Regulatory Acceptance

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Regulatory acceptance (RA) is the formal adoption of a validated test method by a regulatory agency/authority. Principles and criteria for the regulatory acceptance of new or revised toxicological test methods were developed simultaneously with validation criteria by the Organisation for Economic Cooperation and Development (OECD) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). An important reason for this synchrony is that the requirements for regulatory acceptance should also be considered during the design and conduct of the validation study. The validation authorities have emphasized the importance of the involvement of regulatory authorities in all stages of the validation process.

The following are examples of regulatory acceptance criteria (OECD, 2005, p. 48):

- Test method and validation study data should have been subjected to a transparent and independent peer review process
- Test method should generate data useful for hazard/risk assessment purposes
- Submitted test method and data should adequately cover a spectrum of chemicals and products representative of those overseen by the regulatory authority for which the method is proposed
- Applicability and limitations of the test method should be clearly described
- Test method should be time and cost effective and likely to be used in a regulatory context

The OECD Approach

The OECD's approach to test method acceptance is described in its *Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment* (OECD, 2005). Validated test methods can be submitted to the OECD for formal adoption as an OECD Test Guideline (TG).

The OECD seeks to promote the "harmonization of international regulatory acceptance of adequately validated test methods" (OECD, 2005). The OECD notes that regulatory acceptance practices differ by country and even among agencies within a particular country, so acceptance by one authority does not indicate universal acceptance. Regulatory authorities may accept a test that has not undergone formal validation, or they may not accept a test that has undergone formal validation. The OECD provides guidance on *international* regulatory acceptance for its member countries, and encourages worldwide mutual acceptance of data.

According to the OECD, formal validation "contributes strongly to the international acceptance of any proposed test method" however, validation in not a requirement for the development of a

method as a TG (OECD, 2005). The OECD recommends that the acceptance of any test method in the absence of validation should be accompanied by a written justification.

An unusual approach to test method acceptance without formal validation took place for *in vitro* dermal absorption. European industry submitted in-house performance data to the OECD, and after peer review and international discussions, an OECD TG for *in vitro* dermal absorption testing was adopted (Liebsch & Spielmann, 2002).

The ECVAM Approach

One of the primary roles of the European Centre for the Validation of Alternative Methods (ECVAM) is to "initiate the progression of scientifically validated methods toward regulatory acceptance" (Worth & Balls, 2001). ECVAM provides guidance on regulatory acceptance through their workshops and publications, ensures publication of validation studies, provides access to the test method protocols and standard operating procedures (SOPs), and facilitates the adoption of validated methods by including the OECD acceptance principles and criteria as part of their test method review.

EU policy supports the adoption of validated test methods. Article 7.2 of the Council Directive 86/609/EEC states that "an experiment shall not be performed if another scientifically satisfactory method of obtaining the result sought, not entailing the use of an animal, is reasonably and practicably available" (Anon, 1986).

Following the issuance of an ECVAM Scientific Advisory Committee (ESAC) statement on the validity of a new test method, the Chemical Substances Unit of the Environment Directorate General (DG) communicates the ESAC statement to other Commission Services and to outside organizations such as the European Union (EU) Competent Authorities, OECD, and ICCVAM. The other Commission Services may accept and/or endorse the ESAC statement, suggest further study, or request clarification (Worth & Balls, 2001). The Commission Services then coordinate discussions with EU authorities that make the acceptance decision. ESAC members disseminate information to regulatory authorities in their respective countries. When requested, ECVAM participates in the drafting of test guidelines for the EU or OECD.

The first success story for regulatory acceptance of an *in vitro* test method in the EU occurred in 2000 with the adoption of several *in vitro* methods that had been validated by ECVAM: the 3T3 neutral red uptake phototoxicity (3T3 NRU PT) test; the EpiSkin™ skin corrosivity test; and the EpiDerm™ skin corrosivity test. OECD TGs were developed for all of these methods.

Alternative test methods accepted by one or more EU authority following ESAC's endorsement are listed in AltTox's table of *Validated/Accepted Alternative Methods*.

The NICEATM-ICCVAM Approach

The regulatory acceptance criteria established by ICCVAM are described in the 1997 guidance document, *Validation and Regulatory Acceptance of Toxicological Methods: A Report of the ad*

hoc Interagency Coordinating Committee on the Validation of Alternative Methods (NIEHS, 1997, p. 22). This document also contains regulatory acceptance process recommendations (p. 22-25), and describes some of the barriers to getting new methods accepted (p. 45-46).

"Validated test methods are not automatically accepted by regulatory agencies; they need to fit into the regulatory structure" (NIEHS, 1997, p.22). Following the scientific peer review of a new or revised toxicological test method and ICCVAM's endorsement of its validity, the peer review panel's evaluation and ICCVAM's recommendations are forwarded to relevant federal agencies for their consideration. Each agency determines whether to adopt the validated method (NICEATM-ICCVAM, 2007).

NICEATM-ICCVAM supports regulatory acceptance by stipulating the publication of validation study results, providing peer review documents and test protocols on the ICCVAM website, and encouraging and providing opportunities for interaction among stakeholders and involvement of regulators throughout the development to acceptance spectrum. ICCVAM also works collaboratively on relevant programs with other international authorities such as ECVAM and the OECD.

The first success story for regulatory acceptance of an *in vitro* test method in the US occurred in 2000 with the adoption of the Corrositex® assay, an *in vitro* method for assessing skin corrosivity potential that had been assessed as scientifically valid by ICCVAM in 1999. The OECD TG 435 was later adopted for this method.

The ICCVAM website provides information on the status of US regulatory acceptance for each test method it has reviewed and endorsed. They also provide a summary table on *Regulatory Acceptance of Alternative Toxicological Methods: United States, 1998-2008*.

Alternative test methods accepted by one or more US agency following ICCVAM's endorsement are listed in AltTox's table of *Validated/Accepted Alternative Methods*.

Stakeholder Programs to Promote Regulatory Acceptance

TestSmart: TestSmart was developed to promote the application of alternative test methods in the high production volume (HPV) chemicals screening program. The Screening Information Data Set (SIDS) is a series of toxicological tests recommended by the OECD for screening HPV chemicals. Alternatives to some of the tests in the SIDS were examined by academic, industry, and regulatory agency scientists and classified according to their readiness for use (Green, *et al.*, 2001). This approach helped scientists and regulators assess the stage of alternative methods readiness for testing HPV chemicals and identified areas where specific work could lead to reductions in animal testing.

European Partnership for Alternative Approaches to Animal Testing (EPAA): EPAA is a partnership between the European Commission, companies, and industry trade associations to promote the validation and acceptance of alternative test methods within the EU. Current

approaches to regulatory acceptance were the topic of EPAA's 2007 Annual Meeting on November 5, 2007 entitled *Regulatory Acceptance and Implementation of 3R Approaches*.

Regulatory Authority's Expertise

Information on the procedures and successes in adopting new toxicological test methods at various regulatory agencies/authorities is particularly beneficial in facilitating the development, validation, and regulatory acceptance of new alternative methods. Scientists at regulatory agencies are expected to be the leading experts on how to promote the regulatory acceptance of new test methods and how to incorporate their use into the regulatory decision-making processes.

There are a number of publications by regulatory scientists that describe the uses, adoption, processes, and/or policy for alternative test methods for regulatory purposes within their agencies (Carere, *et al.*, 2002; Gauthier, 2002; Hofer, *et al.*, 2004; Indans, 2002; Jaworska, *et al.*, 2003; Louekari, *et al.*, 2006; Ohno, 2002; Richmond, 2002; Schechtman, 2002; Sterling & Rispin, 2002). AltTox.org encourages regulatory agency representatives interested in submitting a Way Forward commentary on this topic for posting on AltTox.org to contact info@www.alttox.org.

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