REPORT FOR THE INTERNATIONAL COOPERATION ON COSMETICS REGULATION (ICCR)

Applicability of Animal Testing Alternatives in Regulatory Frameworks within ICCR Regions

Author:
ICCR Industry Committee (Cosmetics Europe, PCPC, CCTFA, JCIA)

TABLE OF CONTENTS

1. PURPOSE

Today's drivers (legal, scientific, business and ethical) towards alternatives to animal testing in the area of cosmetics are of international relevance.

The topic of alternatives to animal testing has been a working item for ICCR since its first meeting in 2007, where ICCR regulatory authorities committed to increased collaboration in the area of validation of alternative methods, leading to the creation of ICATM in 2008.

At the ICCR-3 meeting in September 2009, participants welcomed the progress made by ICATM regarding international validation of alternative methods.

Moving the debate beyond the positive and encouraging developments in ICATM, ICCR-4 concluded in 2010 that, in the next phase, attention should be given to regulatory acceptance as a means of promoting the use of alternative approaches to animal testing. Industry presented at ICCR-4 contributions from the four ICCR regions, describing the processes and proposed mechanisms for regulatory acceptance of the use of alternative methods. These contributions were prepared by the respective lead industry associations, in consultation with their respective regulatory representatives to ICCR. Industry committed to consolidating these contributions and to preparing an updated draft document for ICCR consideration, including an introductory section.

Within the existing legal frameworks, this ICCR report can contribute to the development of

- easier identification of alternative methods that can or must be used by industry in compliance with the respective legal frameworks
- reducing the risk of duplication of testing
- identifying areas of opportunity to streamline the regulatory acceptance process between ICCR regions

2. SCOPE

This report provides an overview of processes and mechanisms for the use of alternatives in human safety assessments of cosmetic products and ingredients in the four ICCR jurisdictions.

This report may serve as a basis for further discussions and possible development of principles for the use of alternatives to animal testing in safety assessment.

3. ACRONYMS AND DEFINITIONS

CIR	Cosmetic Ingredient Review
ECVAM	European Centre for the Validation of Alternative Methods
EEC	European Economic Community
ICATM	International Cooperation on Alternative Test Methods
ICCR	International Cooperation on Cosmetics Regulation
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
JaCVAM	Japanese Center for the Validation of Alternative Methods

KoCVAM	Korean Center for the Validation of Alternative Methods
NICEATM	National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods
OECD	Organisation for Economic Co-operation and Development
REACH	European Community Regulation on Registration, Evaluation, Authorisation and Restriction of Chemical substances
SCCS	European Commission's Scientific Committee on Consumer Safety

4. RESPONSIBILITIES

This report for ICCR has been prepared jointly by the lead industry associations represented in ICCR: Cosmetics Europe (EU); Canadian Cosmetic, Toiletry and Fragrance Association**,** CCTFA (Canada); Japan Cosmetic Industry Association, JCIA (Japan); and Personal Care Products Council, PCPC (US).

It was presented at the ICCR-5 meeting on June 29, 2011 in Paris.

5. DISCUSSION

5.1 Introduction

All ICCR jurisdictions have a general legal framework for cosmetic products which requires them to be safe for consumers under normal use conditions. In order to establish this safety prior to marketing companies carry out safety assessments, which use relevant safety and toxicology information on the product and its ingredients in a weight-of-evidence approach. Such safety assessments can become subject to inspection by authorities be it as part of established in-market control systems (existing in some ICCR jurisdictions) or in case of safety concerns over a marketed product. In addition, applicable chemical legislation may require cosmetic companies to obtain or submit safety data on cosmetic ingredients for occupational and/or environmental regulations.

Animal studies to assess toxicity have historically been considered as the "gold standard" information with which to build a safety assessment. Although the authorities in the four ICCR regions do not prescribe specific test protocols, using alternative studies or approaches to standard OECD test protocols (mainly animal studies) carries a risk that the resulting safety assessment might be challenged or not accepted by regulators.

Common drivers exist in the four ICCR regions towards the use of alternative methods:

The EU has enacted a **legal requirement** as follows (refer to http://ec.europa.eu/consumers/sectors/cosmetics/files/doc/200315/200315_en.pdf):

- End animal testing for cosmetic products and ingredients by a certain deadline (2013). Given the internationalisation of cosmetic business, this ban has consequences for the trade between ICCR regions.
- Consumer safety should be established on the basis of **best available science**. Current animal models are well established in routine safety assessments and their limitations

with regard to correlation with human effects are well understood. However, recent and emerging tools and technologies will allow a priori identification of specific toxicity mechanisms and pathways and prediction of toxicity, as opposed to empirical observations after the fact in animals, and this with even higher relevance for human safety assessments *(NRC Tox21c –Toxicity Testing in the 21st Century: A Vision and a Strategy. Washington, DC, USA: The National Academies Press. 2007).*

- There is a clear **business interest** to use well designed and scientifically valid alternative approaches that are faster and cheaper, allowing higher throughput while providing equal or better predictivity of the human situation, provided that these approaches are also accepted in a regulatory context.
- Simple **ethics** dictate that pain is an intrinsic evil whether it is experienced by a child, an adult, or an animal. Society, including companies and regulators, has an obligation to act in ways that will minimize harm and maximize benefits, i.e., to choose an alternative method when it is proven to provide adequate basis for consumer protection.

No uniform definition exists for regulatory acceptance of alternative methods in the area of cosmetics. The term has different meaning in different regulatory contexts, such as:

- In-house cosmetic product/ingredient safety assessment
- Ingredient safety assessments submitted for review by (regulatory) authorities
- Cosmetic companies acting as manufacturers or importers of chemicals

Likewise, mechanisms/procedures for regulatory acceptance differ and include:

- Recognition/tolerance by (control) authorities that manufacturers routinely use alternative approaches in their in-house safety assessments
- Acceptance of scientifically valid safety alternative approaches as part of safety reviews by authoritative review bodies (e.g., CIR, SCCS)
- Formal recommendation/obligation to use certain validated alternative methods in the registration of chemicals (e.g., OECD, REACH)

Regulatory acceptance for alternative methods in the area of cosmetics can therefore ultimately be defined as the acceptance of a safety assessment of a specific product in a given regulatory context.

Validation is an important step leading towards regulatory acceptance of alternative methods. To validate an (alternative) test method is to establish the reliability and relevance of the method for a particular purpose:

- reliability: reproducibility of results (within and between laboratories and overtime)
- relevance: extent to which a test method correctly predicts the biological effect of interest)

Validation, like regulatory acceptance, needs to be seen in the context of the purpose for which the alternative method is used. Alternative methods for in-house purposes are generally validated by the company using them (within defined domains of applicability). Alternative methods intended to replace legally required animal studies (e.g., chemical registration) have to undergo validation by an official validation body.

Valid(ated) alternative methods are today routinely and successfully used by companies as part of cosmetic safety assessments, with some methods being also formally accepted by ICCR authorities and/or OECD (also see the document, “ICATM Current Alternative Test Method Validation and Regulatory Acceptance Status Report for ICCR” dated June 21, 2012,

http://ihcp.jrc.ec.europa.eu/our_activities/alt-animal-testing/alt_test_cosmetics/ICATM%20Table%20of%20Assays%2021%20June%202012.pdf for details):

- Phototoxicity
- Dermal penetration
- Skin corrosivity/skin irritation
- Genotoxicity
- Eye irritation
- Skin sensitisation

It has become clear, however, that one-for-one replacement of one animal study with one in-vitro method is only possible for a limited number of toxicity endpoints. Single *in vitro* assays are generally insufficient to simulate a whole pathway of toxicity, although they may be reliable and relevant for a particular step in a toxicity pathway. Alternative approaches for more complex toxicity endpoints will need to be made from tool boxes of non-animal (*in silico*, *in chemico,* and *in vitro)* test methods, where each test method is:

- mechanistically relevant
- robust and reproducible

Individual tests will need to be combined differently in testing strategies to allow hazard characterisation and/or risk assessment of a large variety of chemicals and products. Safety assessments (and their regulatory acceptance) will increasingly require knowledge and understanding of how non-animal methods need to be combined and applied in a case-by-case approach.

Therefore, researchers, safety assessors, and regulators need to agree on general acceptance criteria to allow assessment whether the methods and strategies that they develop, use, or control in a given context are scientifically sound and mechanistically based, reliable, relevant, predictive, robust, easily applicable to cosmetics, backed by data.

ICATM was formed to improve the procedures and timelines for international acceptance alternative methods. ICATM is an international cooperation established under a memorandum of understanding among ICCVAM (USA), ECVAM (EU), JaCVAM (Japan), KoCVAM (Korea) and Health Canada. The agreement is to collaborate where possible on the design, conduct, and peer review of validation studies for alternative methods. This is intended to increase the likelihood that a method is validated and to promote agreement on recommendations regarding the suitability of alternative methods for regulatory use. Ultimately, the goal is a harmonized ICATM recommendation. A table of alternative methods validated by ICATM can be obtained from the ICCR Secretariat.

5.2 Situation in the EU

In the EU there are three main scenarios under which the concept of "regulatory acceptance" of alternative methods becomes specifically relevant in the context of cosmetic products and ingredients:

- In market-control of a cosmetic product safety assessment by the National Control Authorities under the terms of the EU Cosmetics Directive (76/768/EEC)
- Submission of a safety dossier to the European Commission/SCCS with a view of listing a substance in the Annexes of the Cosmetics Directive (76/768/EEC)
- Registration of a new chemical substance above 1 tonne (1000 kg), with an intended use as a cosmetic ingredient under the EU Chemical Regulation REACH

The traditional way of thinking about regulatory acceptance (and validation) has been along the lines of a one-to-one equivalency in which one specific regulatory animal test is replaced by one alternative method. This paradigm has shifted and it is now largely accepted that the way forward is in integrated testing strategies, in particular when addressing complex toxicological endpoints. Besides their inherent scientific complexity, integrated testing strategies will also pose new challenges for the established procedures for validation and regulatory acceptance. This is acknowledged by EU validation experts, where work has started to adapt the standard procedures. However, the topic has yet to be raised as a priority in discussions on regulatory acceptance.

5.2.1 In market-control of a cosmetic product safety assessment by the National Control Authorities

The EU Cosmetics Directive 76/768/EEC and its successor EU Regulation 1223/2009, require that cosmetic products must be safe, i.e., not cause damage to human health when applied under normal or reasonably foreseeable conditions of use. The person (legal or physical person) responsible for placing the product on the market must be able to demonstrate this safety on the basis of a safety assessment. The Competent Authorities of the EU member states are under the legal obligation to enforce this legal requirement and will therefore carry out control inspections to ensure that companies have carried out adequate safety assessments.

The EU legislation does not require a fixed data set or specific methods for a cosmetic-product safety assessment. It recognizes, however, that the safety assessment of a finished cosmetic product can be based on the toxicological profiles of its ingredients and in-use exposure conditions.

The vast majority of cosmetic ingredients are substances or mixtures with multiple industrial uses beyond cosmetics. A basic (tonnage driven) data package is established under chemical legislation for classification/labelling and registration purposes, and generally provided by the chemical supplier to the downstream manufacturers. As a result, the testing methods used to characterise the toxicological profile of cosmetic ingredients are in most cases those described under EU Chemical legislation (REACH Test Methods Regulation (EC 440/2008) and in the "OECD Guidelines for the Testing of Chemicals"). Among them are some alternative methods to animal tests. These alternative testing methods, being officially recognised by EU legislation for chemicals, are also accepted by the control authorities in the context of cosmetic safety

assessments. REACH strongly encourages the use of alternative test methods, but does not prohibit (and in some cases may actually require) the use of animal-based toxicity tests.

The EU Cosmetics legislation considers, in theory, the possibility that alternative methods might become available for cosmetic product/ingredient safety assessments which are not applicable for all uses of chemical ingredients. After formal validation of such cosmetic-specific methods by ECVAM, and an opinion by the SCCS, they can be adopted at the EU level through listing in Annex IX of the EU Cosmetics Directive. There is currently no alternative method listed in Annex IX, because the alternative methods validated so far are applicable to wide chemical use categories.

The chemical data package described above is tonnage-driven and focused on hazard identification rather than on dose-response. Consequently, it is not always sufficient for a full safety assessment of a substance in a specific cosmetic product. In that case, the cosmetics company complements the basic safety data package with additional data available 'upstream' or 'sidestream' to the cosmetic use of the substance (i.e., from the chemical industry or downstream users other than cosmetics), with peer reviewed literature and/or with additional studies. Data may be available/generated according to standard testing protocols or in-house validated methods and approaches.

The EU legislation encourages the use of data from all existing sources following a weight-of-evidence approach.[1] Examples of safety information that is used as part of a weight-of-evidence approach to address pivotal toxicological endpoints include:

- Existing animal data that may not have been generated in accordance with the latest test guideline method, but which can be considered by the safety assessor as are scientifically sound.
- Threshold of Toxicological Concern (TTC), based on the principle of a human threshold exposure for all chemicals, below which there is a very low probability of an appreciable risk to human health
- *In vitro* data or alternative data from valid test systems (in-house experience or formally validated) to use as a screening study to predict toxicity.
- Human (clinical) data, including data from other industries such as food and medicinal products manufacturers. Data from human studies can also be required by the safety assessor, if the formulation is considered innovative.
- Data gathered from post-marketing surveillance, including information from self reporting from consumers as well as information from medical professionals such as dermatologists.
- Read-across approaches, based on the chemical structure and properties in order to predict toxicity of the ingredient (including QSAR or other *in-silico* computational tools.

[1] "Weight of evidence" is based on collecting and using data from all available sources, including multiple toxicological studies in both humans and animals, but also alternative data with consideration to the quality of the data obtained. In essence, it means the maximization of the use of existing toxicological information where ever possible.

There is no formal process for regulatory acceptance of a weight-of-evidence approach in cosmetic safety assessments. In practice, companies will demonstrate scientific validity and appropriateness on a case-by-case basis to demonstrate the safety of a specific cosmetic product.

5.2.2 Submission of a safety dossier to the European Commission/SCCS with a view of listing a substance in the Annexes of the Cosmetics Directive (76/768/EEC)

The Cosmetics Directive ensures that substances can only be listed on the Annexes of the Cosmetics Directive after an evaluation of their safety by the SCCS. The legislation does not specify a fixed data set or methods that need to be submitted in such a case. However, guidance is given by the SCCS with regard to the areas of potential toxicity that need to be addressed.

The SCCS commonly accepts results from toxicological test procedures reported in the REACH Test Methods Regulation (EC 440/2008) and from the OECD Guidelines for the Testing of Chemicals. They represent the basic toxicity testing procedures needed to evaluate different toxicological endpoints and are internationally accepted as being the result of long-term scientific agreement. Over the years, several alternative methods have been formally validated and taken up in the REACH Test Methods Regulation (EC 440/2008). The SCCS has assessed all of them for their applicability in the context of cosmetics ingredient safety assessment and issued formal endorsements. On an annual basis, the SCCS issues an updated memorandum where it reviews, by toxicological endpoint, the status of availability of acceptable alternative methods.

As described above, in theory alternative methods could be validated specifically for cosmetic safety assessments, be reviewed by the SCCS, and receive formal regulatory acceptance through inclusion in Annex IX of the Cosmetics Directive. For the reasons stated before, this is not a likely scenario (i.e., alternative methods are not cosmetic-specific but applicable to wide chemical use categories).

Beyond this formal acceptance of generally recognized methods, the SCCS recognises that safety assessment should not be seen as a checklist and that many possible data sources exist (data obtained from animal studies, *in vitro* experiments, QSAR calculations, clinical studies, epidemiological studies, and human accident data). Although attempts have been made to incorporate some standardised procedures, exposure patterns, formulation types, etc., the SCCS states that the safety evaluation of cosmetic ingredients and finished products remains a scientific exercise that can only be performed on a case-by-case basis.

In this context the SCCP (Scientific Committee on Consumer Products, forerunner to SCCS) has on some occasions accepted in the past certain methods as "valid" in the assessment of specific ingredient dossiers on a case-by-case basis (e.g., test methods for assessing salicylic acid in rinse-off hair care products). These methods have not necessarily gone through the complete validation process, but the Committee considered them acceptable when they had a sufficient amount of experimental data supporting their relevance and reliability. The SCCS also emphasizes the potential usefulness of methods which have not been formally fully validated for screening purposes and for the testing of finished cosmetic products.

5.2.3 Registration of a new chemical substance with an intended use as a cosmetic ingredient under the EU Chemicals Regulation REACH (above one tonne)

Certain classes of active ingredients are often developed specifically for cosmetic use (e.g., hair dyeing ingredients, ultraviolet (UV) filters). For companies (including suppliers) developing new chemical substances as cosmetic ingredients, information on toxicity (hazard identification) is needed early on in the development process for:

- early screening of the toxicity of substances to identify suitable candidates for further development
- prediction of the toxicity of substances under in-use conditions in order to assure the safety of participants in human trials
- Registration dossier under REACH

REACH prescribes a certain data set, following specific test methods. As stated above, the content is tonnage driven and focusing on hazard identification. Where in-vitro tests have been formally validated and adopted into the REACH Test Methods Regulation (EC 440/2008), they may be used for hazard identification and as part of a Chemical Safety Assessment (CSA).

Adaptation of the prescribed standard protocols is possible under certain circumstances. Specific rules for adaptation are provided in the testing annexes of REACH and general rules are laid down in Annex XI, supplemented by guidance in REACH Guidance Documents.

- Weight-of-evidence assessment can be acceptable to combine the information from a number of studies, none of which were conducted to recognised international standards. However, when taken together they can be used to meet the REACH information requirements and be sufficient for a CSA.
- The use of (Quantitative) structure activity relationships (QSAR) is considered a potential useful way to minimise animal testing for the future.
- Grouping and read across have been recognized in a regulatory context, for example, in the OECD High Production Volume Chemical (HPV) programme. This experience has been adapted by the EU for REACH and included in the REACH guidance document.
- In order to identify the presence of a hazard (positive results) a test is considered acceptable if it meets the ECVAM criteria for acceptance into the pre-validation process. For negative outcomes to be accepted; the test must have been formally validated.

Regulatory acceptance of alternative results/waiving of standard animal tests will become apparent after the first registration deadline under REACH (end 2010).

5.3 Situation in Canada

5.3.1 Test methods in current Canadian Legislation applicable to cosmetics and personal care products

The regulation of personal care products in Canada tends to be complex since products and their ingredients are regulated by a number of laws. This section on Canada will outline the laws that govern personal care products and the conditions under which data may be required, which may or may not be based on animal testing.

5.3.1.1 Definitions and applicable legislation

All personal care products are regulated under the *Food and Drugs Act* (F&DA), and, depending on their purpose, representation and/or ingredients, may be regulated by one of three regulations under the Act:

- Products that cleanse, improve, or change the complexion, skin, hair or teeth are defined as cosmetics and fall under the *Cosmetic Regulations*. Cosmetics include beauty preparations (makeup, perfume, skin cream, nail polish) and grooming aids (soap, shampoo, shaving cream, deodorant).
- Products that treat, mitigate, or prevent a disease or disorder, or that modify an organic function of the body are defined as drugs. If the active ingredients are synthetically derived, they fall under the *Food and Drug Regulations*. Where the active ingredients are from a naturally-occurring source, they fall under the *Natural Health Products Regulations*.

In addition to the *Food and Drugs Act*, all raw materials found in personal care products, prior to their manufacture and sale as cosmetics, drugs or natural health products, are subject to *Canadian Environmental Protection Act* (CEPA) (see Section 5.2.2 for more information).

5.3.1.2 Requirements for animal tests

Although manufacturers are required to demonstrate the safety of their personal care products, there are no prescribed test methods that a company must use under the F&DA and its regulations. Regulators recognize that the global cosmetics industry strives for alternatives to animal testing, and in many cases, where appropriate, allow a company to demonstrate safety or efficacy under the regulations using data available in the scientific literature, in-house read-across data on analogues, quantitative structure-activity relationships (QSARs), alternative-to-animals test methods or human clinical tests. These are determined case by case by Health Canada risk assessors, depending on a number of factors such as the history of the substance, its use, the regulatory requirements that are being triggered, as well as the quality and validity of the alternative data. In spite of these allowances, there may be circumstances where the demonstration of safety cannot be achieved without the use of animals, for example, where an *in vitro* test is positive for mutagenicity or in the rare case where a personal care product active ingredient may need to undergo clinical trials, which would entail a battery of *in vivo* animal tests prior to testing in humans.

The only regulations that clearly prescribe specific test methods for personal care product ingredients under Canadian law are the *New Substances Notification Regulations* under the *Canadian Environmental Protection Act* (CEPA). The OECD Guidelines for the Testing of Chemicals are considered the "gold standard" for test methods, but the New Substances Program can accept analogues, QSARs, *in vitro* tests, or other alternative tests for assessment where appropriate. Further details can be found in the following section (5.2.2).

5.3.2 Canadian Environmental Protection Act (CEPA)

The ingredients used in cosmetics and other F&DA regulated commodities are currently subject to CEPA. Such substances are divided into "new" and "existing" categories, depending on whether they are found on the Domestic Substances List (DSL). Existing substances are those found on the DSL and are currently subject to prioritization for assessment under the Chemicals Management Plan. While "new substances" are considered to be those which are not on the DSL, there is a special subcategory of products found on the In-Commerce List (ICL) that are not on the DSL, but were on the Canadian market prior to 2001. The regulation, assessment and screening of these ICL substances have been deferred to future management outside of the "new" or "existing" management frameworks.

5.3.2.1 New Substances

New substances are those which are introduced to Canada (manufactured domestically or imported) as raw materials or contained in a formulation, and are not found on the DSL. These substances are subject to the *New Substances Notification Regulations* (NSNR), which outline the endpoints that companies must submit for assessment for potential human and environmental risks. The data required for submission depends on the type of substance (chemical versus polymer) and the annual amount a company is importing or producing domestically, and are separated into "Schedules". While very little toxicological test data may be required for the lower annual levels of import/manufacture, animal data may be required at higher annual levels (1000 kg/year or more), such as:

- Acute oral, dermal, or inhalation mammalian toxicity test
- Ecotoxicological data in the form of data from one acute fish, daphnia, or algae toxicity test in respect of the chemical
- *In vivo* mammalian mutagenicity test
- A 28-day mammalian repeated dose toxicity test

Currently, validated non-animal testing alternatives exist to address typical endpoints for the first two types of data above. Although the NSNR specify that an *in vivo* mammalian mutagenicity test is required, there are validated *in vitro* testing methods that could be substituted to address this third endpoint in the NSNR mutagenicity/genotoxicity test battery, particularly where these *in vivo* endpoints clearly demonstrate that the substance is negative for mutagenicity and clastogenicity, further supported by the absence of known structural alerts. In this case, a waiver for *in vivo* mammalian mutagenicity can be requested. With respect to repeated-dose toxicity, there are no adequate non-animal test methodologies at this time.

The NSNR prescribe test protocols consistent with OECD Guidelines for the Testing of Chemicals that are current at the time the test data are developed. The Guidelines are set out in Annex 1 of the OECD Decision of the Council Concerning the Mutual Acceptance of Data in the

Assessment of Chemicals, adopted by the Organisation for Economic Co-operation and Development on May 12, 1981.

5.3.2.2 Existing Substances

There are no specific test requirements for existing substances (i.e., on the DSL). Assessment of these substances are based on a weight-of-evidence approach taking into account modeled information, existing information found in the scientific literature or that manufacturers already have in their possession, and supplemental data, as might be provided by interested stakeholders. The methodologies and endpoints of such additional studies are not prescribed by law.

5.3.3 The Food and Drugs Act

5.3.3.1 Cosmetic Regulations

There are no specific requirements under the *Cosmetic Regulations* for manufacturers to provide animal test data. Manufacturers are only required to provide safety substantiation data to support the safety of certain ingredients and none specifically request the generation of animal data. Normally, existing data are used, with a weight-of-evidence approach taken in the risk assessment of an ingredient or product. Therefore, should alternative test methods be endorsed by Health Canada, a regulatory amendment to the *Cosmetic Regulations* is not likely to be required.

5.3.3.2 Food and Drug Regulations

The *Food and Drug Regulations (FDR)* differentiate between a New Drug and a drug previously authorized and in use in the Canadian market for an extended period of time, specifically:

C.08.001 For the purposes of the Act and this Division, “new drug” means
(a) a drug that contains or consists of a substance, whether as an active or inactive ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug;

(b) a drug that is a combination of two or more drugs, with or without other ingredients, and that has not been sold in that combination or in the proportion in which those drugs are combined in that drug, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that combination and proportion for use as a drug; or

(c) a drug, with respect to which the manufacturer prescribes, recommends, proposes or claims a use as a drug, or a condition of use as a drug, including dosage, route of administration, or duration of action and that has not been sold for that use or condition of use in Canada, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that use or condition of use of that drug.

All New Drugs are required to undergo testing as per Division 8 of the FDR to demonstrate that these are safe and effective. Older products subject to Division 1 may also necessitate testing for a new associated claim. In either of these instances, the FDR do not specify the precise required testing in detail. Instead, Health Canada employs guidance documents to address recommended test methods for a particular category of drug products. Should alternative test methods be endorsed by Health Canada for products regulated under the FDR, this would either be done on a case-by-case submission specific basis or through development of guidance to industry. A regulatory amendment is not likely to be required.

5.3.3.3 Natural Health Product Regulations

There are no specific requirements under the *Natural Health Product Regulations* (NHPR) for manufacturers to provide animal test data. Manufacturers are only required to provide data to support the safety of ingredients and no requirements for this data specifically request the generation of animal data. Normally, existing data are used, with a weight of evidence approach taken in the risk assessment of an ingredient or product.

Health Canada employs guidance documents to address recommended data for natural health products. Should alternative test methods be endorsed by Health Canada for products regulated under the NHPR, this would either be done on a case-by-case submission specific basis or through development of guidance to industry. A regulatory amendment is not likely to be required.

5.3.4 Adoption of alternative test methods

Canada accepts OECD Guidelines for the Testing of Chemicals as the standard for toxicity testing, and where possible, the OECD is striving to develop alternative methods. Such OECD adopted alternative test methods are accepted by Health Canada for the purposes of risk assessment if the test is appropriate for the endpoint and type of chemical tested. Validation and adoption of such alternative tests remain a lengthy process.

Health Canada is an active participant in the ICATM process, which strives to promote agreement on recommendations for alternative methods among the participating jurisdictions. Therefore, an alternative method may be accepted by Health Canada under ICATM prior to adoption under the OECD Guidelines for the Testing of Chemicals.

5.4 Situation in the United States

5.4.1 Statutory and Regulatory Requirements for Cosmetic Products

In the United States, both industry and regulatory authorities have a long-established commitment to reduce or replace the need for animal testing. From this arises a collective interest, across all sectors, for accelerating meaningful and rapid progress for research to develop alternative methods; for lab investigations to validate alternative methods; and importantly, for a regulatory framework to adopt validated alternatives.

Section 601(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) prohibits the use in a cosmetic of any unsafe substance that may render the cosmetic injurious to health. FDA has not prepared a formal list of toxicology test methods for use in determining the safety of cosmetic ingredients and cosmetic products. The preamble to Section 740.10 is the only formal guidance that FDA has provided on cosmetic ingredient and cosmetic product safety substantiation, and that document purposely did not provide a list of required tests or test methods. Instead, FDA has relied on general scientific principles of risk assessment.

In 1997, the United States created ICCVAM to reduce animal testing. At the same time, NICEATM was established to administer and provide scientific support for ICCVAM activities, and to conduct validation studies on alternative test methods. These were created by administrative action, not by legislation. However, in 2000, the ICCVAM Authorization Act of 2000 was signed into law, establishing ICCVAM as a permanent interagency coordinating committee under NICEATM. The law directs ICCVAM to carry out specific duties, including the coordination of technical reviews of proposed alternative methods and submitting ICCVAM test recommendations to appropriate Federal agencies. The Act charges Federal agencies to review ICCVAM recommendations and to notify ICCVAM of their findings within 180 days. The Act further requires ICCVAM to make ICCVAM test recommendations and Agency responses available to the public.

FDA serves on the ICCVAM and works closely with the NICEATM. In evaluating whether a proposed new method is adequately validated and has sufficient performance for use in regulatory decisions, ICCVAM coordinates with and takes into consideration the views of its counterpart national validation organizations, which include ECVAM, JaCVAM, and Health Canada. This coordination is accomplished in accordance with the provisions of a Memorandum of Cooperation for the International Cooperation on Alternative Test Methods (ICATM) signed in 2009 by the four participating countries, and was re-signed in 2011 with the addition of KoCVAM to include Korea.

Once ICCVAM recommends that an alternative method, with a defined scope and caveats, has been adequately validated it may be forwarded to Federal agencies to consider for potential regulatory application. Agency acceptance is on a case-by-case basis.

5.5 Situation in Japan

5.5.1 The background of alternative methods for animal testing in Japan

The Act on Welfare and Management of Animals (Law No.105, 1973) was revised in 2006, incorporating basic consideration for animal testing, handling of animals, and reduction, refinement, and replacement (3Rs) principles, together with requirements when animal tests are carried out.

As one of the enforcement regulations of this law, The Guidelines for Raising and Keeping of Laboratory Animals, Ministrial Ordinance No. 88, Ministry of Environment, 2006 was published. The Ministry of Health, Labour and Welfare (MHLW); Ministry of Education, Culture, Sports, Science and Technology; and the Ministry of Agriculture, Forestry and Fisheries notified respectively guidelines regarding proper conduct of animal experiments addressed to public research laboratories of their own jurisdiction

The guidelines stipulate the responsibility of the director of the laboratory and of researchers, the establishment and defining the role of the Animal Care and Use Committee, and care and management of laboratory animals.

For the promotion of 3Rs principles, it was considered important to have an institution to evaluate alternative testing methods to relieve the pain of animals. This is the background in which JaCVAM was inaugurated in November 2005 within the National Institute of Health Sciences with a mission to promote the 3Rs and to establish guidelines for new alternative experimental methods through international collaboration.

JaCVAM has its role to promote 3Rs in animal testing through validation and evaluation of alternative test methods under international collaboration, always keeping the protection of human health as an ultimate goal. The evaluation of whether proposed methods by sponsors are appropriate to be regulatorily accepted and the clarification for their application are also an important mission of JaCVAM.

JaCVAM has the Steering Committee, which is responsible for management of JaCVAM. The Regulatory Acceptance Board examines regulatory acceptance of validation studies submitted by the ad hoc validation team, which is organized under delegation of the Steering Committee for each study.

The process of regulatory acceptance starts with the validation study by the ad hoc validation management team, evaluation by the ad hoc peer review panel, and then examination of appropriateness of regulatory acceptance as well as its application by the Regulatory Acceptance Board, and ends with approval by the Steering Committee, as well as publication of these reports on the website.

JaCVAM collaborates with ICCVAM, ECVAM, KoCVAM, and Health Canada under the framework of ICATM for promotion of validation studies as well as international cooperation in this field.

5.5.2 Legal acceptance of alternative testing methods for safety evaluation of cosmetics

In 2006, “Questions and Answers (Q&A) on Data to be attached to Marketing Approval Applications for Quasi-drugs and Requests for Revision of Cosmetic Standards” was published by MHLW, stating that the reports obtained using alternative methods adopted by OECD could be accepted as the documents to be attached for application of Quasi-drugs and also for application of revision of Cosmetic Standards.

To clarify the regulatory acceptance process with test methods which are evaluated by JaCVAM, MHLW published a notice in February 2011 stating the results obtained with tests accepted by JaCVAM and properly carried can be used for the application of Quasi-drugs, and also for the revision of Cosmetic Standards.

After validations and peer reviews of JaCVAM, including a case under international cooperation in the framework of ICATM for its scientific appropriateness, the test method is sent to the Regulatory Acceptance Board for examination of regulatory acceptance and the scope of application to be used for Cosmetics and Quasi-drug safety tests. Then the Steering Committee approves and publishes the test method.

Just to clarify, as stated in the above, the results obtained using testing methods which have been adopted by OECD in the past can be also accepted as the documents for application of Quasi-drugs and for revision of Cosmetic Standards.

Aside from the regulatory acceptance process, there are no limitations that new testing methods are used as screening methods for in-house study, even if the method is not regulatorily accepted by JaCVAM.

Japan Cosmetic Industry Association (JCIA) revised in 2008 “2001 Guidelines for the Safety Evaluation of Cosmetics,” considering important changes in the cosmetic environment incorporating the 2006 SCCP Guidance revised to cope with the 7th amendment of European Cosmetic Directive 76/768 and the revision of CTFA Guidelines. JCIA Guidelines show available alternative methods for each type of safety evaluation together with conditions for the testing laboratories, which must have sufficient scientific background data on such tests and must be able to explain the appropriateness of using such tests.

6. CONCLUSIONS

Alternatives to animal testing for cosmetics are a topic of international relevance. The scientific, business, ethical, and `, to some extent, legal drivers towards alternative test methods are common across the ICCR regions.

Today, there are still diverging levels of acceptance of alternative methods across the world.

Companies considering the use of non-animal safety information face the uncertainty that the resulting safety assessment might be challenged or not accepted by regulators. Companies also

face uncertainty concerning how such alternative methods to animal testing would fare in product liability civil lawsuits at trial in court cases, which has never been tested.

Validation and regulatory acceptance have to be understood as broad concepts that may have different practical meanings in different contexts (e.g., in-house method vs. OECD Guidelines for the Testing of Chemicals).

Valid(ated) alternative approaches are routinely and successfully used in the following regulatory safety assessments :

- Phototoxicity
- Dermal penetration
- Skin corrosivity/skin irritation
- Genotoxicity
- Eye irritation
- Skin sensitisation

These alternative methods should be the preferred options for testing. However, one-for-one replacements of an animal study with one alternative method works only in few cases; future successes will be built on test batteries/tiered approaches.