The Japanese Center for the Validation of Alternative Methods (JaCVAM): Recent ICATM Contributions and Future Plans

Hajime Kojima

Japanese Center for the Validation of Alternative Methods (JaCVAM), National Institute of Health Sciences (NIHS), Japan

Summary

In November 2005, the Japanese Center for the Validation of Alternative Methods (JaCVAM) was established at the National Center for Biological Safety and Research affiliated with the National Institute of Health Sciences (NIHS) in Japan. JaCVAM's mission is: 1) to ensure that new or revised tests are validated, peer reviewed, and officially accepted by the regulatory agencies; and 2) to harmonize international alternatives to animal testing through participation in the International Cooperation on Alternative Test Methods (ICATM). Here, JaCVAM is making steady progress in validation and peer reviewed studies under the ICATM framework.

Keywords: validation, peer review, alternative, Japanese Center for the Validation of Alternative Methods (JaCVAM)

In November 2005, the Japanese Center for the Validation of Alternative Methods (JaCVAM)[1] was established at the National Center for Biological Safety and Research affiliated with the National Institute of Health Sciences (NIHS) in Japan. JaCVAM's mission is to facilitate the 3Rs (Reduction, Refinement and Replacement) with regard to animal testing, with special priority in Japan given to reduction and replacement. Specifically, the key objectives of JaCVAM are:

1) To ensure that new or revised tests are validated through comparison with domestically developed or internationally certified standard tests, peer reviewed, and officially accepted by the regulatory agencies.
2) To work towards harmonization of international alternatives to animal testing. Each validation center has signed a Memorandum of Cooperation with the International Cooperation on Alternative Test Methods (ICATM[2]). Countries and regions participating in ICATM include JaCVAM; the European Center for the Validation of Alternative Methods (ECVAM[3]); the United States NTP Interagency Center for the Evaluation of Alternative Toxicological Methods/Interagency Coordinating Committee on the Validation of Alternative Methods (NICEATM/ICCVAM[4]); Health Canada; and, as of March 2011, the Korean Center for the Validation of Alternative Methods (KoCVAM[5]). Under the ICATM framework, JaCVAM expects to experience more efficient test validation and review, as well as more rapid national and international acceptance of scientifically valid methods.

In the six years that JaCVAM has been active, seven methods have been accepted by the JaCVAM regulatory acceptance board, including: 1) the bovine corneal opacity and permeability (BCOP) test for identifying ocular corrosives and severe irritants; 2) the isolated chicken eye (ICE) test for identifying ocular corrosives and severe irritants, 3) the local lymph node assay (LLNA): DA, a non-radioactive modification to the LLNA, which quantifies adenosine triphosphate (ATP) content via bioluminescence as an indicator of lymphocyte proliferation; 4) the LLNA:BrdU-enzyme linked immunosorbent assay (ELISA), a non-radioactive modification to the LLNA test method, which utilizes non-radiolabelled 5-bromo-2-deoxyuridine (BrdU) in an ELISA-based test system to measure lymphocyte proliferation; 5) the Reconstructed Human Epidermis Test Method, EPISKIN for *in vitro* skin irritation testing; 6) the Human Skin Model Test, Vitrolife-Skin, EpiDerm for *in vitro* skin corrosion testing; and 7) an *in vitro* cytotoxicity test for estimating starting doses for acute oral systemic toxicity tests.

In February 4, 2011, the Ministry of Health, Labor and Welfare of Japan was notified that data obtained with alternative testing methods approved by the JaCVAM Steering Committee could be used for the submission of quasi-drug applications or for petitions to include ingredients in the Standards for Cosmetics. Therefore, JaCVAM decided to accelerate new *in vitro* testing methods to take advantage of this opportunity to strongly impact testing throughout Japan. Accordingly, JaCVAM is currently coordinating the validation studies and peer review of several tests

[1] http://jacvam.jp/

[2] http://iccvam.niehs.nih.gov/about/icatm.htm

[3] http://ecvam.jrc.ec.europa.eu/

[4] http://iccvam.niehs.nih.gov/

[5] http://www.nifds.go.kr/nitr/contents/m91100/view.do

Tab. 1: On-going test methods at JaCVAM under the ICATM framework

No.	Test method	Stage		
		Validation	Peer review	Regulatory acceptance
1	Comet assay (*in vivo* & *in vitro*)	On-going		
2	Stably Transfected Transactivation Assay (STTA)	On-going		
3	human Cell Line Activation Test (hCLAT)	ECVAM on-going		
4	Phototoxicity testing, ROS (Reactive Oxygen Species) assay	On-going		
5	Eye irritation testing, SIRC assay	On-going		
6	IL-8 Luc assay	On-going		
7	Balb 3T3 cell transformation assay	Pre-validation finished	ESAC finished	
8	Bhas cell transformation assay	Validation finished	JaCVAM (in preparation)	
9	Eye irritation testing, STE (Short Time Exposure) assay	Validation finished	ICCVAM (in preparation)	
10	*In vitro* Skin irritation assay LabCyte EPI-Model	Validation finished		OECD on-going

(Tab. 1). Most of the tests are for the safety assessment of cosmetic ingredients and/or products. The methods currently undergoing national or international peer review include the Bhas cell transformation assay and the short time exposure (STE) assay for eye irritation testing. Additionally, JaCVAM is participating, along with several other international collaborators, in ongoing validation studies, which include the human cell line activation test (h-CLAT), *in vivo*/*in vitro* Comet assays, the stably transfected transactivation assay (STTA) antagonist test for screening of endocrine disruptors, and an assay for phototoxicity.

Particularly notable are JaCVAM's efforts towards the validation, nearly complete, of the *in vivo*/*in vitro* Comet assay, which has been in development since 2006. The last International Validation Management Team meeting took place in September 2011 in Kyoto. JaCVAM is also working on validation studies of the STTA antagonist assay and a reactive oxygen species (ROS) assay for phototoxicity testing, which is based on the hypothesis that ROS may induce photochemical or toxic reactions. It is expected that the STTA antagonist assay will be included as an additional element in OECD TG 455: the Stably Transfected Human Estrogen Receptor-alpha Transcriptional Activation Assay for Detection of Estrogenic Agonist-Activity of Chemicals (OECD, 2005). The high throughput ROS assay is under development, and the corresponding validation study is projected to be completed by December 2011. JaCVAM has also begun validation studies of *in vitro* immunotoxicity assays.

To facilitate regulatory acceptance of the skin sensitization assay IL-8 Luc assays, JaCVAM is making steady progress in validation and peer reviewed studies under the ICATM framework.

Reference

OECD (2005) Series on testing and assessment Number 34, Guidance document on the validation and international acceptance of new or updated test methods for hazard assessment, ENJ/JM/MONO(2005) 14 Institute of Environmental Health Sciences (NIEHS).

Correspondence to

Hajime Kojima, PhD
Japanese Center for the Validation of Alternative Methods (JaCVAM)
National Institute of Health Sciences (NIHS), Japan
1-18-1 Kamiyouga, Setagaya-ku
158-8501 Tokyo, Japan
Phone/Fax: +81 3 3700 9874
e-mail: h-kojima@nihs.go.jp