Activities updates on alternative methods from international validation centers

Japanese Activity Update

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JaCVAM, NIHS, Japan

JaCVAM: Japanese Center for the Validation of Alternative Methods

This Center was established at the National Institute of Health Sciences (NIHS) in Japan, 2005 by the Ministry of Health, Labour and Welfare (MHLW).

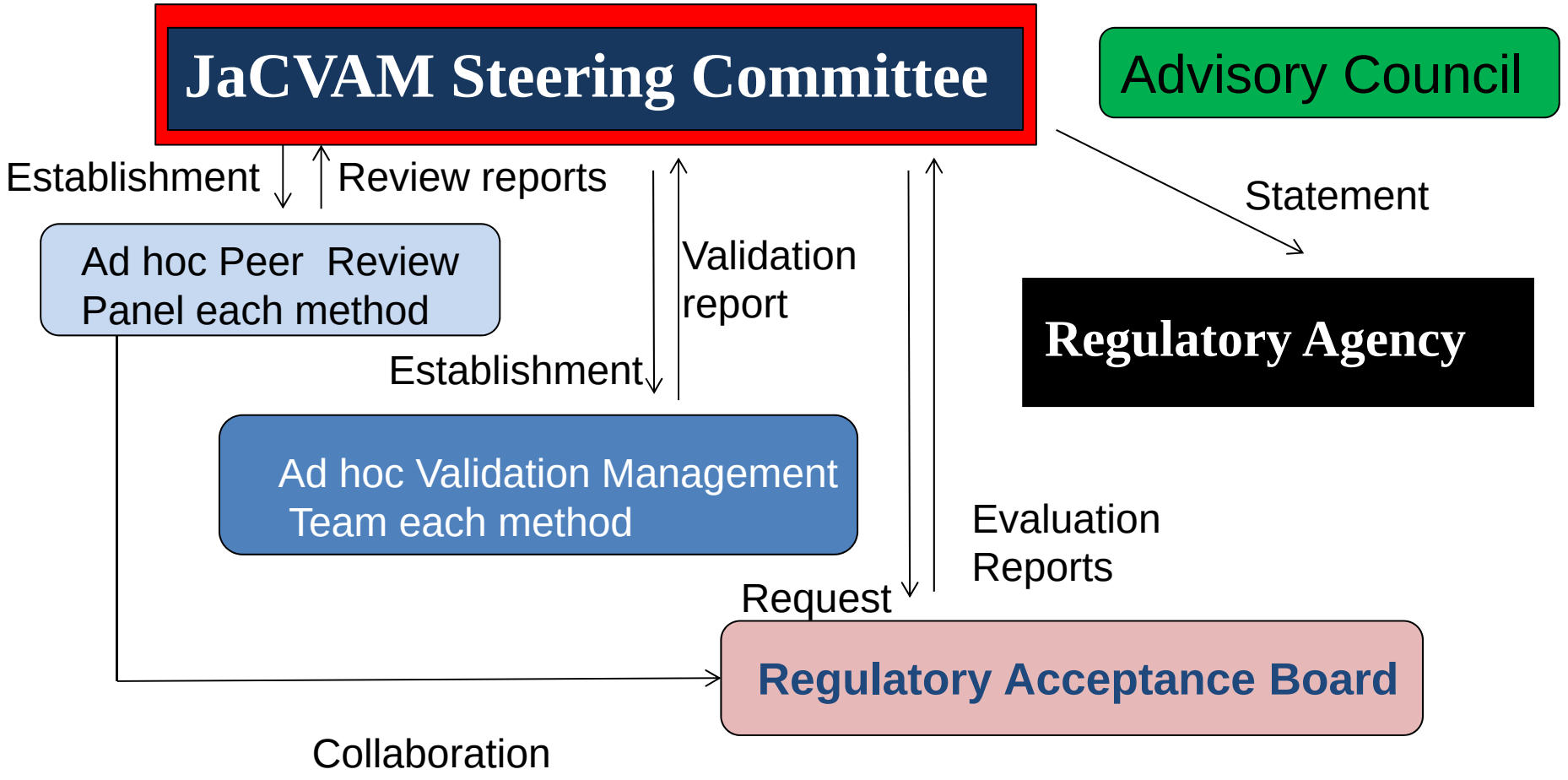
JaCVAM's Goals

- To promote the 3Rs in animal experiments for the evaluation of chemical substance safety in Japan.
- To establish guidelines for new alternative experimental methods through international collaboration.

JaCVAM roles

- JaCVAM assesses the utility, limitations, and suitability for use in regulatory studies of test methods for determining the safety of chemicals and other materials and also performs validation studies when necessary. In addition, JaCVAM cooperates and collaborates with similar organizations in related fields, both in Japan and internationally.
- JaCVAM activities are also beneficial to application and approval for the manufacture and sale of pharmaceutical chemicals, pesticides and other products as well as to revisions to standards for cosmetic products.

Organization of JaCVAM since April, 2011



JaCVAM Steering Committee

Akiyoshi Nishikawa	Director, Biological Safety Research Center, National Institute of Health Sciences
Toru Kawanishi	Director General, National Institute of Health Sciences
Jun Kanno	Division of Cellular and Molecular Toxicology, National Institute of Health Sciences
Yuko Sekino	Division of Pharmacology, National Institute of Health Sciences
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Akihiko Hirose	Division of Risk Assessment, National Institute of Health Sciences
Atsuya Takagi	Animal Care Section, Division of Cellular and Molecular Toxicology, National Institute of Health Sciences
Hajime Kojima	Division of Risk Assessment, National Institute of Health Sciences
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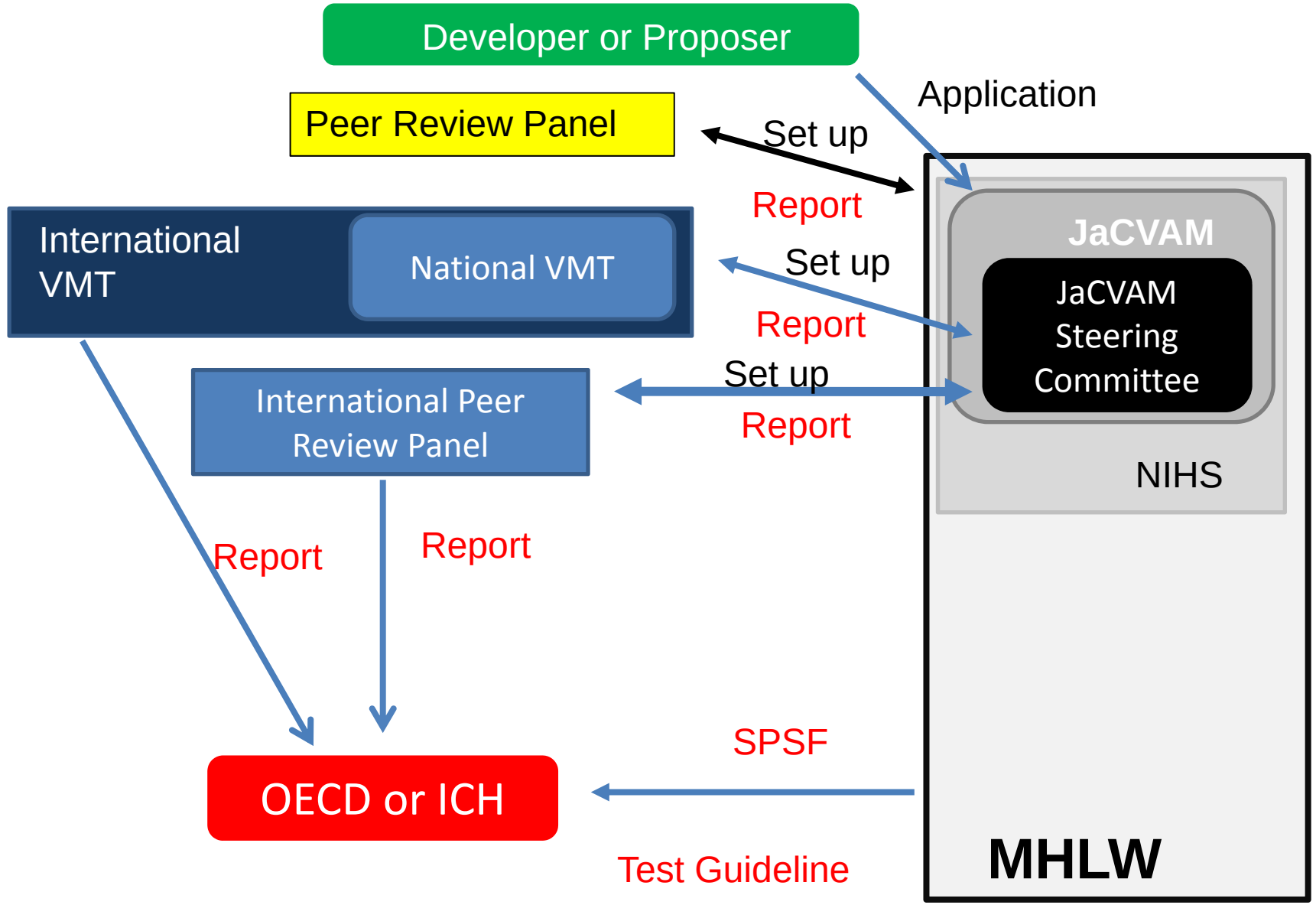
Masaaki Tsukano	Office of Chemical Safety, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Mitsuru Hida	Office of Chemical Safety, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Takatoshi Nakamura	Office of OTC/Genetic Drugs, Pharmaceuticals and Medical Devices Agency
Kazutoshi Shinoda	Expert, Pharmaceuticals and Medical Devices Agency

NIHS JaCVAM

To develop new alternative experimental methods through international collaboration



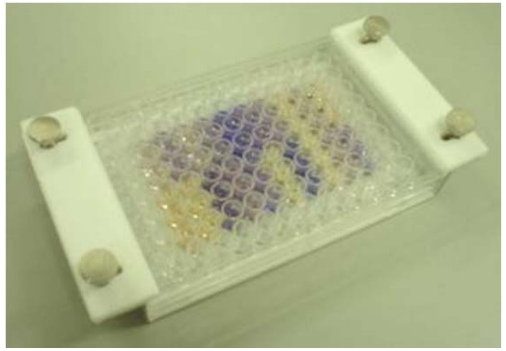
Japanese System for a new or revised test method

ICH guideline

ICH HARMONISED TRIPARTITE GUIDELINE

Guideline on Photosafety Evaluation of Pharmaceuticals S10 (Step 4 Version: 2013)

ROS (Reactive oxygen species) assay including superoxide anion and singlet oxygen approved in the guideline.



OECD Test Guidelines developed by Japan

- Skin sensitization assay, LLNA：DA, TG 442A (2010)
- Skin sensitization assay, LLNA：BrdU-ELISA , TG 442B (2010)
- Skin irritation assay with LabCyte EPI-MODEL 24, TG 439 (2013)
- *In vivo* comet assay TG 489 (2014)

✓ Performance-based Test Guideline for stably transfected transactivation *in vitro* assays to detect estrogen receptor agonists and antagonist, Revised TG 455 (2015)

✓ Short time exposure (STE) assay for eye irritation testing TG490 (2015)

Draft Test Guideline proposed by Japan in the OECD Work Plan

- ✓ Bhas 42 cell transformation assay → To Guidance Document (GD)
- ✓ Short time exposure (STE) assay for eye irritation testing
- ✓ h-CLAT assay for skin sensitization testing
- ✓ IL-8 Luc assay for skin sensitization testing
- ✓ Stable transfected transcriptional activation (STTA) antagonist assay for endocrine disruptor screening
- ✓ Stable transfected transcriptional activation (STTA) assay for androgen disruptor screening (AR-Ecoscreen)

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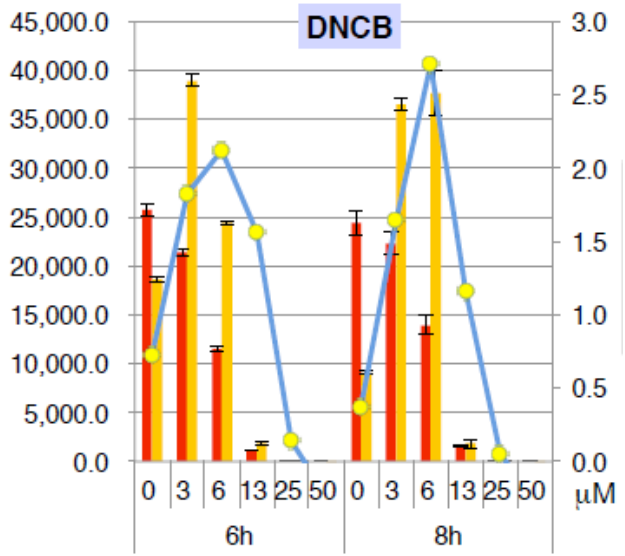
Japan organized on-going International peer review

1. SIRC-CVS assay for eye irritation tesitng by JaCVAM
2. IL-8 Luc assay
   for skin sensitization
   by JaCVAM

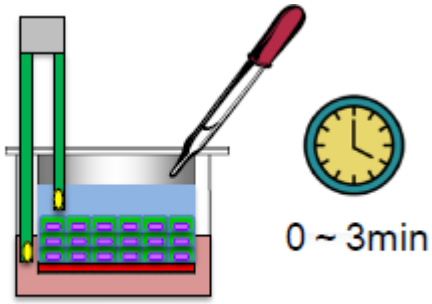


3. Stable transfected transcriptional activation (STTA) assay for androgen disruptor screening (AR-EcoScreen) supported by OECD VMG-NA

NIHS JaCVAM

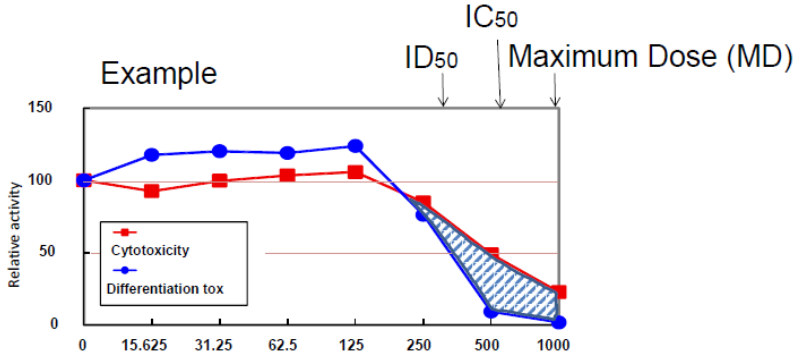
Japan organized on-going International validation studies using coded chemicals

1. Vitrigel-EIT for eye irritation tesitng (supported by MAFF)



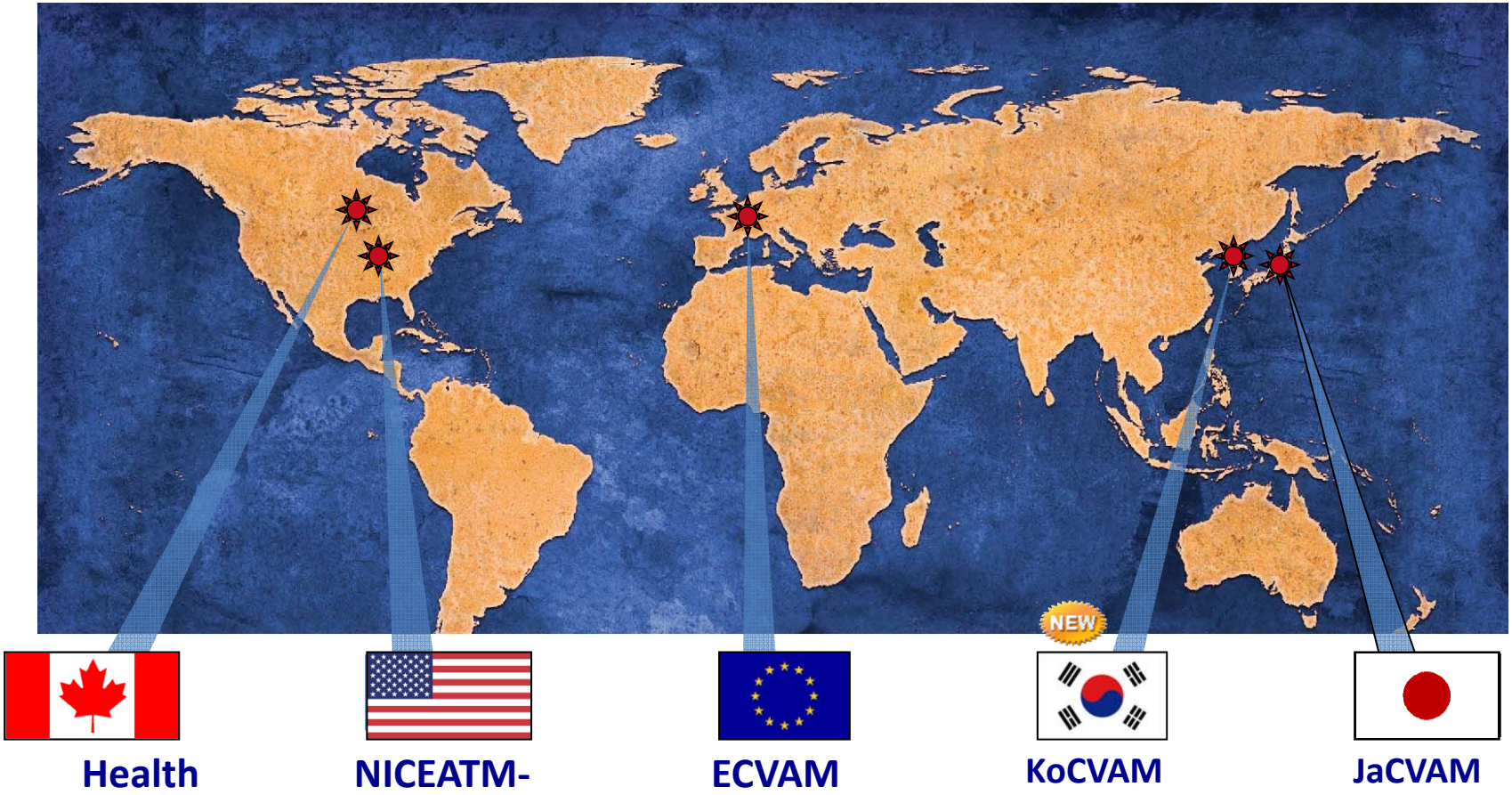
Chemical exposure experiment

2. Hand-1 Luc EST for developmental screening (supported by METI)



ICATM

ICATM is a **voluntary** international cooperation of national organizations: Canada, the European Union, Japan, South Korea, and the United States.



Japanese developed test methods and regulatory acceptance

No.	Test methods	Alternative field	Validation	Peer review	Test guideline
1	Comet assay	Genotoxicity	JaCVAM	OECD expert	OECD TG489
2	ER-STTA antagonist	Endcrine distrupter	CERI, NIHS, NICEATM	OECD VMG-NA	OECD TG455
3	AR-EcoScreen		NIHS	OECD VMG-NA	OECD work plan
4	LabCyte EPI-MODEL	Skin irritation	JaCVAM	OECD	OECD TG439
5	ROS assay	Ptototoxicity	JaCVAM	JaCVAM	ICH S10
6	STE test method	Eye irritation	JSAAE, JaCVAM	ICCVAM	OECD TG490
7	SIRC-CVS		JaCVAM	JaCVAM	
8	Vitrigel-EIT		JaCVAM		
9	LLNA：DA	Skin sensitisation	JSAAE	ICCVAM	OECD TG442A
10	LLNA：BrdU-ELISA		JSAAE	ICCVAM	OECD TG442B
11	h-CLAT		EURL ECVAM	ESAC	OECD work plan
12	IL-8 Luc assay		JaCVAM	JaCVAM	OECD work plan
13	Hand-1 Luc assay	Developmental toxicity	JaCVAM		
14	Balb assay	Cell transformation	EURL ECVAM	ESAC	
15	Bhas42assay		JaCVAM	ESAC	OECD Guidance document

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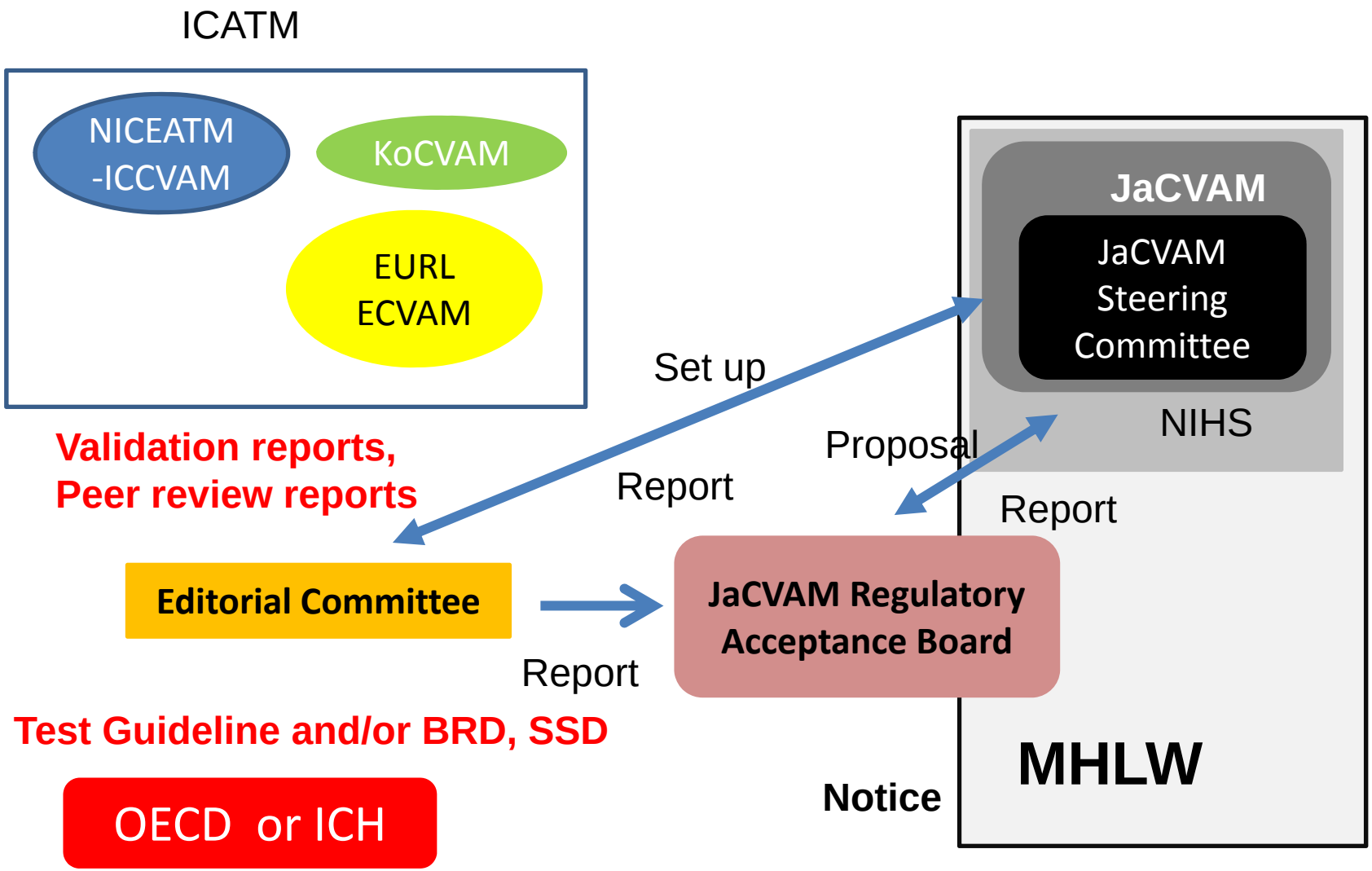
International collaboration

International validation and peer review by Japanese developed test methods

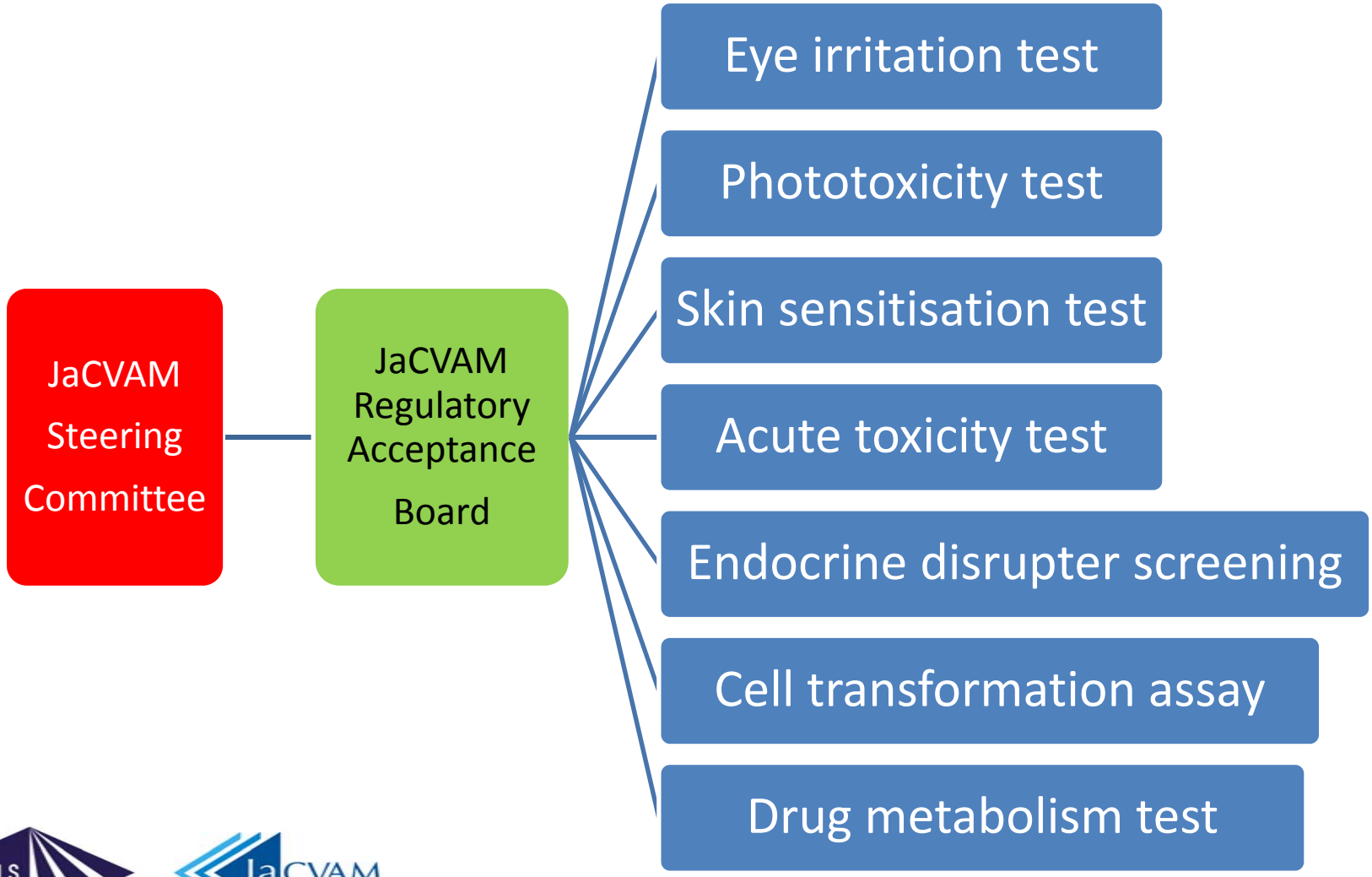
No.	Test methods	Alternative field	Validation				Peer review				
			EURL ECVAM	NICEATM/ICCVAM	KoCVAM	JaCVAM/NIHS	OECD	EURL ECVAM	NICEATM/ICCVAM	KoCVAM	JaCVAM/NIHS
1	Comet assay	Genotoxicity	○	○		◎	◎				
2	ER-STTA antagonist	Endcrine distrupter		○/◎	○	◎/○	◎				
3	AR-EcoScreen				○	◎	◎				
4	LabCyte EPI-MODEL	Skin irritation				◎	◎				
5	ROS assay	Ptototoxicity	○	○		◎		○	○	○	◎
6	STE test method	Eye irritation				◎		○	◎		○
7	SIRC-CVS			○		◎		○	○	○	◎
8	Vitrigel-EIT		○	○	○	◎					
9	LLNA：DA	Skin sensitisation				◎			◎		
10	LLNA：BrdU-ELISA					◎			◎		
11	h-CLAT		◎			○		◎		○	
12	IL-8 Luc assay		○	○	○	◎		○	○	○	◎
13	Hand-1 Luc assay	Developmental toxicity	○	○	○	◎					
14	Balb assay	Cell transformation	◎			○		◎			
15	Bhas42assay		○	○		◎		◎			

Beneficial to application and approval for regulatory use



Regulatory acceptance system in JaCVAM

JaCVAM editorial committees



OECD TG work plan and activity of JaCVAM editorial committee

OECD work plan

- Establishment of an editorial committee (including academia, industries, governmental Institutes)

Expert meeting

- Delegate to attend the meeting
- Communication with the editorial committee

Commenting round

- Corresponding to draft TG
- Start drafting evaluation report

TG

Evaluation of the test method based on TG, validation report, peer review report and back ground review document

NIHS JaCVAM

On-going methods by the JaCVAM regulatory acceptance board

- Eye irritation — Cytosensor Microphysiomether, STE(TG490), EpiOcular(TG491)
- Skin sensitization — KeratinoSense (TG442D), h-CLAT
- Genotoxicity — *In vitro* mammalian assay (TG437, TG488)
- Cell transformation — SHE assay(GD), Bhas assay (GD)
- Phototoxicity — ROS assay (ICH S10)
- Acute toxicity — 3T3 NRU assay
- Drug metabolism — Biotransformation assay
- Endocrine disrupter screening — ER-STTA(TG455)

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JaCVAM Regulatory Acceptance Board

Yasuo Ohno	Kihara Memorial Yokohama Foundation for the Advancement of Life Sciences	
Akiyoshi Nishikawa	Director, Biological Safety Research Center, National Institute of Health Sciences	
Hiroko Tanigawa	Japanese Society for Alternatives to Animal Experiments	Academia
Eiji Maki	The Japanese Society of Immunotoxicology	
Takeshi Morita	The Japanese Environmental Mutagen Society	
Hiroo Yokozeki	Japanese Society for Dematoallergology and Contace Dermatitis	
Takemi Yoshida	The Japanese Society of Toxicology	
Yumiko Iwase	Japan Pharmaceutical Manufacturers Association	Industries
Kazuhiro Kaneko	Japan Chemical Industry Association	
Mariko Sugiyama	Japan Cosmetic Industry Association	
Naofumi Iizuka	Pharmaceuticals and Medical Devices Agency	Regulator
Kazutoshi Shinoda	Pharmaceuticals and Medical Devices Agency	
Takashi Yamada	National Institute of Technology and Evaluation	
Yoshiaki Ikarashi	Division of Environmental Chemistry, National Institute of Health Sciences	
Midori Yosida	Division of Pathology, National Institute of Health Sciences	
Isao Yoshimura	Tokyo University of Science	

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Accepted methods by the JaCVAM regulatory acceptance board by 2015

No.	Test Method
1	*In vitro* skin corrosion testing: Vitrolife-Skin, EpiDerm
2	The bovine corneal opacity and permeability (BCOP) test method
3	The isolated chicken eye (ICE) test method
4	Fluorescein leakage (FL) test methods for identifying ocular corrosives and severe irritants
5	Skin sensitization assay, LLNA：DA
6	The revised acute eye irritation / corrosion
7	Skin sensitization assay, LLNA：BrdU-ELISA
8	Skin sensitization assay, rLLNA
9	*In vitro* skin irritation testing: Episkin, EpiDerm, SkinEthcs, LabCyte EPI-MODEL
10	*In vitro* skin absorption assay
11	Utilization of cytotoxicity test for acute oral toxicity testing
12	BG1Luc estrogen receptor transactivation test method for identifying estrogen receptor agonists and antagonists
13	In chemico directive peptide binding Aasay (DPRA) for skin sensitization

MWLW Administrative Notices

- JaCVAM could be used for the submission of quasi-drug applications, or for petitions to include ingredients in the Standards for Cosmetics in 2011.
- MHLW Evaluation and Licensing Division publicized the availability of alternative test methods for phototoxicity testing, eye irritation testings and skin sensitization testings for use in safety evaluations of cosmetics and quasi-drugs based on the JaCVAM evaluation reports in 2012 to 2015.

NIHS JaCVAM

MHLW Evaluation and Licensing Division publicized the availability of alternative test methods for use in safety evaluations of cosmetics and quasi-drugs in 2012 to 2015.

No.	Test Methods
1	Guidance for skin sensitization testing, LLNA
2	Guidance for phototoxicity testing, *in vitro 3T3 NRU*
3	Guidance for skin sensitization testing, LLNA：DA
4	Guidance skin sensitization testing, LLNA：BrdU-ELISA
5	Guidance for eye irritation testing , BCOP
6	Points to be considered regarding eye irritation test
7	Guidance for eye irritation testing , ICE

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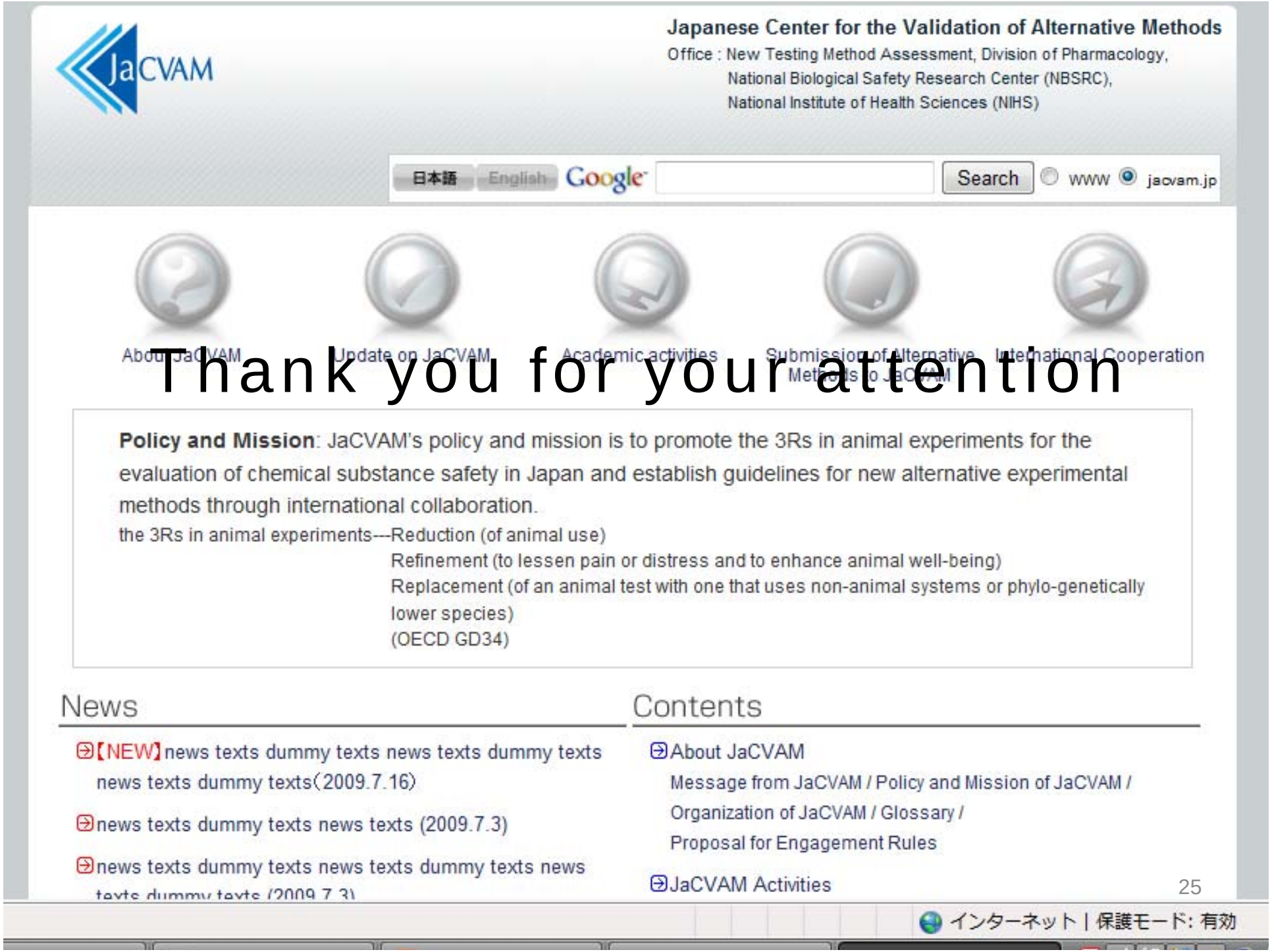
JaCVAM
Japanese Center for the Validation of Alternative Methods
Office : New Testing Method Assessment, Division of Pharmacology,
National Biological Safety Research Center (NBSRC),
National Institute of Health Sciences (NIHS)
日本語 English Google Search www jacvam.jp
About JaCVAM
Update on JaCVAM
Academic activities
Submission of Alternative Methods to JaCVAM
International Cooperation
Thank you for your attention
Policy and Mission: JaCVAM's policy and mission is to promote the 3Rs in animal experiments for the evaluation of chemical substance safety in Japan and establish guidelines for new alternative experimental methods through international collaboration.
the 3Rs in animal experiments---Reduction (of animal use)
Refinement (to lessen pain or distress and to enhance animal well-being)
Replacement (of an animal test with one that uses non-animal systems or phylo-genetically lower species)
(OECD GD34)
News
【NEW】news texts dummy texts news texts dummy texts news texts dummy texts(2009.7.16)
news texts dummy texts news texts (2009.7.3)
news texts dummy texts news texts dummy texts news texts dummy texts (2009.7.3)
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JaCVAM Activities
インターネット | 保護モード: 有効