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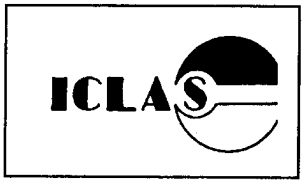

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Implementation of the 3Rs (Refinement, Reduction, and Replacement): Validation and Regulatory Acceptance Considerations for Alternative Toxicological Test Methods

Leonard M. Schechtman

Abstract

Toxicological testing in the current regulatory environment is steeped in a history of using animals to answer questions about the safety of products to which humans are exposed. That history forms the basis for the testing strategies that have evolved to satisfy the needs of the regulatory bodies that render decisions that affect, for the most part, virtually all phases of premarket product development and evaluation and, to a lesser extent, postmarketing surveillance. Only relatively recently have the levels of awareness of, and responsiveness to, animal welfare issues reached current proportions. That paradigm shift, although sluggish, has nevertheless been progressive. New and alternative toxicological methods for hazard evaluation and risk assessment have now been adopted and are being viewed as a means to address those issues in a manner that considers humane treatment of animals yet maintains scientific credibility and preserves the goal of ensuring human safety. To facilitate this transition, regulatory agencies and regulated industry must work together toward improved approaches. They will need assurance that the methods will be reliable and the results comparable with, or better than, those derived from the current classical methods. That confidence will be a function of the scientific validation and resultant acceptance of any given method. In the United States, to fulfill this need, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and its operational center, the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), have been constituted as prescribed in federal law. Under this mandate, ICCVAM has developed a process and established criteria for the scientific validation and regulatory acceptance of new and alternative methods. The role of ICCVAM in the validation and acceptance process and the criteria instituted toward that end are described. Also discussed are the participation of the US Food and Drug Administration (FDA) in the ICCVAM process and that agency's approach to the application and implementation of ICCVAM-recommended methods.

Key Words: 3Rs (refinement, reduction, replacement); alternative toxicological methods; animal welfare; ECVAM (European Centre for the Validation of Alternative Methods); FDA (Food and Drug Administration); ICCVAM (Interagency Coordinating Committee for the Validation of Alternative Methods); regulatory acceptance; validation

Introduction

The idea of the more humane treatment of animals used in science was first given serious consideration less than a half century ago (Russell and Burch 1959), and with it emerged the concept of refinement, reduction, and replacement (3Rs[1]). In the United States, the Animal Welfare Act (AWA[1]) (USDA 1966) was originally drafted to regulate the care and use of laboratory animals, but operationally, it also legislates the treatment of animals used in research and for other purposes. Compliance with the AWA is enforced by regulations and related definitions, standards, and rules of practice governing administrative proceedings applied to the AWA (USDA 1998). As an outgrowth of the AWA and other related legislative directives, the refinement in the way animals are used, with respect to limiting pain and distress, the reduction in the numbers of animals used, and their ultimate replacement for scientific purposes have realized a groundswell of support.

Within the scientific community, fulfillment of the 3Rs paradigm has necessitated a re-evaluation of the extent and manner in which animals are used. Thus, laboratory animal usage proposed for scientific studies now warrants prior consideration of factors such as relevance, ethical concerns, potential benefits, and scientific justification. Furthermore, legal and moral accountability to the principles of the 3Rs has compelled consideration of alternative methods that have the potential to achieve refinement, reduction, and replacement of laboratory animal experimentation.

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[1]Abbreviations used in this presentation: 3Rs, refinement, reduction, replacement of animals used in research and testing; AWA, Animal Welfare Act; ECVAM, European Centre for the Validation of Alternative Methods; EWG, expert working group; FDA, Food and Drug Administration; ICCVAM, Interagency Coordinating Committee on the Validation of Alternative Methods; NICEATM, National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods; NIEHS, National Institute of Environmental Health Sciences; NIH, National Institutes of Health; NTP, National Toxicology Program; OECD, Organisation for Economic Co-operation and Development; PRP, peer review panel; SACATM, Scientific Advisory Committee on Alternative Toxicological Methods.

The ideal situation would be the complete replacement of animals used for scientific and medical evaluations with efficient nonanimal methods that provide comparable or superior results relative to currently used methods and that satisfy the regulatory requirements of the agency to which such data would be provided. Only relatively recently, however, has there been significant progress in the application of alternative test methods in areas previously (and still) dominated by classical tests that use large numbers of animals.

To provide direction to the scientific collective (e.g., test developers, end-users, and regulatory authorities) regarding the availability of alternative methods, their quality and robustness relative to existing methods, their range of utility, their scientific validity and the processes by which to ascertain it, and their regulatory potential, particular authoritative centers and committees have been established both in the United States and in Europe that are dedicated to such issues and to the promotion of alternative methods. Two such specialized organizations are the European Centre for the Validation of Alternative Methods (ECVAM[1]) and, in the United States, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM[1]) (Stokes and Hill 2000). ECVAM was established in 1991 by the European Commission; its main goal is to promote the scientific and regulatory acceptance of alternative methods (Balls and Karcher 1995). ICCVAM operates under the auspices of the US National Institutes of Health (NIH[1]) National Institute of Environmental Health Sciences (NIEHS[1]) National Toxicology Program (NTP[1]); it functions out of the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM[1]). The discussion below focuses on the role of ICCVAM in the implementation of the 3Rs within the US regulatory system.

Genesis and Evolution of ICCVAM

ICCVAM evolved from the ad hoc Interagency Regulatory Alternatives Group in 1994. Members were drawn from different federal agencies that use toxicological testing or data generated by such tests. ICCVAM's initial charge was to formulate recommendations for fulfilling NIEHS mandates under the NIH Revitalization Act of 1993 (Public Law 103-43: NIH 1993), which directed NIEHS to

1. develop and validate improved methods for acute and chronic safety testing, including alternative methods;
2. establish criteria for the validation and regulatory acceptance of alternative methods; and
3. develop processes for the regulatory acceptance of alternative methods.

In 1997, the ad hoc committee was established as a standing committee, and the NICEATM was created in 1998 to serve as the ICCVAM scientific and technical operational center at NIEHS in Research Triangle Park, North Carolina. ICCVAM's responsibility had been broadened to include (1) the administration of a process by which new test methods of interest to federal agencies could be evaluated, and (2) the coordination of interagency issues on the development, validation, acceptance, and national/international harmonization of toxicological test methods. Passage of the ICCVAM Authorization Act of 2000 (Public Law 106-545: ICCVAM 2000) in December of that year established ICCVAM as a permanent body of the NIEHS under the NTP's NICEATM. Public Law 106-545 defines itself as an Act "to establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness." ICCVAM's current composition, as outlined by the Act, consists of 15 federal regulatory and research agencies (Table 1). In addition, the Act allows for any other agency that is involved in the development of tests that use animals, that uses test data derived from such methods, or that regulates on the basis of the use of animals in toxicity testing to participate in ICCVAM.

To advise ICCVAM on scientific, technical, and administrative issues, and on intra- and extramural partnering, leveraging, and collaborations, the Advisory Committee on Alternative Toxicological Methods (ACATM[1]) was formed under a Department of Health and Human Services charter. The ACATM consists primarily of nongovernmental ex-

Table 1 Federal agency composition of the Interagency Coordinating Committee on the Validation of Alternative Methods

Nonregulatory components	Regulatory components
Agency for Toxic Substances and Disease Registry	Consumer Product Safety Commission
Department of Agriculture	Department of Interior
Department of Defense	Department of Transportation
Department of Energy	Environmental Protection Agency
National Cancer Institute	Food and Drug Administration
National Institute of Environmental Health Sciences	Occupational Safety and Health Administration
National Institute for Occupational Safety and Health	
National Library of Medicine	
National Institutes of Health	

perts drawn from such stakeholder sectors as academia, industry, nonprofit research institutes, and public interest groups. In compliance with the Act, the ACATM has been replaced by the NIH-chartered Scientific Advisory Committee on Alternative Toxicological Methods (SACATM[1]).

The Act also clarifies terminology by which ICCVAM meets its objectives and defines an "alternative test method" as one that "includes any new or revised test method that reduces the number of animals required, refines procedures to lessen or eliminate pain or distress to animals, enhances animal well-being, or replaces animals with non-animal systems or one animal species with a phylogenetically lower animal species, such as replacing a mammal with an invertebrate." The Act also establishes what constitutes an "ICCVAM test recommendation"—a positive or negative commentary regarding such parameters as the scientific validity and acceptability of a method that had undergone an independent peer review by a panel of scientific experts. ICCVAM endorsement of a method prompts consideration of its assessment of the method by ICCVAM member agencies for possible applicability and implementation of the method for regulatory purposes.

ICCVAM Goals and Activities

The broad goals of ICCVAM and NICEATM are

1. to encourage the development of new tests and the revision of existing tests, which result in improved methods that use systems of nonanimal origin, that reduce the numbers of animals used, or that minimize pain and distress experienced by animals on test;
2. to promote the scientific validation and regulatory acceptance of new and/or improved alternative test methods, which are more predictive of human health and ecological effects than current methods; and
3. to contribute to improved public health, which results in better risk assessments and reduced injury and disease caused by chemicals.

To accomplish these goals, ICCVAM's efforts have been directed at

- increasing the efficiency and value of the review process performed on test methods by federal agencies;
- minimizing or eliminating unwarranted redundancies associated with method evaluation performed by federal agencies;
- facilitating communication and the exchange of information between federal agencies;
- optimizing the utilization of both intramural and extramural (nongovernmental) expertise in evaluating alternative methods submitted for ICCVAM consideration;
- establishing cogent validation criteria against which the relevance and reliability of a test method would be measured;
- providing guidance on suitable validation studies that need to be conducted;
- ensuring the appropriate validation of new and revised test methods to meet the needs of federal agencies that could make use of such methods; and
- advancing the refinement, reduction, and replacement of animal experimentation and testing where practical and in a manner that maintains scientific credibility and ensures public safety.

Supporting ICCVAM activities, the NICEATM has a number of responsibilities, which include

- providing scientific, technical, and administrative assistance;
- managing and coordinating various committee-related activities;
- coordinating interagency expert working groups and peer review panels and their respective meetings;
- organizing technical workshops, seminars, and training workshops;
- interfacing with test developers and sponsors to help guide them through the submission process;
- evaluating the content of submissions for completeness and compliance with ICCVAM requirements;
- interfacing with federal research and regulatory agencies involved in the ICCVAM process;
- interacting with the scientific advisory committee (ACATM/SACATM) to ICCVAM;
- serving as a conduit between test developers/sponsors, stakeholders, and federal agencies involved in the ICCVAM; and
- assisting in the preparation and publication of ICCVAM reports, technical documents, meeting materials, among others.

In conducting activities to meet its goals, ICCVAM functions as an intermediary between the federal agencies and the test developers and between federal agencies and other national and international organizations involved in ICCVAM-like activities. ICCVAM reviews and evaluates new, revised, or alternative methods that show promise as procedures useful for specific regulatory purposes. In making such determinations, ICCVAM oversees the technical reviews of candidate methodologies and coordinates issues relating to the development, evaluation, validation, and acceptance of test methods that come before the committee. For the most part, those methods considered for evaluation through the ICCVAM process are those of potential multiagency interest. In this respect, the ICCVAM process provides a forum for interagency communication and consensus building. However, when a particular method is considered important, with the potential for widespread regulatory use by a single agency, the method could be a candidate for ICCVAM assessment. ICCVAM also promotes the international harmonization of validated and accepted test protocols that lead to their ultimate adoption

throughout the scientific community, thereby introducing new, modified, and improved toxicity test methods and advancing the refinement, reduction, and replacement of animal testing.

ICCVAM Evaluation Process

The process followed by ICCVAM/NICEATM in assessing a proposed method is illustrated in Figure 1. Typically, there are two principal ICCVAM evaluation stages that the documentation in support of a test method submission encounters: (1) review by an ICCVAM-assembled expert working group (EWG[1]) of government scientists, and (2) an autonomous review performed by an independent expert peer review panel (PRP[1]) drawn primarily from the nongovernmental national and international scientific community of academicians and the private sector. The EWG interfaces with the test developer or sponsor of a method, reviews the contents of a submission, assesses the status of the validation effort put forth, ensures the completeness and organization of the submission, and determines whether the validation and acceptance criteria established by ICCVAM have been addressed. The extent to which the required information has been reported determines whether the sponsor will be asked to furnish additional information to complete the portfolio, or whether there is adequate information provided for the method to advance toward the next evaluation phase of independent scientific peer review.

The independent PRP evaluates the technical and practical aspects of the submission, assessing the validity, utility, limitations, and regulatory applicability of the method, the resultant improvements in the ability to assess risk, and the attention to animal welfare issues. If the panel determines that supplementary information would be useful in its evaluation, it can offer recommendations for the conduct of additional studies as necessary. These studies can further ensure the robustness of the protocol and the sufficiency and quality of the data and can help clarify other technical issues. Through its deliberations, the PRP ascertains the extent to which the ICCVAM criteria for validation and acceptance of methods have been satisfied. The efforts of the PRP result in a consensus determination of the overall validation status of the method, its regulatory relevance, and test method performance. Parameters considered for their evaluation include sensitivity, specificity, variability, reproducibility, transferability, and suitability for international acceptance.

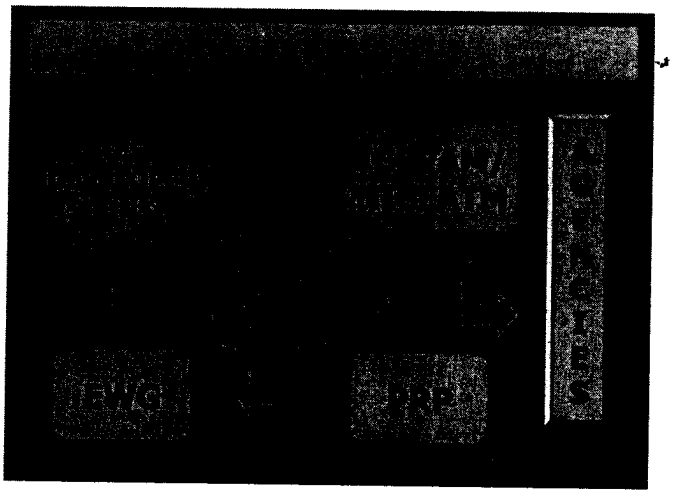

Figure 1 The evaluation process of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). NICEATM, National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods; EWG, expert working group; PRP, peer review panel.

Conclusions and recommendations derived from this EWG/PRP process are reported to ICCVAM, which in turn formulates its recommendations, which are then provided to federal agencies. The ICCVAM recommendations address the validation status of the method, its technical merit, its potential applicability, and its acceptability vis-à-vis its intended purpose. Regulatory agencies, each responding to different regulatory directives and promulgating different statutory requisites, consider the ICCVAM recommendations in the context of their respective regulatory domain and render independent decisions as to the acceptability and applicability of the recommended method. ICCVAM will then coordinate the responses of regulatory agencies regarding the scientific acceptability and likelihood of implementation of methods in compliance with the ICCVAM Authorization Act.

Acceptance of a method and its incorporation into the testing regimen by a regulatory agency triggers a cascade of subsequent implementation actions, which can include such events as (1) notification of end-users regarding the availability of the method; (2) notification of regulators that the method will be incorporated into existing testing requirements; (3) education of regulatory review staff regarding the technical aspects of the method; and (4) revision of existing regulations, guidelines, and/or guidance documents that reflect regulatory adoption of the method. As necessary, and in cooperation with federal agencies, ICCVAM can conduct or facilitate training workshops to train laboratory personnel in the use of the accepted method and to instruct reviewers on interpretation of results.

ICCVAM Guidance

Guidance is provided to test developers regarding the necessary documentation for submission to ICCVAM. This guidance helps to ensure the adequacy of the information and data reported for evaluation and allows for a proper assessment of whether the criteria for validation of alternative methods established by ICCVAM have been satisfied. The guidance provided to test developers seeking an ICCVAM endorsement is made available in two ICCVAM publications: (1) *Validation and Regulatory Acceptance of*

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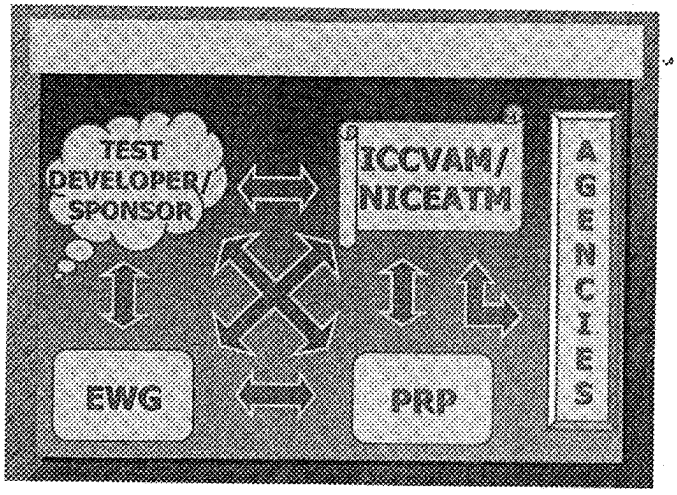

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Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM 1997), and (2) *Evaluation of the Validation Status of Alternative Toxicological Methods: Guidelines for Submission to ICCVAM* (ICCVAM 1999).

The first document, *Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods,* was prepared by the original ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods and was released in 1997. It identifies various stages through which a proposed test method traverses as it evolves from conceptualization to regulatory acceptance. It also provides criteria and guidance for the validation and regulatory acceptance of new and revised toxicological test methods and establishes the processes for regulatory acceptance of validated methods. The recommendations in the ad hoc ICCVAM report are considered by ICCVAM to be broadly applicable to all proposed toxicological testing methods, whether they are original, modifications of existing methods, or alternative methods that could potentially substitute for currently used ones. The guidance was developed by ICCVAM to facilitate the assessment of such methods by federal research and regulatory agencies as well as to increase the probability of the acceptance of appropriately validated methods.

The second document, *Evaluation of the Validation Status of Alternative Toxicological Methods: Guidelines for Submission to ICCVAM,* was prepared by the standing ICCVAM and was released with revision in 1999. Those guidelines were drafted to supplement the 1997 ad hoc ICCVAM report and to be used in concert with it for submitting new, revised, or alternative toxicological methods for consideration by ICCVAM. The guidelines present additional instruction to test developers regarding the organization of information and data necessary for the thorough evaluation of (1) the test method performance and reliability, (2) the current validation status of the method, and (3) responsiveness to animal welfare issues. They provide guidance on the substantive content of a submission needed to assess a test method's current validation status, and that would enable an understanding of the extent to which the validation and acceptance criteria have been addressed or the intended strategies and prospective studies that will address those criteria. Also detailed are the standard outline and basic format for a test method submission, for the concomitant background review document, for describing the rationale for the standardized protocol, for describing the design for the validation studies for methods under development, and for delineating the various phases involved in the validation process. The basis for decisions made regarding standardized protocols and the design of proposed validation studies are also included in the guidelines.

The guidance presented in these two essential ICCVAM documents is shown in Table 2. Although each document was prepared to accomplish a specific objective, the intentional overlap of information presented in these ICCVAM publications underscores their complementary aspect and the importance of using them in concert. Collectively, they provide comprehensive information and guidance that would be necessary for the validation assessment of new, modified, or alternative methods used ultimately for regulatory purposes and directed at refining, reducing, and replacing animal usage for scientific purposes. Furthermore, the considerations described would be useful to test developers, test method sponsors, EWG and PRP reviewers, agency evaluators, and the scientific community at large. Together, the documents offer extensive details regarding

- the method validation process;
- study design for achieving validation;
- criteria for test method validation;
- direction on test method acceptance for regulatory purposes;
- standardization of proposed protocols;
- information/data requirements;
- content and organization of submissions for ICCVAM evaluation; and
- animal welfare considerations.

ICCVAM Prerequisites for Regulatory Use of New Methods

ICCVAM has established a number of basic principles that need to be addressed before any committee recommendations to federal agencies regarding regulatory consideration of a given method. The primary condition is a method must undergo a comprehensive validation assessment. For ICCVAM purposes, the concept of *validation* is that of a process, that is, a systematic and progressive evaluation procedure by which the reliability and relevance of a test method are established for a specific purpose. *Reliability* is a measure of the extent to which a test can be performed reproducibly within and among laboratories over time. *Relevance* is the extent to which a test method will correctly predict or measure the biological effect of interest.

A recommendation by ICCVAM serves as an initial step by a regulatory agency to consider the acceptability of a method for its purposes. As stated in the 1997 ICCVAM report (ICCVAM 1997),

> "Validation is a prerequisite for regulatory acceptance of a new test method, but it is not sufficient. The validation process determines the practicality of a method in terms of its reliability and relevance for a particular application in a given regulatory program. The degrees of reliability and relevance are then considered by the regulatory agency in determining the acceptability of the method."

Acceptance is the determination by regulatory agencies of the acceptability of a method for regulatory risk assessment purposes. It is based on the premise that use of data from the

Table 2 Information, considerations, and guidance available in ICCVAM[a] documents

Validation and regulatory acceptance of toxicological test methods[b]	Guidelines for submissions to ICCVAM[c]
Prevalidation considerations (i.e., intra-/interlaboratory use of a procedure and protocol standardization)	General principles regarding the validation process, the material and format required
The process and planning of validation; components of a validation effort	Introduction and rationale for the proposed test method (mechanistic basis and context)
Validation criteria to be met for regulatory hazard/risk assessment purposes	Proposed test method protocol
Criteria, information/data requirements for regulatory consideration and acceptance of test methods; the regulatory acceptance process	Characterization of materials tested (e.g., chemicals and chemical classes)
Recommended processes for evaluating new and revised methods for regulatory acceptance	Reference data used for performance assessment (comparison of data from proposed method and reference method to be replaced)
Evaluation of test performance	Test method data and results
Issues of test method development, test batteries, and tiered testing strategies	Test method performance assessment (i.e., accuracy, sensitivity, specificity, positive and negative predictivity, false-positive and -negative rates) of the proposed test method compared with the reference test method)
Regulatory review and evaluation of test methods leading to their regulatory acceptance	Test method reliability (repeatability/reproducibility)
Intra- and interagency communication, coordination, and harmonization of the evaluation of proposed test methods	Test method data quality (adherence to good laboratory practice guidelines)
International harmonization of test guidelines	Other scientific reports and reviews on the proposed method (published or unpublished)
Implementation considerations	Animal welfare considerations (refinement, reduction, and replacement)
The ICCVAM Expert Working Group and Independent Peer Review processes	Other considerations (e.g., test method transportability, cost, time, equipment)
Establishment, goals, activities, organization/operation of ICCVAM, and the ICCVAM process	Supporting materials (e.g., relevant publications, unpublished data, nontransformed original data, laboratory notebooks)
Glossary of terms, general information, applicable regulations	General outline for organizing the submitted information

[a]ICCVAM, Interagency Coordinating Committee on the Validation of Alternative Methods.
[b]ICCVAM [Interagency Coordinating Committee on the Validation of Alternative Methods]. 1997. Validation and regulatory acceptance of toxicological test methods: a report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods. NIH publication no. 97-3981. Research Triangle Park: NIEHS. <http://iccvam.niehs.nih.gov/docs/guidelines/validate.pdf>.
[c]ICCVAM [Interagency Coordinating Committee on the Validation of Alternative Methods]. 1999. Evaluation of the validation status of alternative toxicological methods: guidelines for submission to ICCVAM. Research Triangle Park: NIEHS. <http://iccvam.niehs.nih.gov/docs/guidelines/subguide.htm>.

new method will provide a comparable or better level of protection of human health or the environment than the currently used test method (ICCVAM 1997; OECD 1996).

It is important to appreciate that regulatory acceptance of a method does not automatically confer regulatory implementation. A scientifically validated method judged to be technically acceptable may or may not be considered useful for a given agency's regulatory purposes. Thus, although a test may be judged technically adequate for a hazard/safety determination, that method may not be put into practice if it does not relate to the regulatory structure of the governing body, cannot be integrated into its regulatory mandates, or is considered inappropriate for, or inapplicable to, specific products or product classes regulated by a particular agency or regulatory unit.

Explicit criteria have been developed by ICCVAM for both test method validation and test method acceptance for regulatory purposes. These criteria have broad applicability throughout the scientific community in areas of development, evaluation, and application of testing procedures used for risk assessment. Specific validation and acceptance criteria include those listed in Tables 3 and 4, respectively. Detailed descriptions of each of the ICCVAM criteria for test method validation and acceptance appear in the 1997 ICCVAM report (ICCVAM 1997).

There is a degree of overlap between the criteria for

Table 3 ICCVAM[a] criteria and requirements for test method validation[b]

1. Explicit statement of scientific and regulatory rationale and proposed use of method
2. Complete description of the test methodology
3. Biological basis of the method
4. Relationship to the biological effect of interest
5. Formal detailed protocol and related standard operating procedures
6. Reliability (intra- and interlaboratory reproducibility) assessed
7. Relevance (accuracy of predictivity) assessed
8. Performance of test method relative to the standard/classical method in use
9. Strengths and limitations identified and described
10. All data available for review
11. Data quality (quality assurance audit; compliance to good laboratory practices)
12. Independent scientific peer review

[a]ICCVAM, Interagency Coordinating Committee on the Validation of Alternative Methods.
[b]Adapted from ICCVAM [Interagency Coordinating Committee on the Validation of Alternative Methods]. 1997. Validation and regulatory acceptance of toxicological test methods: a report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods. NIH publication no. 97-3981. Research Triangle Park: NIEHS. <http://iccvam.niehs.nih.gov/docs/guidelines/validate.pdf>.

Table 4 Criteria and considerations for test method acceptance[a]

1. Method has undergone an independent scientific peer review
2. Fits into the agency regulatory testing structure
3. Detailed protocol and standard operating procedures available
4. Strengths and limitations specified and described
5. Adequately predicts toxic endpoint of interest
6. Generates data useful for risk/hazard assessment
7. Adequate data available for agency-specified uses
8. Can be used independently or as a component of a test battery or tier
9. Robust and transferable
10. Time- and cost-effective
11. Compatible with similar domestic and international testing approaches
12. Ultimately acceptable for international use
13. Adequate animal welfare consideration (3Rs[b])

[a]Adapted from ICCVAM [Interagency Coordinating Committee on the Validation of Alternative Methods]. 1997. Validation and regulatory acceptance of toxicological test methods: a report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods. NIH publication no. 97-3981. Research Triangle Park: NIEHS. <http://iccvam.niehs.nih.gov/docs/guidelines/validate.pdf>.
[b]3Rs, refinement, reduction, and replacement of animals used in research and testing.

validation and those for regulatory acceptance of alternative methods. This overlap exists because the validation process and many of the basic elements that comprise it (e.g., reliability and relevance) are generally the very same qualifying factors that should be met before consideration and acceptance of a method for regulatory purposes. There are some exceptions to this general principle. For example, methodologies that are specifically designed to examine the underlying mechanistic basis of a test method or the results derived therefrom, or serve to augment or reinforce the information obtained using an accepted procedure, may be used for regulatory purposes without having themselves been subjected to a comprehensive validation process.

Participation of the US Food and Drug Administration (FDA[1]) in the ICCVAM Process

The regulatory and research components of the FDA directly engaged in the ICCVAM effort are illustrated in Figure 2. They include the Office of Regulatory Affairs, the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Center for Devices & Radiological Health, the Center for Veterinary Medicine, the Center for Food Safety & Applied Nutrition, and the National Center for Toxicological Research. One or more delegates representing each of the five different product centers, the Office of Regulatory Affairs, and the National Center for Toxicological Research speak for their respective centers; participate in ICCVAM meetings, working groups, and workshops; and communicate Center positions either directly or through the FDA Principal Liaison to ICCVAM.

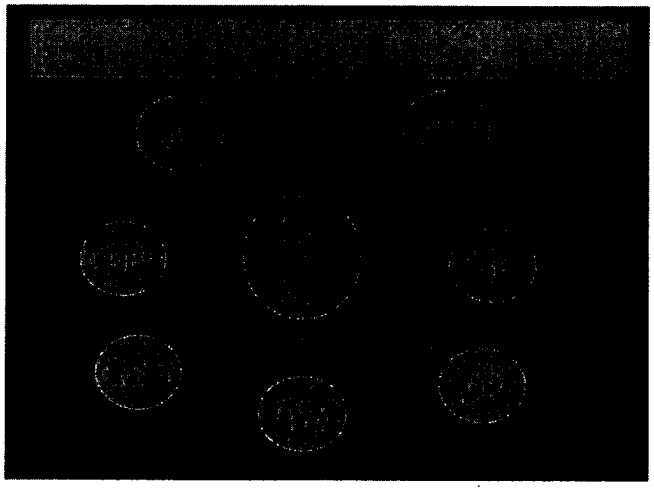

Figure 2 Organizational Components of the US Food and Drug Administration (FDA). ORA, Office of Regulatory Affairs; NCTR, National Center for Toxicological Research; CBER, Center for Biologics Evaluation and Research; CDRH, Center for Devices & Radiological Health; CVM, Center for Veterinary Medicine; CFSAN, Center for Food Safety & Applied Nutrition; CDER, Center for Drug Evaluation and Research.

Table 3 ICCVAM[a] criteria and requirements for test method validation[b]

1. Explicit statement of scientific and regulatory rationale and proposed use of method
2. Complete description of the test methodology
3. Biological basis of the method
4. Relationship to the biological effect of interest
5. Formal detailed protocol and related standard operating procedures
6. Reliability (intra- and interlaboratory reproducibility) assessed
7. Relevance (accuracy of predictivity) assessed
8. Performance of test method relative to the standard/classical method in use
9. Strengths and limitations identified and described
10. All data available for review
11. Data quality (quality assurance audit; compliance to good laboratory practices)
12. Independent scientific peer review

[a]ICCVAM, Interagency Coordinating Committee on the Validation of Alternative Methods.
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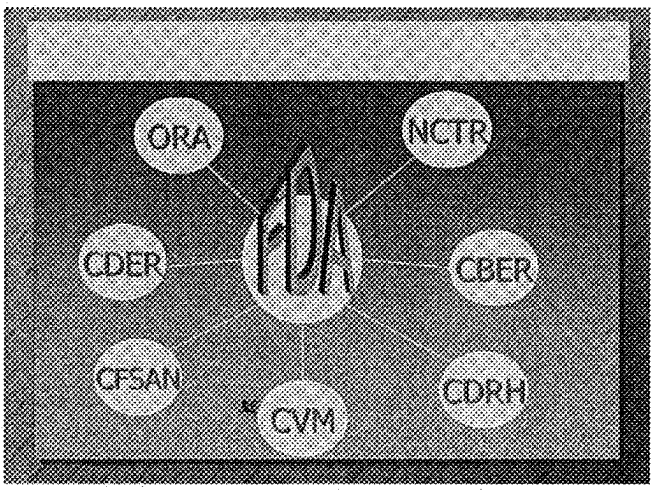

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The FDA process for addressing ICCVAM proposals and responding to ICCVAM test method recommendations is depicted in Figure 3. Completion of an ICCVAM validation effort with a positive outcome allows ICCVAM to advocate use of a method justifiably and to forward its endorsement to member agencies, whereupon an FDA evaluation of the ICCVAM recommendations is initiated. FDA centers and offices review ICCVAM reports and recommendations, evaluate the intended use of a proposed method vis-à-vis the products that fall within their purview, and determine whether the method meets their acceptance parameters. Center/office acceptance of an ICCVAM-recommended test is also based on its scientific merits, validation status, and whether the method provides data comparable with or superior to that derived from the customarily used test. At the conclusion of their evaluation, centers/offices submit independent comments to ICCVAM, addressing both the technical acceptability of the method and test method applicability within their regulatory framework. Applicability of ICCVAM-recommended tests is a center-by-center decision and is based primarily on whether the method is considered appropriate for hazard/risk assessment of the products included in their regulatory domain. The overriding consideration regarding the decision to implement any given method is whether the method satisfies the center's scientific criteria in meeting its regulatory commitment to establish product safety.

FDA Information Dissemination

To ensure knowledge and use of a validated and approved method, its acceptance and implementation is communicated both internally and externally. Notification of intra- and intercenter FDA regulatory units involves education of policy administrators and the regulatory review staff. Scientists are informed of the scientific basis, advantages, limitations, reliability, and relevance of the method as well as its conformity with established regulatory standards and the product review process. If the method was developed to refine or replace an existing test, they are provided information regarding the relative responsiveness of the particular methods. The various notification processes include conducting internal seminars and training courses; holding ICCVAM-sponsored training workshops; participating in technical meetings, conferences, and panels; publishing in the scientific literature; and using intranet web sites. Notification of the public and regulated industry involves publicizing the anticipated use of the new test method as it may apply to a center's testing prescripts and/or regulatory guidances. Availability and application of a new ICCVAM-recommended method are communicated via publications, presentations at open meetings, guidance documents, guidelines, regulations, *Federal Register* announcements, and internet web sites.

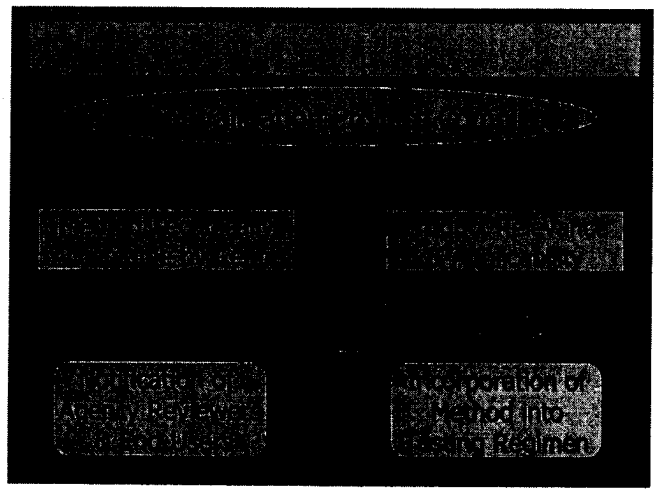

Figure 3 Steps to method implementation. ICCVAM, Interagency Coordinating Committee on the Validation of Alternative Methods.

ICCVAM's Benefits and Challenges

Federal agencies, the scientific community, and the public at large realize a number of direct benefits that are derived from ICCVAM and its national and international activities. Benefits include the following:

1. ICCVAM provides a federal agency-based committee composed of all of the critical relevant and affected research and regulatory agencies;
2. ICCVAM has devised a validation process that is responsive to scientific, regulatory, and public concerns;
3. ICCVAM has established a standardized reliable evaluation procedure for the coordinated, comprehensive, interagency scientific assessment of new, revised, and alternative test methods conducted by acknowledged experts;
4. the ICCVAM paradigm serves as a stimulus for developers/sponsors of methods with potential regulatory application to commit time and resources to the development, characterization, and validation of methods that are responsive to animal welfare considerations and satisfy regulatory needs with respect to their utility for hazard/risk assessment;
5. ICCVAM efforts make available promising test methods with standardized protocols and potential regulatory applicability;
6. ICCVAM has established an efficient vehicle for achieving regulatory consideration, acceptance, and implementation of candidate test methods;
7. The ICCVAM review process has resulted in savings of time and resources by minimizing redundant review efforts and reducing the need for independent agency evaluation of ICCVAM-reviewed methods;
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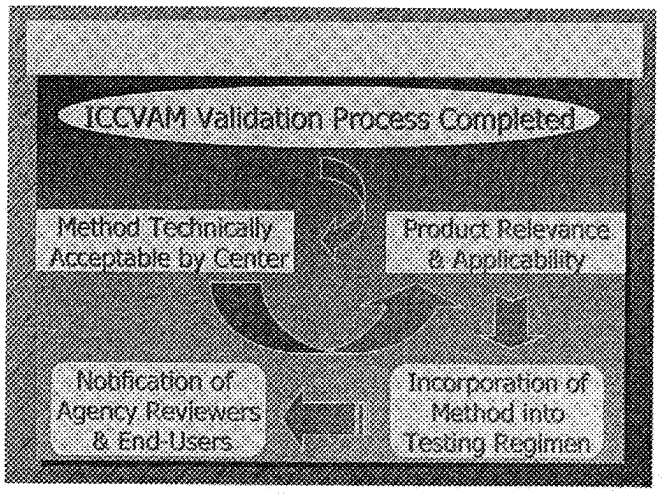

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8. ICCVAM submission guidelines have provided a framework for the generation of a comprehensive information package supporting international adoption of ICCVAM-recommended methods; and

9. ICCVAM is a proponent of animal welfare and champions the refinement, reduction, and replacement of animal use for scientific research and regulatory practices.

With all that ICCVAM has to offer, numerous current and future challenges still remain for the committee and its individual member agencies. As emerging science and new technologies result in an accelerated introduction of new chemical entities and analogues of existing ones, the ramifications for different industries and their regulatory counterparts will have far-reaching economic and health-related effects. For example, in the pharmaceutical industry, such technical advances will affect drug discovery and development, yielding greater numbers of potential drug candidates. As a result, current toxicological practices will be vigorously challenged to keep up with the testing demands imposed. Those demands translate to the need to aggressively develop and validate new and alternative high-capacity test methods for safety assessments, which in turn will affect the volume of product applications that undergo regulatory review.

ICCVAM and NICEATM will need to respond with ever-increasing commitments of their currently limited resources, which will also need to increase substantially to meet the escalating validation and methods review demands, reporting requirements, and national and international obligations. ICCVAM committee activity expansion will be necessary for expert working groups and peer review panels to evaluate the validation status of methods. Increased frequency of workshops, seminars, courses, and forums will be necessary to inform, educate, and train end-users and regulators.

FDA and other participating agencies will need to allocate additional resources (staff, time, funding) from sources already overcommitted and directed elsewhere. Those agencies will be faced with consideration of more and more new/alternative methods judged by ICCVAM to be reliable and relevant and to be potential supplementary or replacement test methods for those currently relied on for regulatory purposes. Agency obligations to acknowledge and consider ICCVAM test recommendations and to respond to ICCVAM within the allowable (180-day) time stipulated by the ICCVAM Authorization Act of 2000 will also increase. Nevertheless, by virtue of their regulatory responsibilities and commitment to public and environmental protection, those agencies will need to maintain the highest scientific standards that ensure product and environmental safety while being responsive to their ICCVAM obligations and to animal welfare issues.

ICCVAM Outlook

FDA's vision for ICCVAM opportunities is multifaceted and involves such prospects as modifying the approaches to methods of procurement, funding of research, and international activities. Currently, ICCVAM has been playing a relatively passive role with respect to attracting test method submissions from sponsors. Typically, test developers seeking opportunities for regulatory application of their methods have come before ICCVAM to present their method proposals and seek evaluation of the method for possible use in a regulatory setting. As one such regulatory agency interested in proven, reliable methods useful in the safety assessment of the products it regulates, FDA envisions a more assertive role for ICCVAM. In this respect, ICCVAM would proactively solicit promising, scientifically credible, new/revised/alternative testing initiatives that are both potentially useful for hazard/risk assessment and responsive to the 3Rs. Funding incentives provided by ICCVAM could take the form of seed money to research institutions (federal and private) to stimulate/support directed research of methods development and validation. Additionally, ICCVAM could provide funding (grants/contracts) to refine and complete research and validation studies for test methods already under development. Such activities would enable ICCVAM to help guide and influence the development and validation of methods of particular interest to federal agencies and to leverage those that show the greatest promise as potential regulatory tools and have the best chance of acceptance.

In addition to these domestic activities, worldwide recognition of ICCVAM also enables it to exploit different international opportunities available through cooperation with analogous associations and directorates abroad, which advocate the validation and implementation of methods that conserve animals that might otherwise be used for experimental purposes. One of the primary organizations with which ICCVAM has been interacting is ECVAM. The association of ICCVAM and ECVAM offers many prospects for future collaborations in areas of mutual interest and the potential for developing greater efficiencies in introducing and validating prospective alternative methods. Examples of opportunities that are currently being explored include the following:

1. partnering to identify areas of commonality in the validation evaluation process;
2. striving to harmonize the respective processes to limit/avoid duplicative efforts;
3. defining a streamlined evaluation process so that a method deemed scientifically validated by one organization will undergo a more abbreviated evaluation by its counterpart;
4. nominating ICCVAM/ECVAM mutually endorsed scientifically validated methods to the Organisation for Economic Co-operation and Development (OECD[1]); and
5. generating OECD test guidelines from ICCVAM/ECVAM-recommended methods for worldwide adoption and application.

By capitalizing on such an interactive arrangement, both ICCVAM and ECVAM can benefit by further strengthening their influence on current and future practices related to the refinement, reduction, and replacement of animals for scientific research and testing. Together, the activities and

decisions of the two organizations will affect all aspects of the 3Rs through methods development, protocol standardization, methods validation, international harmonization and adoption of mutually endorsed test methods, and the ultimate universal regulatory implementation of such methods.

Overall, it is apparent that ICCVAM has evolved into a reputable science-based federal interagency organization whose efforts are of widespread interest and application. In cooperation with the participating regulatory and research agencies, ICCVAM has facilitated and formalized the validation and acceptance processes that are key to the formal adoption and implementation of new, revised, and alternative test methods. The organization has accomplished this work in a manner that maintains the highest scientific standards that fulfill the regulatory mandates to ensure public safety while being responsive to animal welfare issues. Its efforts have resulted in major advances in promoting open lines of communication between industry, public interest groups, and the federal government. As a result, an efficient mechanism has been established by which test developers and proponents of the regulatory use of alternative methods can engage in a dialogue and interact with federal regulatory and research agencies interested in leveraging promising current and pending testing initiatives. For additional information on ICCVAM/NICEATM, relevant guidelines and regulations, documents and publications, and the test methods assessed or under consideration, the reader is referred to the ICCVAM/NICEATM web site at <http://iccvam.niehs.nih.gov>.

Acknowledgment

The author wishes to thank Dr. William S. Stokes, Director, NICEATM, for valuable ICCVAM- and NICEATM-related information.

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