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Institute for Health and Consumer Protection
EU Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM)

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**EURL ECVAM's
European Union Network of Laboratories for the Validation of
Alternative Methods
- EU-NETVAL -**

Terms of Reference

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1. Introduction

EU-NETVAL's mission is to provide support for EURL ECVAM validation studies that serve to assess the reliability and relevance of alternative methods that have a potential to replace, reduce or refine the use of animals for scientific purposes.

This document outlines the Terms of Reference for EU-NETVAL including the legislative anchor, the establishment of the network and the maintenance of its membership, tasks of network members and of EURL ECVAM in support of validation studies, the allocation of tasks to members, and the financing of network activities.

2. Background

2.1. Legislative anchor

The European Union Network of Laboratories for the Validation of Alternative Methods (EU-NETVAL) was established by the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) of the European Commission's Joint Research Centre to address some of the provisions of Directive 2010/63/EU on the protection of animals used for scientific purposes. Article 47 of the Directive provides that;

"1. The Commission and the Member States shall contribute to the development and validation of alternative approaches which could provide the same or higher levels of information as those obtained in procedures using animals, but which do not involve the use of animals or use fewer animals or which entail less painful procedures, and they shall take such other steps as they consider appropriate to encourage research in this field.

2. Member States shall assist the Commission in identifying and nominating suitable specialised and qualified laboratories to carry out such validation studies.

3. After consulting the Member States, the Commission shall set the priorities for those validation studies and allocate the tasks between the laboratories for carrying out those studies.

4. Member States shall, at national level, ensure the promotion of alternative approaches and the dissemination of information thereon."

In line with Article 48 of the Directive, Annex VII lists the duties and tasks of the EU Reference Laboratory, covering *inter alia*:

"(a) coordinating and promoting the development and use of alternatives to procedures including in the areas of basic and applied research and regulatory testing;

(b) coordinating the validation of alternative approaches at Union level;

(c) acting as a focal point for the exchange of information on the development of alternative approaches;

(d) setting up, maintaining and managing public databases and information systems on alternative approaches and their state of development;

(e) promoting dialogue between legislators, regulators, and all relevant stakeholders, in particular, industry, biomedical scientists, consumer organisations and animal-welfare groups, with a view to the development, validation, regulatory acceptance, international recognition, and application of alternative approaches."

EU-NETVAL will facilitate the Union Reference Laboratory meeting its objectives under Article 48. Furthermore, membership in EU NETVAL provides one channel, among others, for both the Commission and the Member States to actively contribute to the development and validation of alternative approaches as required by the Directive.

2.2. Validation of alternative methods

Validation is essential to ensure the acceptance and use of alternative (non-animal) approaches for a range of scientific purposes by a variety of end-users. It is also a prerequisite for the development of international standards and test guidelines that underpin regulatory decision making and global trade. Internationally accepted validation principles for *in vitro* methods are described in the OECD (2005) "Guidance document on the validation and international acceptance of new or updated test methods for hazard assessment"¹ (no. 34) which sets out the essential considerations and steps to assess the *reliability* and *relevance* of an *in vitro* method.

The information required to demonstrate the reliability and relevance of an *in vitro* method in a systematic and comprehensive manner can be captured in seven independent 'validation modules'². These modules address; 1) Definition and description of the method, 2) Within-laboratory reproducibility, 3) Transferability between laboratories, 4) Between-laboratory reproducibility, 5) Predictive capacity, 6) Applicability domain, and 7) Performance standards. Approaching validation in this modular way allows for consistency, flexibility and efficiency in the overall process.

Information addressing these validation modules may be gathered retrospectively from existing data sources. However, for novel *in vitro* methods much of the required data is usually missing and therefore needs to be generated within a prospective validation study, ideally under the Good Laboratory Practice (GLP) quality system. A typical prospective validation study commences with the analysis and optimisation of the *in vitro* method procedure to ensure that it is sufficiently well defined. Subsequently, data are generated on selected reference chemicals to demonstrate its reproducibility within an experienced laboratory. Thereafter the *in vitro* method is transferred to three or more test facilities and a between-laboratory ring trial carried out to demonstrate the between-laboratory reproducibility, thus completing the reliability assessment. Subsequent data generation in one or more laboratories provides the datasets and information required to determine how predictive the method is in relation to its intended purpose, its applicability domain (e.g. biological, physicochemical) and to establish performance standards for the class of assay that the *in vitro* method represents. The results of a validation study are compiled in a validation report and typically undergo review by the EURL ECVAM Scientific Advisory Committee (ESAC) before being released in the form of a EURL ECVAM Recommendation. A description of the EURL ECVAM validation process can be found at http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/eurl-ecvams-validation-process.

¹ OECD 2005. OECD Series on Testing and Assessment. Number 34. Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment. ENV/JM/MONO(2005)14.

² Hartung et. al, "A modular approach to the ECVAM principles on test validity", ATLA 32, 467–472, 2004

3. Appointment of Members

3.1 Establishment of EU-NETVAL

In order to establish EU-NETVAL through the appointment of its first members, the National Contact Points (NCPs) for Directive 2010/63/EU were requested by the Commission to provide a list of candidate test facilities (laboratories) that had shown interest in their respective Member State. These candidates were subsequently contacted by EURL ECVAM and invited to provide information on their test facilities by completing an on-line questionnaire. Each test facility was then evaluated against predefined eligibility criteria that had been previously agreed with NCPs. Out of the initial list of candidates received, 13 were deemed to be eligible. During July 2013 and after consultation with NCPs, these facilities were formally appointed by EURL ECVAM as EU-NETVAL members. The names of these first members were published on the EURL ECVAM website.

3.2 Expanding EU-NETVAL membership

EURL ECVAM intends to publish open calls for selection of new EU-NETVAL members on an ad hoc basis, depending on anticipated tasks, required member profiles, and the overall capacity of the network. The first call for new members was opened in July 2013 and published on the EURL ECVAM website. The closing date for applications is on the 25th October 2013. Currently application for membership of EU-NETVAL is restricted to test facilities based in the EU, EFTA countries and EU candidate countries. Similar to the process adopted for the initial establishment of the network, candidate facilities that apply to EURL ECVAM for membership will be evaluated against the eligibility criteria. Eligible facilities will be appointed by EURL ECVAM after consultation with the NCPs. The names of newly appointed members will be published on the EURL ECVAM website.

3.3 Duration of membership of EU-NETVAL

The duration of EU-NETVAL membership is indefinite as long as a member facility continues to satisfy the eligibility criteria. Members are, however, free to resign from the network at any time by simply sending a formal letter of notification to EURL ECVAM. Members will be expected to resign from the network if their circumstances change resulting in their facility failing to meet the eligibility criteria. The most recent list of EU-NETVAL members will be available from the EURL ECVAM website.

4. Tasks of Members

EU-NETVAL members are expected to support validation studies through the execution of one or more specific tasks. The support sought from members will vary in scope depending on the task and the capacities and the areas of expertise of the members. Tasks constituting this support will address the particular data and information requirements of one or more validation modules applicable to the study. Tasks include;

- i. **Definition and description of *in vitro* methods**
Support the definition of *in vitro* method procedures including the technical assessment (non-experimental or experimental) of Standard Operating Procedures

(SOPs) in terms of their scientific basis, completeness, clarity, robustness and suitability for implementation within a GLP environment. This includes reflecting the definition of an *in vitro* method in a suitably elaborated method description, prepared in a format fit for public dissemination through EURL ECVAM's database on alternative methods, DB-ALM (see <http://ecvam-dbalm.jrc.ec.europa.eu/>).

- ii. **Transfer of *in vitro* methods between laboratories**
Support the demonstration and assessment of the transferability of *in vitro* methods between one laboratory and another. This includes the preparation of technical training courses and related training materials on the method undergoing validation to aid in the transfer process.
- iii. **Assessment of the reproducibility of *in vitro* methods**
Support the generation of datasets on selected reference chemicals for the assessment of within-laboratory and between-laboratory reproducibility of *in vitro* methods. This may include participation in a multi-laboratory ring-trial and acting as a lead laboratory for such trials, if appropriate.
- iv. **Assessment of the predictive capacity and applicability domain of *in vitro* methods**
Support the generation of datasets on selected reference chemicals for the performance assessment of an *in vitro* method in relation to its predictive capacity in relation to its intended purpose and/or its contribution to an integrated testing strategy or testing battery. This will also include the assessment of the mechanistic, chemical, physico-chemical, sectorial and regulatory applicability domains of *in vitro* methods, and the generation of datasets suitable for the establishment of performance standards for particular classes of *in vitro* method.
- v. **Guidance documents and training materials supporting validation**
Support the development of guidance documents and training materials covering various technical aspects of good *in vitro* method development and practices in order to sustain a high level of efficiency and effectiveness of the network in supporting validation studies, and to expand its capacity and expertise in order to keep pace with technological and methodological developments that are reflected in methods submitted for validation.
- vi. **Surveillance of uptake and use of validated *in vitro* methods**
Support the surveillance of the uptake and use of *in vitro* methods that have undergone validation to assess in-field post-validation performance against the originally intended purpose and to exploit data generated by end-users to further refine the method description and review the applicability domain.

5. Tasks of EURL ECVAM

The primary tasks of EURL ECVAM in the context of its participation within EU-NETVAL are the following;

- i. **Coordination of EU-NETVAL**
EURL ECVAM will coordinate the EU-NETVAL network.

- ii. **Definition and description of *in vitro* methods**
Finalise the definition of *in vitro* methods including the technical assessment (non-experimental or experimental) of Standard Operating Procedures (SOPs) in terms of their scientific basis, completeness, clarity, robustness and suitability for implementation within a GLP environment. This includes ensuring that the definition of *in vitro* methods are suitably elaborated as method descriptions and prepared in a format fit for public dissemination through EURL ECVAM's database on alternative methods, DB-ALM³
- iii. **Assessment of the reproducibility of *in vitro* methods**
Generate GLP compliant test data to determine within-laboratory reproducibility of an *in vitro* method subject to validation. This will also serve as a preparatory step towards the design and execution of validation ring-trials carried out by EU-NETVAL members.
- iv. **Management of validation studies**
Manage EURL ECVAM validation studies according to project plans which includes aspects such as finalisation of test definition and SOPs, training and support of facilities participating in validation studies, provision of materials, collection and statistical analysis of test data, and the preparation of validation reports.
- v. **Selection of test facilities for membership of EU-NETVAL**
Select EU-NETVAL members as the need arises through the publication of calls and the assessment of applicant test facilities against eligibility criteria.
- vi. **Selection of test facilities to support validation studies**
Select EU-NETVAL members for the execution of tasks in support of validation studies based on specific allocation criteria as detailed in each task proposal presented to EU-NETVAL members.
- vii. **Guidance documents and training materials supporting validation**
Take the lead in the development of guidance documents and training materials covering various technical aspects of good *in vitro* method development and practices in order to sustain a high level of efficiency and effectiveness of the network in its support of validation studies, and to expand its capacity and expertise in order to keep pace with technological and methodological developments that are reflected in methods submitted for validation.
- viii. **Technical training courses and materials on validated *in vitro* methods**
Development and running of training courses and preparation of related training materials aimed primarily at supporting validation studies but which will also facilitate the dissemination and uptake of *in vitro* methods within the EU and the use of GLP as a quality system for *in vitro* test facilities.
- ix. **Harmonisation and standardisation of *in vitro* methods**
Facilitate the international harmonisation and standardisation of validated *in vitro* methods to aid their translation into internationally recognised standards and test

³ <http://ecvam-dbalm.jrc.ec.europa.eu/>

guidelines and to ensure their acceptance for regulatory use.

- x. **Information exchange on best practice regarding *in vitro* methods**
Facilitate information exchange within EU-NETVAL on best practice concerning *in vitro* method development, validation and application, including exploitation of new technologies.
- xi. **Promotion of EU-NETVAL and informing on activities**
Keep NCPs, collaboration partners (e.g. the European Partnership on Alternative Approaches to Animal Testing, the International cooperation on Alternative Testing Methods), stakeholders and the general public informed on EU-NETVAL activities and take a leading role in promoting the work of EU-NETVAL and ensuring its visibility both within the EU and world-wide.
- xii. **Enabling collaboration**
Provide opportunities, processes, tools and coordination for efficient and effective collaboration between both network members and between EU-NETVAL and cooperation partners.

6. Allocation of tasks and consultation of Member States

EU-NETVAL members will be invited to submit a proposal to EURL ECVAM to undertake a specific task that has been proposed to the network. After receiving these proposals, EURL ECVAM will evaluate them against the allocation criteria defined for that task. Based on this evaluation, EURL ECVAM will select the members to undertake the task. Before final allocation of tasks to selected EU-NETVAL members, Member States will be consulted via the NCPs.

7. Financing of EU-NETVAL activities

The financing model employed to support EU-NETVAL activities will vary in nature depending on the specific task(s). In general however, the costs of EU-NETVAL activities are covered by a combination of direct and indirect (e.g. in-kind) financing from Member States, EU-NETVAL members, and the Commission.

EU-NETVAL members and Member States are typically expected to provide the necessary human resources and to cover related costs when undertaking the execution of a task. Support given by the Commission could include task coordination and reporting of task and study outcomes, the training of participating facilities on an *in vitro* method associated with a validation study, the supply of some *in vitro* method materials such as test systems (e.g. cells or tissues), chemicals and other consumables, the provision of data-reporting templates and bio-statistical support, and the organisation of virtual and physical meetings when necessary.

The model does not impose obligations on the Member States beyond those imposed by Directive 2010/63/EU.

On occasion, the GLP facility of EURL ECVAM will also carry out a laboratory evaluation of *in vitro* methods prior to the launch of a EU-NETVAL validation study to ensure, for example, that the *in vitro* method procedure is optimised and sufficiently described.

8. Abbreviations

EFTA: The European Free Trade Association

EU: European Union

EU-NETVAL: The European Union Network of Laboratories for the Validation of Alternative Methods

EURL ECVAM: European Union Reference Laboratory for Alternatives to Animal Testing

GLP: Good Laboratory Practice

JRC: [European Commission] Joint Research Centre

NCPs: National Contact Points of the Member States as provided under Article 59 of Directive 2010/63/EU on the protection of animals used for scientific purposes

SOP: Standard Operating Procedure