NICEATM and ICCVAM Participation in the International Cooperation on Alternative Test Methods

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Summary

The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) work to promote the validation and regulatory acceptance of new, revised, and alternative test methods that will provide continued or improved protection of people, animals and the environment while reducing, refining, and replacing the use of animals. On April 27, 2009, the United States, Canada, European Union, and Japan signed a Memorandum of Cooperation on International Cooperation on Alternative Test Methods (ICATM). The agreement provides for regular collaborations of NICEATM and ICCVAM with the Japanese Center for the Validation of Alternative Methods (JaCVAM), the European Centre for the Validation of Alternative Methods (ECVAM), and Health Canada's Environmental Health Science and Research Bureau during validation studies, scientific peer reviews, and development of harmonized recommendations for new test methods. NICEATM and ICCVAM have implemented processes to support efficient international collaborations in order to achieve more rapid international acceptance of harmonized scientifically valid test methods.

Keywords: NICEATM-ICCVAM, ICATM, international harmonization, alternative test methods

1 Introduction

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is an interagency committee consisting of 15 U.S. Federal regulatory and research agencies that use, generate, require, or disseminate safety-testing information (Fig. 1).

The committee was established in 1997 to coordinate the interagency evaluation of the scientific validity of new, revised, and alternative methods proposed for regulatory safety testing. The ICCVAM Authorization Act of 2000 (USC, 2000) established ICCVAM as a permanent interagency committee of the NIEHS under NICEATM with specific purposes and duties (Fig. 2). NICEATM and ICCVAM work collaboratively to evaluate new and improved test methods applicable to the needs of U.S. Federal agencies (Stokes and Schechtman, 2007). Based on comprehensive scientific evaluations, ICCVAM and NICEATM forward formal recommendations to Federal agencies on test method usefulness and limitations for regulatory testing (Stokes and Hill, 2000, 2002). ICCVAM and NICEATM

ICCVAM Member Agencies	
Regulatory/Research	**Non-Regulatory/Research**
• Consumer Product Safety Commission	• Department of Defense
• Department of Agriculture	• Department of Energy
• Department of Interior	• National Cancer Institute
• Department of Transportation	• National Institute of Environmental Health Sciences
• Environmental Protection Agency	• National Institute for Occupational Safety and Health
• Food and Drug Administration	• National Library of Medicine
• Occupational Safety and Health Administration	• National Institutes of Health, Office of the Director
• Agency for Toxic Substances and Disease Registry	

Fig. 1: ICCVAM Member Agencies

work collaboratively to promote the validation and regulatory acceptance of new, revised, and alternative test methods that are based on sound science and that will provide continued or improved protection of people, animals and the environment while reducing, refining, and replacing the use of animals where scientifically feasible.

NICEATM administers ICCVAM and provides scientific and technical support for ICCVAM activities. NICEATM organizes test method peer reviews and workshops in conjunction with ICCVAM and carries out independent validation studies on high priority test methods (Stokes, 2003).

Since its establishment, ICCVAM has contributed to the evaluation of 27 alternative test methods that have been accepted or endorsed by national and international authorities. These methods provide alternatives that reduce, refine, or replace the use of animals for the hazard assessment of acute systemic toxicity (ICCVAM, 2001, 2006b), dermal corrosivity and irritation (ICCVAM, 2002), dermal phototoxicity, allergic contact dermatitis (ICCVAM, 2009a), ocular corrosivity and irritation (ICCVAM, 2006a), vaccine potency and safety testing, and pyrogenicity testing (ICCVAM, 2008a). ICCVAM completed additional evaluations for new alternatives for allergic contact dermatitis and ocular irritation in 2009 (ICCVAM, 2009b, 2009c). All of the materials associated with the ICCVAM evaluations, including background review documents, peer review panel reports, and ICCVAM test methods recommendations can be found on the NICEATM-ICCVAM website (http://iccvam.niehs.nih.gov).

2 International cooperation on alternative test methods

ICCVAM has long history of international collaborations with the European Centre for the Validation of Alternative Methods (ECVAM) and the Japanese Center for the Validation of Alternative Methods (JaCVAM) (Fig. 3), and these collaborations have been steadily increasing (Schechtman and Stokes, 2002; Stokes et al., 2002).

On April 27, 2009, the United States, Japan, European Union, and Canada signed a Memorandum of Cooperation (MoC) establishing the International Cooperation on Alternative Test Methods (ICATM). The MoC provides for cooperation and collaboration in three critical areas: 1) the design and conduct of validation studies, 2) independent scientific peer review meetings and reports, and 3) development of harmonized test method recommendations for regulatory acceptance consideration (ICATM, 2009). Figure 4 summarizes the ICATM framework, progressing from validation studies through national and international regulatory acceptance of new alternative test methods.

ICCVAM's Purpose
• Increase the efficiency and effectiveness of U.S. Federal agency test method review
• Eliminate unnecessary duplicative efforts and share experience between U.S. Federal regulatory agencies
• Optimize utilization of scientific expertise outside the U.S. Federal government
• Ensure that new and revised test methods are validated to meet the needs of U.S. Federal agencies
• Replace, reduce, or refine the use of animals in testing, where feasible
ICCVAM's Duties
• Review and evaluate new, revised, or alternative test methods
• Facilitate interagency and international harmonization of test methods
• Facilitate and provide guidance on test method development, validation criteria, and validation processes
• Facilitate acceptance of scientifically valid test methods
• Submit test recommendations to U.S. Federal agencies
• Consider petitions from the public for review and evaluation of validated test methods

Fig. 2: The ICCVAM Authorization Act of 2000 defines ICCVAM's purpose and duties.
(Adapted from USC, 2000)

1993	• NIEHS Director serves as keynote speaker at First World Congress on Alternatives and Animal Use in the Life Sciences
1995	• Ad Hoc ICCVAM International Workshop on Validation and Regulatory Acceptance Criteria
1998	• ICCVAM holds its first international independent scientific peer review panel on the Murine Local Lymph Node Assay
2001	• First joint NICEATM – ECVAM International Validation Study (Cytotoxicity Assays estimate acute systemic toxicity
2002	• ECVAM liaison invited to participate in SACATM meetings
2003	• NICEATM and ICCVAM liaisons designated for ESAC
2007	• JaCVAM liaisons invited to participate in SACATM meetings
	• First NICEATM-ECVAM-JaCVAM International Validation Study (ER STTA Assay)
2009	• ICATM Memorandum of Cooperation signed

Fig. 3: Selected Highlights: NICEATM and ICCVAM international cooperation.

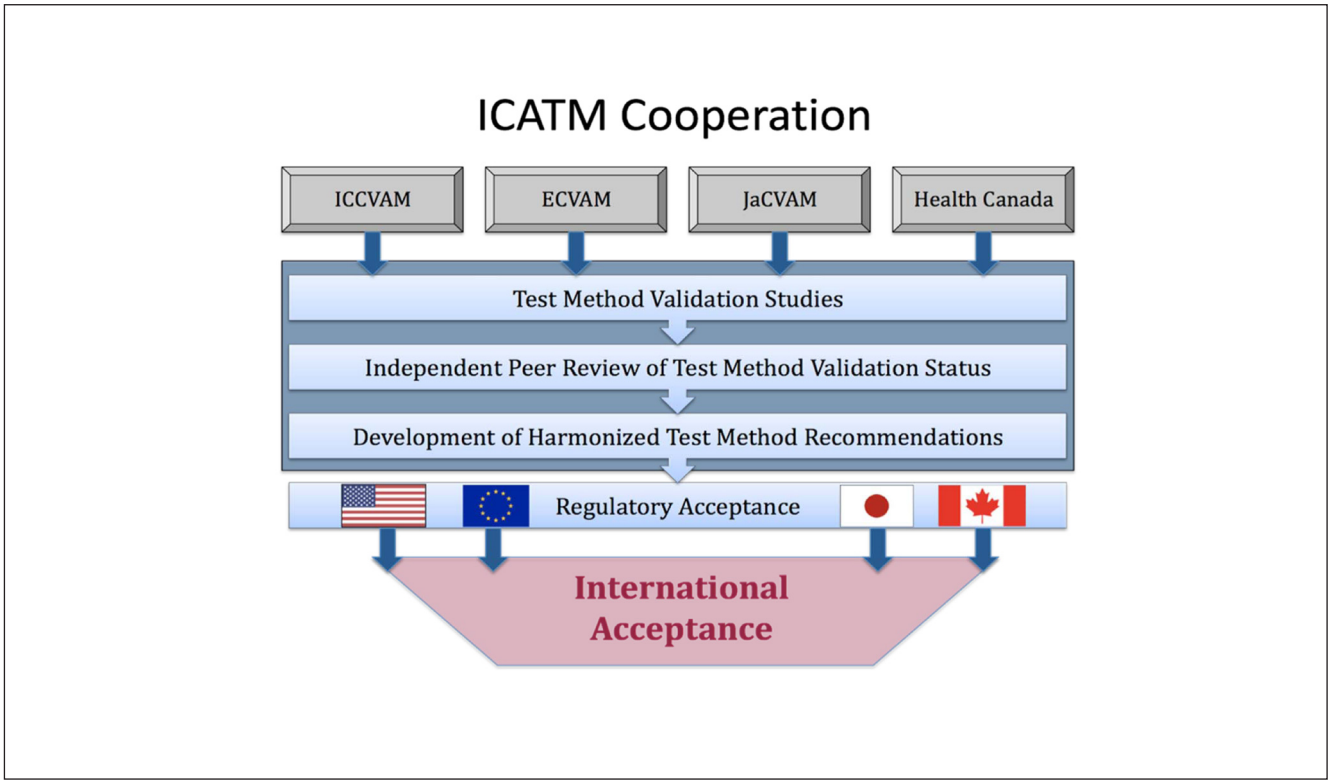

Fig. 4: ICATM framework for cooperation and collaboration between participating organizations.

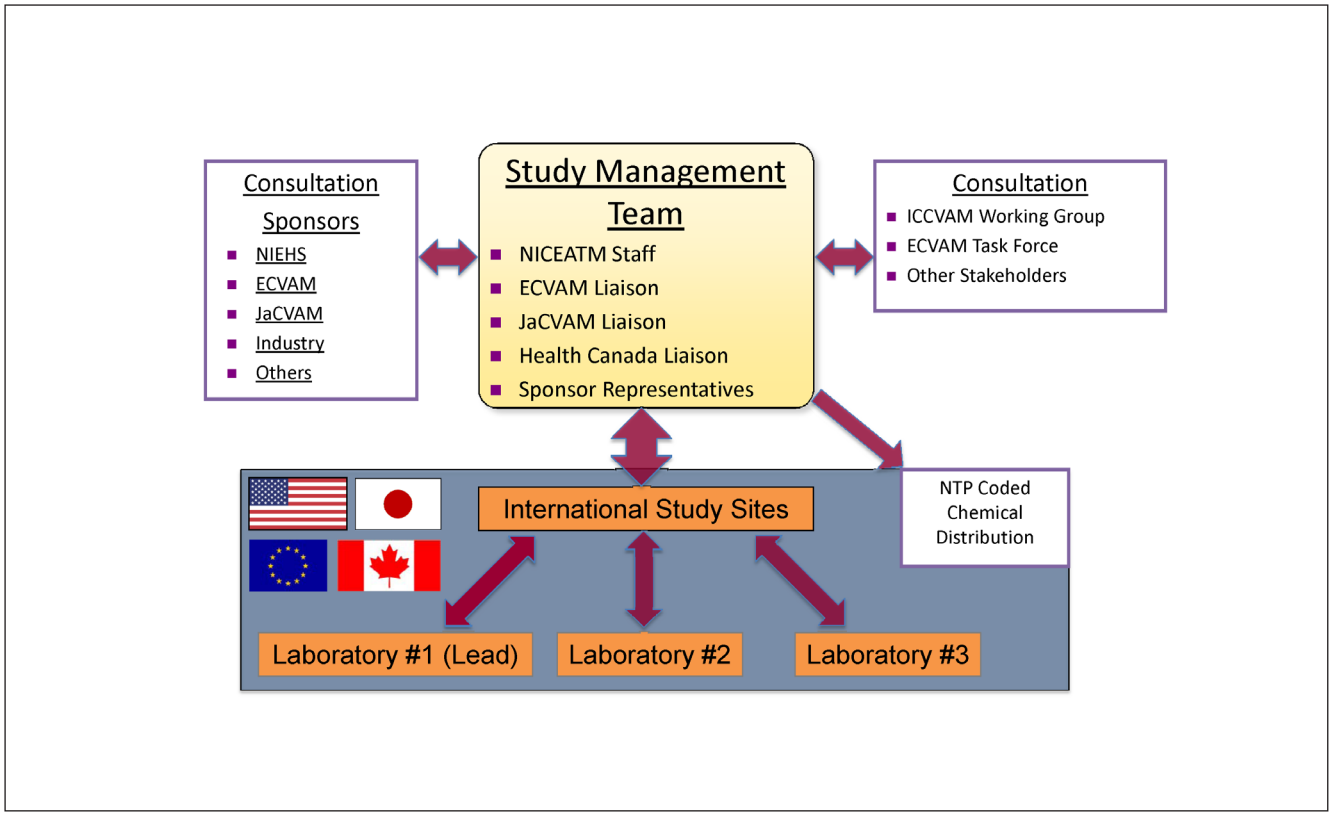

Fig. 5: The NICEATM-ICCVAM model for cooperative international validation studies includes active involvement and consultation with ICATM participants and stakeholders.

Prior to the development of the ICATM framework, collaborations among the national validation organizations were on an *ad hoc* informal basis. The lack of consistent coordination and the different processes used by each of the validation organizations often contributed to validation studies, peer reviews, and development of formal recommendations by one organization without adequate consultation and input from the others. This sometimes led to test method recommendations by one organization that could not be considered by another organization without extensive additional review efforts, and wide variations in transparency and outcomes of peer review processes.

The new cooperation agreement provides for communication and cooperation throughout the test method validation and evaluation processes. The ICATM agreement seeks to develop harmonized recommendations for scientifically sound test methods that will maintain or enhance protection of human and animal health and the environment, while reducing, refining, and replacing the use of animals where scientifically feasible.

3 International validation study cooperation

NICEATM and ICCVAM have developed a model for managing validation studies based on experience gained in managing two international validation studies and participating on the validation management teams for validation studies led by ECVAM and JaCVAM (ICCVAM, 2006b, 2006c; Stokes et al., 2008; Tice et al., 2009). In order to ensure early and consistent contributions from other ICATM participants, the Study Management Team (SMT) for NICEATM-led validation studies includes liaisons from ECVAM, JaCVAM, and Health Canada. (Fig. 5)

The SMT is charged with the development and approval of the validation study design, test method protocol, and selection of appropriate reference substances. The SMT consults with the appropriate ICCVAM Test Method Working Group to obtain regulatory and scientific input on these critical aspects. SMT liaison members from ECVAM, JaCVAM, and Health Canada

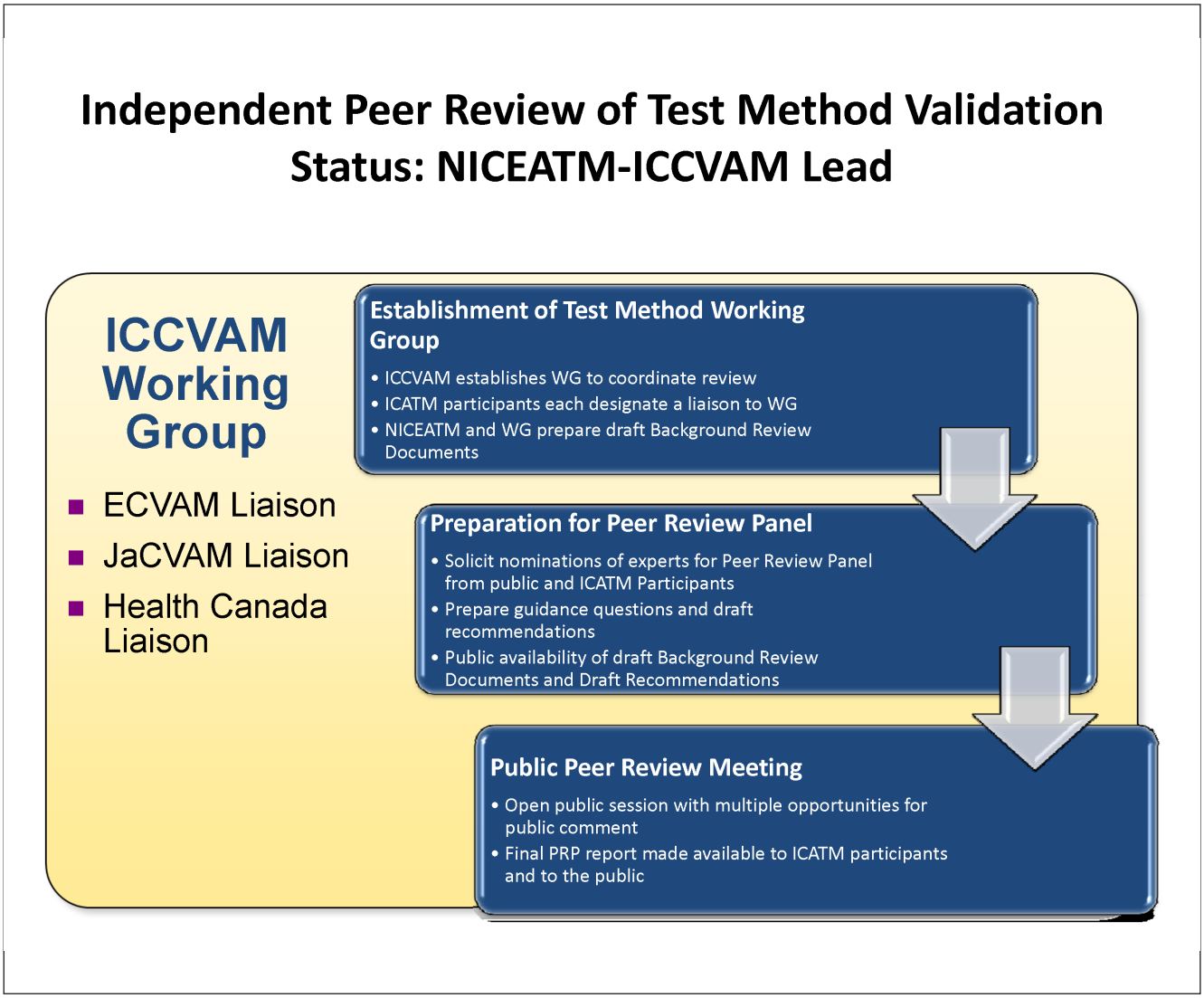

Fig. 6: NICEATM and ICCVAM Working Group Test Method Evaluation Process: Independent Scientific Peer Review.

are responsible for obtaining input from their appropriate regulatory and scientific stakeholders.

The NICEATM SMT is responsible for overall scientific coordination and management of the study in conjunction with the participating labs. The SMT evaluates the performance and results of the study at key points and determines any protocol optimization or modifications needed between study phases, and approves progression to the next phase of the study. ICATM liaisons on the SMT serve as a key conduit for information exchange throughout the study. After completion of the study, the SMT is responsible for data evaluation and interpretation, including review and approval of all reports resulting from the study.

NICEATM is currently using this model to manage an international validation study evaluating the LUMI-CELL® ER stably transfected transcriptional activation assay (ICCVAM, 2008b). ICCVAM and NICEATM liaisons also actively participated in the design and conduct of a recently completed ECVAM-led validation study on *in vitro* reconstructed human epidermis test methods and are participating in a similar role on three additional ECVAM-led validation studies: an *in vitro* testing strategy for skin sensitization (h-CLAT; DPRA; MUSST), an *in vitro* hepatic biotransformation enzyme induction assay, and human reconstituted tissue models for ocular irritation (i.e., EpiOcular™ and SkinEthic HCE™). ICCVAM and NICEATM also have liaisons contributing to two JaCVAM-led validation studies: the *in vivo/in vitro* comet assay and the BHAS cell transformation assay.

4 Independent scientific peer review of the validation status of test methods

NICEATM-ICCVAM evaluations of test method scientific validity are coordinated by a specific ICCVAM Working Group (WG) assisting NICEATM. The evaluation includes independ-

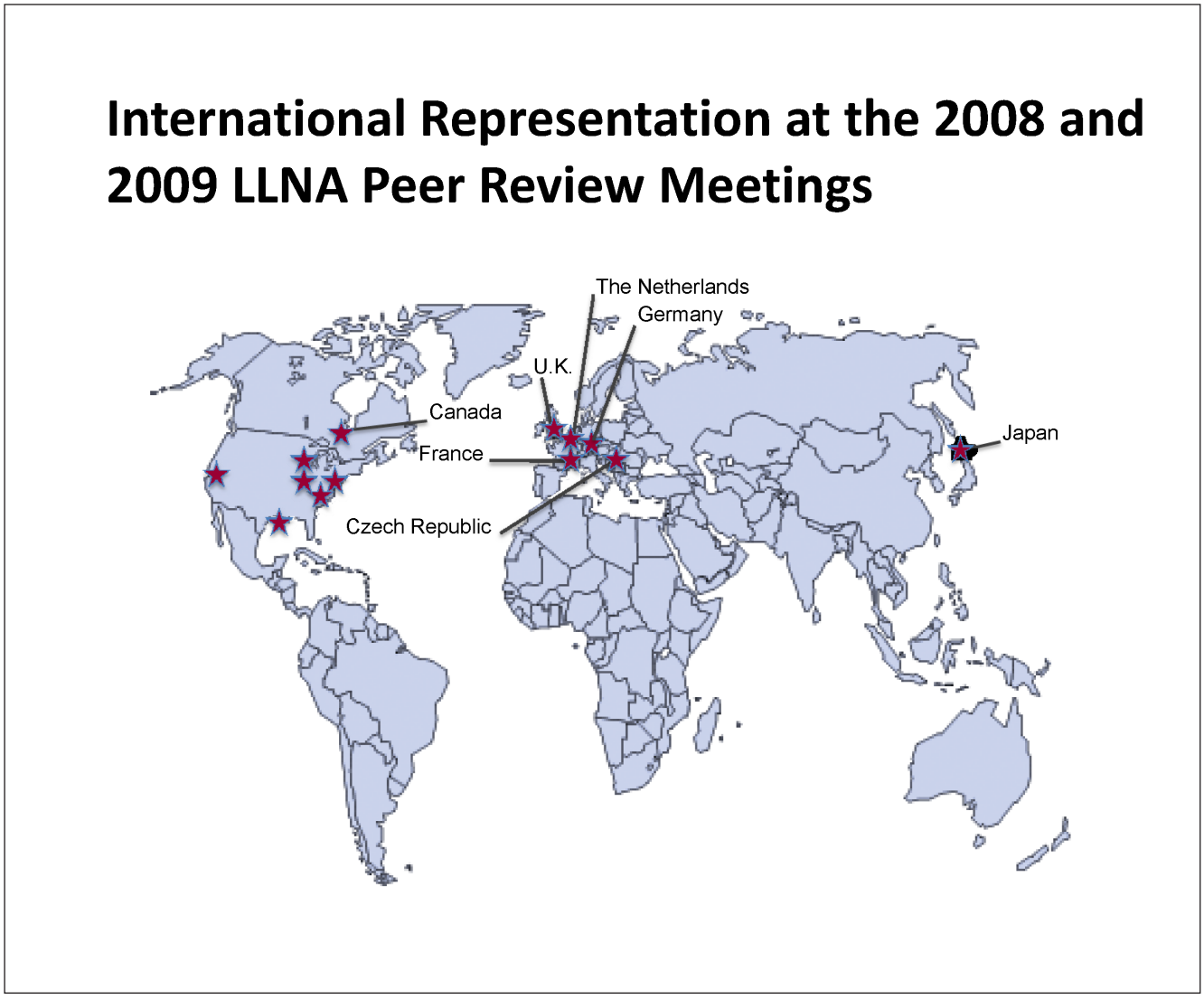

Fig. 7: The 2008 and 2009 International LLNA Peer Review Panels included members from eight countries.

ent scientific peer by an international panel of experts convened as an NIH Special Emphasis Panel in accordance with provisions of the Federal Advisory Committee Act (General Services Administration, 2001). Working groups are established for each toxicity area and consist of scientists from ICCVAM Federal Agencies and liaisons from the other ICATM participating organizations. The peer review panel consists of outside subject matter experts from industry, academia, other stakeholder groups, and the international scientific community. An important role of the ICCVAM Working Group is to recommend appropriate experts for the panel. ICATM liaisons are asked to identify appropriate international experts.

Figure 6 outlines the role of NICEATM and the ICCVAM Working Group in coordinating test method evaluations and independent scientific peer reviews. Key aspects of the process include public availability of all materials (i.e., draft background review documents and draft test method recommendations) made available to the peer review panel for review, public meetings of the peer review panel, the opportunity for public comments at the peer review panel meeting, and public availability of the panel's independent peer review report.

Two recent NICEATM-ICCVAM coordinated international peer reviews exemplify the commitment to international collaboration and transparency. On April 28-29, 2009, NICEATM-ICCVAM convened a Peer Review Panel Meeting on *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* (ICCVAM, 2009c). The ICCVAM Immunotoxicity Working Group included liaison members from both ECVAM and JaCVAM. In addition to other collaborations, the liaisons provided recommendations for panel membership. The combined panel membership from the 2009 peer review meeting and a similar peer review meeting held in 2008 included 19 members from eight countries: U.S., Canada, Europe (Czech Republic, France, Germany, The Netherlands, and U.K.), and Japan (Fig. 7).

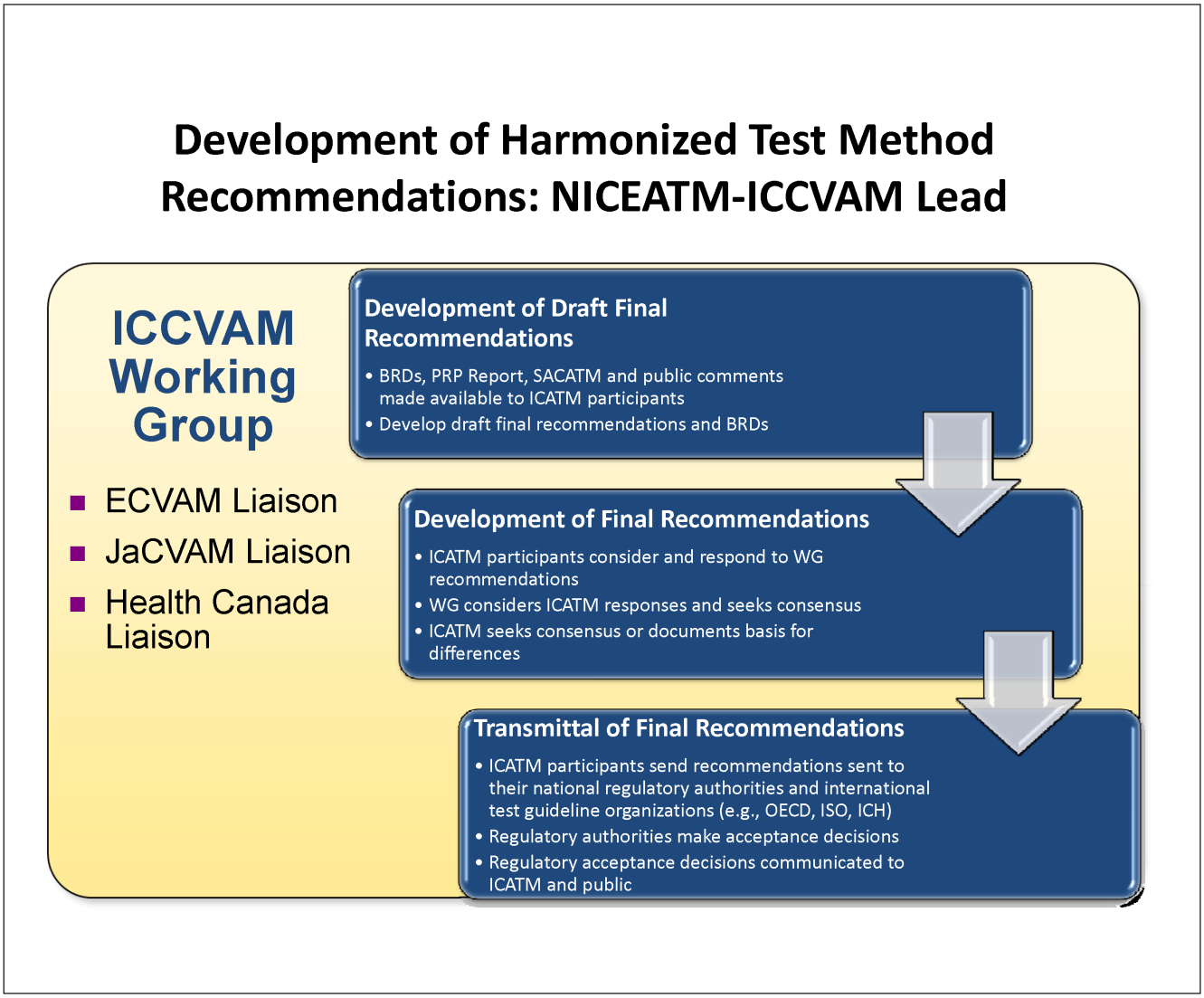

Fig. 8: ICCVAM's process for development of ICATM harmonized test method recommendations.

Similarly, on May 19-21, 2009, NICEATM-ICCVAM convened an international Peer Review Panel Meeting on *Alternative Ocular Safety Testing Methods and Approaches* (ICCVAM, 2009b). The ICCVAM Ocular Toxicity Working Group also included liaisons from ECVAM and JaCVAM. This panel was composed of 22 members, including members from six countries: Belgium, Canada, Japan, the Netherlands, Spain and the United States.

5 Development of harmonized test method recommendations

The third critical area of ICATM cooperation is the development of harmonized test method recommendations to forward to regulatory authorities for their acceptance consideration. Figure 8 summarizes the process for developing final test method recommendations. The ICCVAM WG, which includes the liaisons from the other ICATM participants, develops draft final test method recommendations after considering the peer review panel report and all comments received during the evaluation process from the public and from the NICEATM-ICCVAM Scientific Advisory Committee on Alternative Toxicological Methods (SACATM). The ICATM participants then consider and respond to the WG recommendations. The WG considers the ICATM participants' responses and works to develop a consensus on the final recommendations. If a consensus cannot be reached, then the scientific rationale for any areas where the validation organizations differ on their recommendations are documented in writing and included as part of the final test method evaluation report. The ICATM participants then forward the final test method recommendations and reports to their respective national regulatory authorities for acceptance decisions. Each ICATM participant then communicates to the other ICATM participants the regulatory authority acceptance decisions. The lead ICATM organization coordinating the evaluation then forwards recommendations, on behalf of all of the ICATM organizations, to appropriate international test guideline organizations, such as the Organization for Economic Coordination and Development (OECD), International Standards Organization (ISO), and the International Conference on the Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Examples of recent harmonized test method recommendations include performance standards for the murine local lymph node assays (LLNA) and two *in vitro* ocular safety-testing methods (ICCVAM, 2006a; OECD, 2009a, 2009b). ICCVAM's recommendations on non-radioactive LLNA methods (LLNA: DA and LLNA: BrdU-ELISA) both resulted in new draft OECD Test Guidelines (OECD, 2009c, 2009d). The harmonized recommendations on LLNA performance standards and the reduced LLNA were incorporated into a draft update to OECD Test Guideline 429 submitted in June of 2009 (ICCVAM 2009a, 2009d; OECD, 2009e). Recommendations on the bovine corneal opacity and permeability and isolated chicken eye tests resulted in new OECD Test Guidelines 437 and 438, respectively, that were adopted by the OECD Council more rapidly than any previous test guideline (OECD, 2009a, 2009b).

6 Conclusions

The establishment of ICATM promotes enhanced international cooperation and collaborations on the scientific validation and evaluation of alternative test methods that are expected to further reduce, refine, and replace the use of animals in regulatory safety testing. As a result of this international cooperation, test methods determined to be sufficiently accurate and reproducible for identifying health hazards or safety of chemicals and products are expected to be more readily and rapidly accepted for regulatory testing by national and international organizations.

This international cooperation will serve an important role in translating research advances into more effective public health prevention tools. It will speed the validation and adoption of new test methods based on advances in science and technology that will provide more accurate predictions of safety or hazard. Animal welfare will also be improved by the national and international acceptance of alternative test methods that reduce, refine, and replace the use of animals.

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