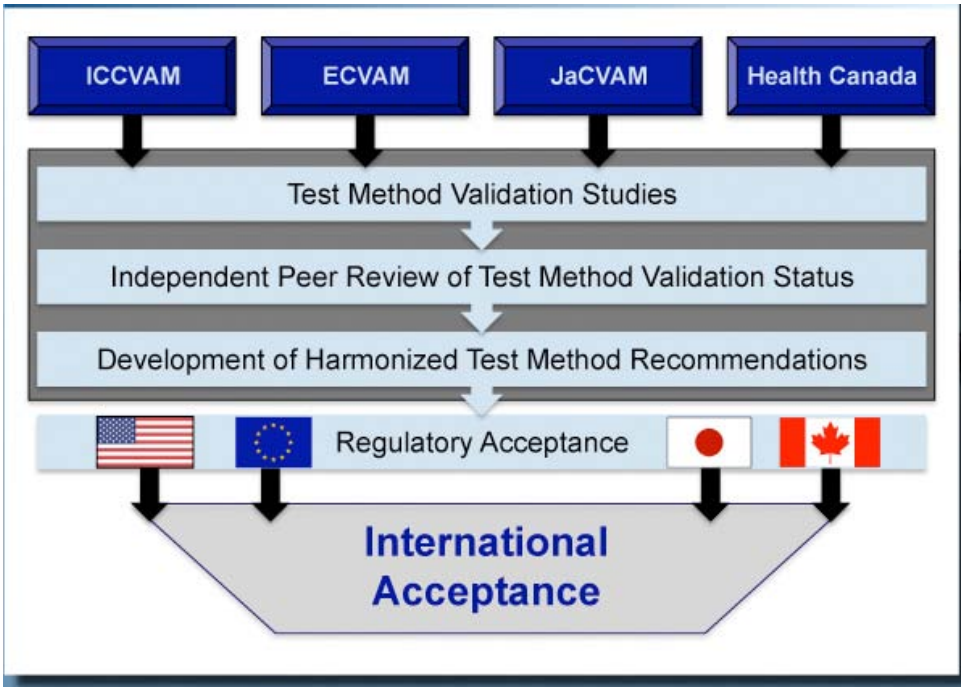
Also present at the signing were (standing, left to right):

- Marilyn Wind. Ph.D., Chair ICCVAM, U.S. Consumer Product Safety Commission;
- Linda Katz, M.D., M.P.H., Director, Office of Cosmetics and Colors, U.S. Food and Drug Administration; and
- William Stokes, D.V.M., DACLAM, Director NICEATM, NTP, NIEHS.

ICATM Development

September 2007	ICCR Initial Meeting
February/March 2008	VAMS (ECVAM, ICCVAM, and JaCVAM) Develop DraftFramework
April 2008	VAMS Present Draft Framework to ICCR Working Group
July 2008	Revised Draft Discussed at Second ICCR Working Group Meeting
October 2008	Framework Adopted by ICCR
April 2009	Memorandum of Cooperation (MoC) Signed

Figure 2. Framework for ICATM Memorandum of Cooperation



Critical Area #1 – Test Method Validation Studies

Objective:
To share information and develop consensus on critical scientific aspects of validation studies prior to their initiation.

Methods:
Participants will collaborate and seek consensus on the proposed validation study design, study protocol, and selection of reference substances to be tested, prior to the start of validation studies.

Outcome:
Data developed in such studies are more likely to be usable by all members and meet the needs of their regulatory authorities, reducing the cost and time wasted in duplication of efforts.

Critical Consensus Areas for Validation Studies

- Study objectives
- Specific regulatory testing purpose
- Proposed validation study design
- Detailed study protocols
- Substances to be tested
- The basis for the selection of test substances
- Participating laboratories

International Coordination of Current Validation Studies

Stably Transfected Transcriptional Activation Estrogen Receptor Agonist and Antagonist Assays (LUMI-CELL®)

- Lead Organization: NICEATM-ICCVAM
- Study Management Team includes representatives from ECVAM and JaCVAM
- Labs in U.S., Europe, and Japan
- Testing completed; analysis in progress.
- SOT Abstract #101, Poster Board Location 117, Toxicity Testing – Alternative Models Session, Monday March 8, 9:00 AM – 12:30 PM

MCF-7 Cell Proliferation Estrogen Receptor Agonist and Antagonist Assays (CertiChem Inc.)

- Lead Organization: NICEATM-ICCVAM
- Study Management Team includes representatives from ECVAM and JaCVAM.
- Intralaboratory validation study completed.
- International validation study planned.

EpiOcular™ and SkinEthic™ Human Corneal Epithelium Test Methods: Validation Study to Assess Usefulness for Identifying Substances as Not Classified as Eye Irritant Hazards

- Lead Organization: ECVAM
- Validation Management Group includes liaisons from NICEATM-ICCVAM and JaCVAM.
- Prevalidation studies in progress;

Direct Peptide Reactivity Assay (DPRA), Human Cell Line Activation Test (h-CLAT), and the Myeloid U937 Skin Sensitization Test (MUSST) for Identifying Skin Sensitization Potential of Chemicals

- Phase III Prevalidation Study
- Lead Organization: ECVAM
- Validation Management Group includes liaisons from NICEATM-ICCVAM and JaCVAM.
- Study design and chemical selection finalized; training of labs to begin in March 2010 with subsequent transfer and proposed completion of the prevalidation study by early 2011.

Assessment of Indicator Biotransformation Enzyme Induction Using HepaRG Cells and Cryopreserved Human Hepatocytes

- Lead Organization: ECVAM
- Validation Management Group includes liaisons from NICEATM-ICCVAM and JaCVAM.
- Study design SOP currently being reviewed and chemical selection is in progress for prevalidation and validation studies.

In Vivo and In Vitro Comet Assay Validation

- Lead Organization: JaCVAM
- Validation Management Team includes members from ECVAM and NICEATM-ICCVAM.
- Phases I and II of the study are complete; Phase III is currently ongoing.

Critical Area #2 – international Cooperation: Evaluating the Scientific Validity of Test Methods

Objective:
High quality independent scientific peer reviews of alternative test methods that incorporate transparency and opportunity for stakeholder involvement.

Methods:
- ICATM members have agreed to consider the needs of all ICATM Validation Organizations when organizing and conducting such meetings.
- Member organizations will share and seek input from each other during the preparation of background review documents and draft recommendations and make these publicly available when provided to peer review panels.
- Peer review panels will have international representation including solicitation of nominations from other ICATM Validation Organizations.
- Peer review panel reports will be made publicly available

Outcome:
Improved quality of independent scientific peer review and reduced need for duplication of effort between members resulting in more efficient use of limited resources. The organization and conduct of Independent Scientific Peer Review Meetings is a critical but timely and costly component of evaluating alternative test methods. ICATM is also committed to making the review process as open and transparent as possible by holding public peer review meetings or providing other opportunities for stakeholder and public comment, and by making peer review panel reports available to the public and to ICATM Validation Organizations to consider in developing final recommendations.

Recent International Cooperation: Peer Review Meetings and Expert Consultations

Evaluation of the Validation Status of Alternative Ocular Safety Testing Methods and Strategies

- Independent Scientific Peer Review Panel convened May 19-21, 2009
- Organized by NICEATM-ICCVAM. Included panel member nominations from ICATM organizations
- Composed of 22 members from six countries: Belgium, Canada, Japan, the Netherlands, Spain and the United States
- Report available at: http://iccvam.niehs.nih.gov/docs/ocutox_docs/OcularPRPRept2009.pdf

Updated Validation Status of New Versions and Applications of the Murine Local Lymph Node Assay: A Test Method for Assessing the Allergic Contact Dermatitis Potential of Chemicals and Products

- Independent Scientific Peer Review Panel convened April 28-29, 2009
- Organized by NICEATM-ICCVAM. Included panel member nominations from ICATM organizations.
- Combined panel membership from 2009 and a similar panel in 2008 included 19 members from eight countries: U.S., Canada, Europe (Czech Republic, France, Germany, The Netherlands, and U.K.), and Japan
- Report available at: http://iccvam.niehs.nih.

NICEATM-ICCVAM Peer Review of In Vitro Estrogen Receptor Methods for Endocrine Disruptor Screening

- Independent Scientific Peer Review panel planned for Fall 2010.
- Sponsored by NICEATM-ICCVAM. Panel will include experts nominated by ICATM organizations.

Critical Area #3 – International Cooperation on the Development of Harmonized Test Method Recommendations

Objective:
Consensus by all of the national validation organizations on test method recommendations to forward to regulatory authorities for acceptance decisions.

Methods:
- Draft final recommendations will be shared within ICATM and will be considered along with the peer review panel reports and other supporting documents.
- Members will notify each other of their respective draft positions.
- In cases where all of the ICATM Validation Organizations mutually agree, each organization will finalize and forward their recommendations to their respective regulatory authorities as authorized by applicable law.
- Dissenting views will be discussed with the goal of resolution and consensus.
- If there are unresolved different positions among the ICATM Validation Organizations, the scientific rationale for the differing positions will be documented and provided by each validation organization with recommendations forwarded to appropriate regulatory authorities.

Outcome:
More rapid international adoption of new alternative test methods is expected by harmonizing recommendations prior to regulatory consideration of test methods by various countries. This in turn will reduce issues created by differing national regulatory guidelines, thereby facilitating more rapid adoption of new alternative test methods internationally.

International Cooperation: Recent Progress

Ocular Toxicity:

- Proposed New OECD Test Guideline: The Isolated Chicken Eye (ICE) Test Method for Identifying Ocular Corrosives and Severe Irritants
  - Accepted by OECD September 2009
- Proposed New OECD Test Guideline: The Bovine Corneal Opacity and Permeability (BCOP) Test Method for Identifying Ocular Corrosives and Severe Irritants
  - - Accepted by OECD September 2009

Skin Irritation:

- Draft OECD Test Guideline: In Vitro Testing for Skin Irritation: Reconstructed Human Tissue (RhT) Skin Model To be considered at the OECD Test Guidelines Program meeting on March 23-25, 2010

Skin Sensitization:

- Updated OECD Test Guideline 429: Skin Sensitisation: Local Lymph Node Assay
  - The Reduced Murine Local Lymph Node Assay
- Proposed New OECD Test Guideline: Skin Sensitisation: Local Lymph Node Assay: DA Version
  - Nonradioisotopic Alternative Test Method to Assess the Allergic Contact Dermatitis Potential of Chemicals and Products
  - Based on International Peer Review and ICCVAM Evaluation
  - To be considered at the OECD Test Guidelines Program meeting on March 23-25, 2010
- Proposed New OECD Test Guideline: Skin Sensitisation: Local Lymph Node Assay: BrdU-ELISA
  - Nonradioisotopic Alternative Test Method to Assess the Allergic Contact Dermatitis Potential of Chemicals and Products
  - Based on International Peer Review and ICCVAM Evaluation
  - To be considered at the OECD Test Guidelines Program meeting on March 23-25, 2010

ICATM Memorandum of Cooperation

The purpose of the MoC is to promote consistent and enhanced voluntary international cooperation, collaboration, and communication among national validation organizations in order to:

- Further the optimal design and conduct of validation studies to support national and international regulatory decisions on the usefulness and limitations of alternative methods
- Further high quality independent scientific peer reviews of alternative test methods that incorporate transparency and opportunity for stakeholder involvement
- Enhance the likelihood of harmonized recommendations by validation organizations on the usefulness and limitations of alternative test methods for regulatory testing purposes
- Achieve greater efficiency and effectiveness by avoiding duplication of effort and leveraging limited resources
- Support the timely international adoption of alternative methods

The goals of the MoC are to:

- Ensure that alternative methods/strategies are more readily accepted worldwide though international cooperation in three critical areas:
  - Validation studies
  - Independent peer review
  - Development of harmonized recommendations
- Establish international cooperation necessary to ensure that new alternative test methods/strategies adopted for regulatory use will provide equivalent or improved protection for people, animals, and the environment, while reducing, refining (causing less pain and distress), or replacing animal use whenever scientifically feasible

Other Examples of ICATM Collaboration and Communication

Scientific Workshop and Symposia:

- International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Vaccine Safety Testing: State of the Science and Future Directions
  - September 14-16, 2010, at the William H. Natcher Conference Center – National Institutes of Health in Bethesda, MD, USA
  - Sponsored by NICEATM-ICCVAM with participation of ECVAM, JaCVAM and Health Canada through their Liaisons to the ICCVAM Biologics Working Group

Regular Updates Provided to Advisory Committees:

- Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)
  - Advises ICCVAM, NICEATM, and the Director of the NIEHS regarding statutorily mandated duties of ICCVAM and activities of NICEATM.
  - Representatives from ECVAM, JaCVAM, and Health Canada invited to provide updates to SACATM.
- ECVAM Scientific Advisory Committee (ESAC)
  - Provides scientific advice to ECVAM and issues opinions on the scientific validity of ECVAM-evaluated Alternative Test Methods and other aspects related to alternatives in animal testing.
  - Representatives from ICCVAM, JaCVAM, and Health Canada routinely invited to provide updates to ESAC during its yearly meetings.

Summary

- The development of the ICATM framework and signing of the MoC has set the stage for a high level of transparency and the opportunity for broad stakeholder involvement during validation, peer review meetings, and preparation of final recommendations.
- ICATM participants are committed to consistent coordination, cooperation, and communication to achieve success in the adoption of scientifically valid alternative test methods.
- Success will be indicated by consensus on the usefulness and limitations of new alternative methods, followed by rapid national and international acceptance.
- ICATM cooperation and coordination will help ensure that new test methods will provide for equivalent or better protection of people, animals, and the environment, while reducing, refining, and replacing animal use where scientifically feasible.

References

ECVAM. 2009. About ECVAM. Available at: http://ecvam.jrc.it/ [accessed 17 February 2010].

Health Canada. 2007. Environmental Health, Science and Research Bureau. Available at: http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hecs-dgsesc/sep-psm/ehsrb-bsser-eng.php [accessed 17 February 2010].

ICATM. 2009. Memorandum of Cooperation on International Cooperation on Alternative Test Methods (ICATM). Available: http://iccvam.niehs.nih.gov/docs/about_docs/ICATMMOC.pdf [accessed 17 February 2010].

ICCVAM. 2009. The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). Available at: http://iccvam.niehs.nih.gov/ [accessed 17 February 2010].

JaCVAM. 2009. Japanese Center for the Validation of Alternative Methods. Available at: http://jacvam.jp/ [accessed 17 February 2010].

U.S. FDA. 2008. Framework for International Cooperation on Alternative Test Methods (ICATM). Available at: http://www.fda.gov/InternationalPrograms/HarmonizationInitiatives/ucm114518.htm [accessed 17 February 2010].

U.S. NIH. 2009. Countries Unite to Reduce Animal Use in Product Toxicity Testing Worldwide: U.S., Canada, Japan and European Union Sign International Agreement. Press Release, April 27, 2009. Available at: http://www.nih.gov/news/health/apr2009/niehs-27.htm [accessed 17 February 2010].

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