

1.0 INTRODUCTION

ICCVAM is responsible for coordinating the interagency technical review of new or modified alternative test methods of interagency interest, and coordinating cross-agency issues relating to the validation, acceptance, and national and international harmonization of toxicological test methods throughout the U.S. Federal government. ICCVAM was established as a permanent interagency committee of the National Institute of Environmental Health Sciences (NIEHS) under NICEATM by the ICCVAM Authorization Act of 2000 (Public Law 106-545) (2; **Appendix E**). Priority is given to test methods that may provide for improved prediction of adverse human, animal, or ecological effects, and those that might reduce¹, refine², or replace³ animal use.

In the *ad hoc* ICCVAM report on the validation and regulatory acceptance of toxicological test methods (1), various stages were identified to move a proposed test method from concept to regulatory acceptance (**Figure 1**). A critical stage is the communication of a proposed test method by the sponsor or nominator to ICCVAM for consideration and review. NICEATM, on behalf of ICCVAM, receives proposed test method nominations or submissions and communicates with the submitting organization or individual. Typically, the ICCVAM evaluation process involves an initial assessment by NICEATM of the adequacy and completeness of the proposed test method nomination or submission, and a determination by ICCVAM of the priority that the proposed test method will have for technical evaluation (see **Section 2**). Once a proposed test method has been accepted for evaluation, ICCVAM assembles an interagency working group of government scientists with scientific and regulatory expertise in the appropriate scientific disciplines to collaborate with NICEATM on the evaluation process. Depending on the validation status of the proposed test method, ICCVAM, in conjunction with NICEATM, develops recommendations and priorities for further efforts. Such efforts might include an expert workshop, an expert panel meeting, a peer review meeting, an expedited peer review process, or a validation study (**Figure 2**).

Following this review process, ICCVAM develops and forwards recommendations on the usefulness and limitations of the proposed test method for regulatory purposes to Federal agencies, in accordance with Public Law 106-545 (2). Based on their specific statutory mandates, each agency then makes a determination regarding the acceptability of the test method. Agencies are required to respond to ICCVAM within 180 days of receipt of an ICCVAM test method recommendation. If the test method is accepted, appropriate actions (e.g., revision of existing regulations, publication of guidelines and/or guidance documents) are taken to inform the regulated community.

¹Reduction alternative: A new or modified test method that reduces the number of animals required.

²Refinement alternative: A new or modified test method that refines procedures to lessen or eliminate pain or distress in animals or enhances animal well-being.

³Replacement alternative: A new or modified test method that replaces animals with nonanimal systems or one animal species with a phylogenetically lower one.

Figure 1. Test Method Validation Process

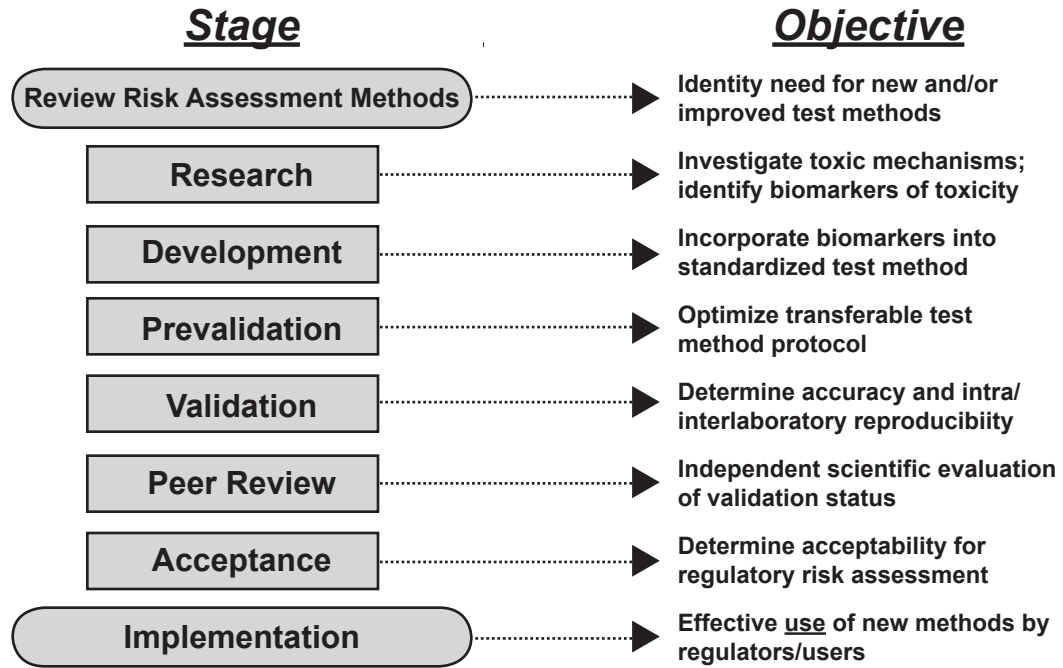
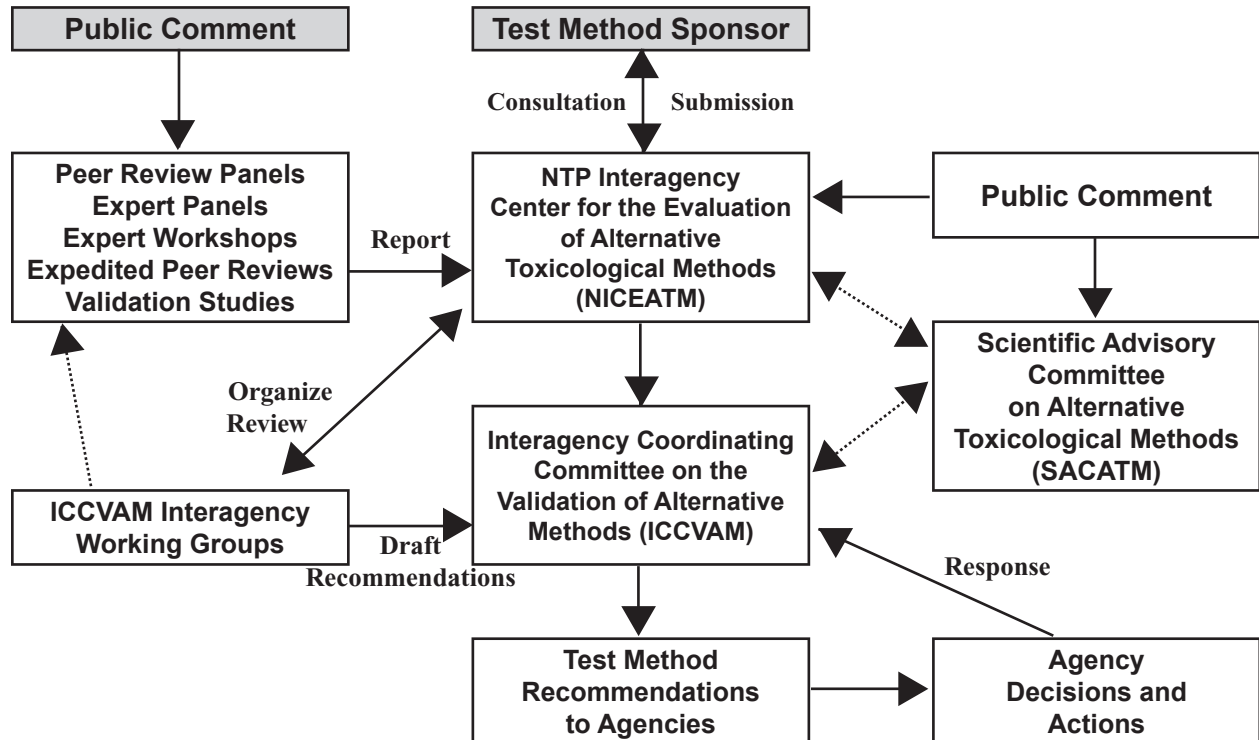


Figure 2. ICCVAM Test Method Evaluation Process



The purpose of this document is to provide guidance to sponsors and nominators on the information needed by ICCVAM to evaluate the validation status of a proposed test method (1, 4, 5). In preparing a nomination or submission, the outline in **Appendix A** should be used to discuss the extent to which each of the validation and acceptance criteria (**Appendix D**) have been addressed or will be addressed in proposed validation studies. Sponsors and nominators may be asked to provide additional information to augment or complement the information described in these guidelines.

Validation is defined as the process by which the reliability⁴ and relevance⁵ of a procedure for a specific purpose are established. The test method submission must contain sufficient information for an independent scientific peer review panel to assess the validation status of the proposed test method and for agencies to assess the acceptability of the proposed test method for providing useful information for hazard or risk assessment. Nominations should be accompanied by as much of the requested information outlined in this document as possible. Although there is no mandatory minimum requirement for information to provide with nominations, complete information will expedite ICCVAM consideration of the proposed test method.

The test method nomination or submission to ICCVAM should include:

- An introduction, including the scientific and regulatory rationale for the proposed test method
- Information on the development of the proposed test method protocol and its key components
- Characterization of the substances used for validation studies on the proposed test method
- The reference data used to assess the accuracy and reliability of the proposed test method
- Test method data and results
- An assessment of the accuracy of the proposed test method
- An assessment of the reliability (repeatability/reproducibility) of the proposed test method
- An assessment of test method data quality
- Other scientific reports and reviews pertinent to the proposed test method
- An assessment of animal welfare considerations (refinement, reduction, and replacement)
- Practical considerations (e.g., test method study costs, time needed to perform a study, ease of transferability of the test method among laboratories)
- A comprehensive and complete list of references
- Supporting materials (e.g., the proposed test method protocol) in appendices

⁴*Reliability*: A measure of the degree to which a test method can be performed reproducibly within and among laboratories over time. It is assessed by calculating intra- and inter-laboratory reproducibility and intralaboratory repeatability.

⁵*Relevance*: The extent to which a test method correctly predicts or measures the biological effect of interest in humans or another species of interest. Relevance incorporates consideration of the “accuracy” or “concordance” of a test method.

Nominations and submissions should be submitted to NICEATM in both printed and electronic formats. The preferred software for electronic submission of text is Microsoft® Word and the preferred format for databases is Microsoft® Excel. However, other software programs may be used.

Although ICCVAM recognizes that there may be a need to maintain confidentiality of proprietary information, the designation of materials as confidential is discouraged because this limits an open and transparent evaluation. Submission of adequate and complete information will facilitate the ICCVAM review process. The amount and type of information needed to substantiate the usefulness of a proposed test method for a specified regulatory purpose will vary depending on its nature and its proposed use. An organizational outline to be followed when preparing the nomination or submission is provided in **Appendix A**.

Sponsors and nominators should communicate with NICEATM/ICCVAM throughout the development, prevalidation, and validation process, and during the nomination or submission process. If requested and appropriate, ICCVAM may solicit interagency comments on proposed test method protocols and prevalidation or validation studies. Requests for comment on proposed prevalidation or validation study designs should include descriptions of the scientific basis and regulatory applicability of the proposed test method, the scientific rationale for the proposed prevalidation or validation studies, and responses to each section of the submission guidelines.

The NICEATM office is located at NIEHS, which is headquartered in Research Triangle Park, NC (NIEHS, P.O. Box 12233, MD EC-17, Research Triangle Park, NC 27709; telephone: 919-541-2384; fax: 919-541-0947; e-mail: iccvam@niehs.nih.gov). NICEATM serves as a communication link between test sponsors and Federal agencies during the development and validation process. In collaboration with ICCVAM, NICEATM convenes expert workshops, expert panel meetings, peer review meetings, and expedited peer reviews, and conducts validation studies when appropriate and recommended by ICCVAM.