EUROPEAN COMMISSION
JOINT RESEARCH CENTRE
Institute for Health and Consumer Protection
Systems Toxicology Unit
EU Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM)

Joint PARERE-ESTAF Meeting

5th and 6th June 2014,

Somma Lombardo, Italy

The agenda of the Joint PARERE-ESTAF meeting is included in Annex I. EURL ECVAM introduced each of the agenda items with a short presentation to inform the discussions and in some cases relevant documents were provided before the meeting. These presentations and documents are available on CIRCABC.

1. Overview of EURL ECVAM activities

- EURL ECVAM introduced its key responsibilities with regard to alternative methods (coordinating/promoting their development, validation and use; facilitating exchange of information on their development; managing dissemination databases/information systems; promoting dialogue between legislators, regulators and stakeholders – more information at https://eurl-ecvam.jrc.ec.europa.eu/) and presented an overview of its recent activities and achievements (e.g. EURL ECVAM Recommendations; release of a survey on test methods in the area of toxicokinetics; international cooperation with 3Rs/validation partners within the framework of ICATM, the International Cooperation on Alternative Test Methods).
- EURL ECVAM presented an overview of its engagement in important OECD projects related to Adverse Outcome Pathway development (within the Extended Advisory Group on Molecular Screening and Toxicogenomics) and Integrated Approaches to Testing and Assessment (within the Test Guideline Programme and in the Task Force on Hazard Assessment). The role of EURL ECVAM within the major research initiative SEURAT-1 (Safety Assessment Ultimately Replacing Animal Testing, www.seurat-1.eu) and details of the upcoming Horizon 2020 call (PHC-33) on predictive approaches to human safety were also briefly described.

2. Updates on the EURL ECVAM validation workflow

- EURL ECVAM described its validation workflow that starts with the initial evaluation of submitted test methods to the issuing of a EURL ECVAM Recommendation (see https://eurl-ecvam.jrc.ec.europa.eu/validation-regulatory-acceptance/eurl-ecvams-validation-process).
- EURL ECVAM Recommendations are considered to be the 'final product' of the validation process, representing an important milestone on the road to regulatory acceptance (e.g. via OECD Test Guideline development) and uptake. The aim of an EURL ECVAM Recommendation is to provide EURL ECVAM views on the validity of the test method in question, to advice on possible regulatory applicability, limitations and proper scientific use of the test methods, and to suggest possible follow-up activities in view of addressing knowledge gaps or pursuing the development of test guidelines (see https://eurl-ecvam.jrc.ec.europa.eu/eurl-ecvam-recommendations).

Recommendations are proving to be an effective instrument in stimulating dialogue regarding regulatory acceptance and uptake, not only within the EU but also internationally.

3. Questions & Answers, 360° session on validation and acceptance

- PARERE, ESTAF and EURL ECVAM exchanged views on several issues during this question and answer session. Questions were posed by different parties [indicated below];

1. ***What drives the pace of ESAC opinions and release of EURL ECVAM Recommendations and can it be speeded up? [ECEAE];*** EURL ECVAM: ESAC peer-reviews take on average less than 6 months. The only recent exception was the review of the KeratinoSens test method which took 12 months due to several difficulties that the ESAC encountered when reviewing the material which led to two requests for clarification that were sent to the submitter on ESAC's behalf. Thus the way in which the data and information are presented has a key impact on the timelines of the peer-review. Furthermore, the actual peer review does not start with the ESAC request since EURL ECVAM may start discussions on projects/requests with ESAC even before the validation studies are completed. The actual peer review rather starts when the ESAC Working Group has its first meeting. EURL ECVAM is constantly looking for ways to expedite the process where possible, without compromising on thoroughness and impartiality.
2. ***Would it be possible to set up special committees at the level of ESAC that would specifically work on similar ('me-too') tests to accelerate their evaluation? [IVTIP];*** EURL ECVAM: A leaner review process is already foreseen at ESAC level for the review of similar ('me-too') tests. Thus such a committee would not bring any additional benefit.
3. ***Is there a process for a test submitter to repeal/question a decision from EURL ECVAM on a certain submission, or question it? [EUSAAT];*** EURL ECVAM: The submitter has always the possibility to contact EURL ECVAM (in writing) at any time to seek clarification or express a concern. At the stage of test submission, a decision is usually taken after a thorough internal review of the submission which often includes dialogue and information exchange between EURL ECVAM and the submitter. When the submitter is informed of the decision, the basis for the decision is clearly communicated, always together with an assessment report. For methods which have progressed through ESAC peer review, before the issuing of a EURL ECVAM Recommendation, the test submitter is invited to formally to comment on the draft Recommendation during the 'right to be heard' process.
4. ***What is your opinion on the usefulness of a Recommendation within a 'non-OECD TG context'? [EURL ECVAM];*** EFPIA: In the pharmaceutical sector, industry uses non-standard methods for screening purposes, rarely OECD TGs. In a regulatory context however, i.e. before clinical testing, they use ICH test guidelines which are based on test methods that have been standardised. During the acceptance process of pharmaceuticals, which is very long, the industry can also discuss with regulators and build a case for the test method(s) they have used and regulators may accept the data on a case by case basis.

5. ***How does the communication between ESTAF and EURL ECVAM function? How are ESTAF comments taken into account? [EUSAAT];*** This question had been addressed to a large extent during the presentation on the EURL ECVAM validation workflow. ESTAF's input may be requested at the level of submitted test methods with regard to the method's relevance (from a stakeholder point of view) and each time at the level of draft EURL ECVAM strategy documents and draft EURL ECVAM Recommendations. In the case of consultations on test submissions and Recommendations, EURL ECVAM endeavours to provide a summary of the feedback received. Overall the aim is to have a continuous reciprocal communication flow and not to restrict it solely to meetings.
6. ***Pros and cons of a fully transparent model of test submissions i.e., if all details of submissions should be made available to the public? [EURL ECVAM].*** It was agreed that industry and research associations in particular (i.e. potential test submitters) will go back to their members to consider this questions carefully.

- Questions that will need a follow-up (due to lack of time to discuss):

1. ***How to progress methods with confidential information and/or (pending) intellectual property rights, for which not all information can be disclosed? [EURL ECVAM]***
2. ***What is the level of uptake by industry? How often is information derived from alternative methods? [SCCS]***
3. ***Could we have a timeline retracing the fate of a test method from the submission to the release of a Recommendation? [ESTIV]***
4. ***Can we speed up the acceptance process at the OECD for new Test Guidelines, and their inclusion in the Test Methods Regulation? [ECHA]***

4. European Union Network of Laboratories for the Validation of Alternative Methods (EU-NETVAL)

- The establishment of EU-NETVAL (see https://eurl-ecvam.jrc.ec.europa.eu/eu-netval) in the context of Directive 2010/63/EU was presented to the PARERE and ESTAF participants.
- Three aspects were explained: (i) Application process to EU-NETVAL and its related calls; (ii) Data management and (iii) Resources.

(i) Applications are assessed according to eligibility criteria which applicant laboratories have to comply with. It was agreed that PARERE and ESTAF would be informed directly about future calls.

(ii) Data generated by EU-NETVAL laboratories are collected and centralised in electronic platforms to prevent any loss of raw data. This system is complementary to the laboratory storage that is mandatory for compliance with GLP.

(iii) According to Directive 2010/63/EU, MS shall contribute to validation studies. Therefore, although it appears that Member States do not typically allocate

dedicated budgets to support validation studies, it is anticipated that this may change to facilitate better compliance with the provisions of the Directive.

5. Dissemination activities

- PARERE-ESTAF members were informed about the status and revisions performed in the Data Base on Alternative Methods (DB-ALM) managed by EURL ECVAM. Entirely revised search interfaces are being implemented providing greater flexibility during data retrieval procedures and allowing method searches from different point of views. The content of the DB-ALM covers a broad range of topics such as methods summary descriptions and protocols; EU integrated projects; validation studies and test results (see http://ecvam-dbalm.jrc.ec.europa.eu/).
- An update was provided on the development status of the Tracking System for Alternative methods towards Regulatory acceptance (TSAR, see http://tsar.jrc.ec.europa.eu/). TSAR is an integrated system that has recently been adopted by ICATM partners to serve as common platform for providing information on the status of test methods submitted for validation to a broad range of actors and stakeholders. The TSAR structure describes the progress of a method through the four main steps of the validation workflow (i.e. assessment of test submissions, validation studies, peer review and recommendations) and the process of regulatory acceptance in various domains/contexts. It will have extended browsing possibilities e.g. searches can be refined by status of the methods, topic area, date of submission etc.
- Public release of TSAR is expected in Q1/Q2 of 2015 and an update of the QSAR (see http://ihcp.jrc.ec.europa.eu/our_databases/jrc-qsar-inventory) model database with new information content will be published still this year. The formal public launch of the revised version of *DB-ALM 2014* is planned for the World Conference this August in Prague .
- The Chemical Lists Information System (Chelist, see http://chelist.jrc.ec.europa.eu/), was recently published. It provides a means of identifying whether a chemical (or a chemical group) is on a particular list associated with, for example, a major EU/international research project, a validation study, or a regulatory inventory.

6. EURL ECVAM strategies and Integrated Approaches to Testing and Assessment

- EURL ECVAM presented strategies that are in preparation in different areas:
    - Toxicokinetics
    - Acute systemic toxicity
    - Fish toxicity and bioaccumulation

Participants had the opportunity to ask questions make comments/suggestions to be taken into account by EURL ECVAM.

- EURL ECVAM strategies (see https://eurl-ecvam.jrc.ec.europa.eu/eurl-ecvam-strategy-papers) serve to give an overview of regulatory information requirements across diverse industrial sectors regarding toxicological hazard of substances (e.g. chemicals, biocidal products, pharmaceuticals, cosmetics) and to propose strategic aims and associated objectives that would have 3Rs impact. These strategy documents are intended to be accessible to a broad range of actors and stakeholders to facilitate consensus forming on key priorities and opportunities, and to encourage cooperation and coordination between key contributors. They also serve as a basis for EURL ECVAM to plan its work programme.
- Participants discussed:
    - Whether the strategies presented were consistent with the scientific state-of-the-art and accurately reflect regulatory needs and priorities.
    - Whether the aims and objectives represent the best ways to achieve 3Rs impact in an efficient and effective manner.
    - The progress made to-date with the implementation of the EURL ECVAM Strategy for Replacement of Animal Testing for Skin Sensitisation Hazard Identification and Classification and how likely it is that approaches based on alternative methods, that are acceptable to regulators, will be available in time for companies to meet the 2018 REACH deadline. Overall progress is on track and EURL ECVAM is therefore optimistic: The OECD Test Guidelines (TG) on the Direct Peptide Reactivity Assay (DPRA) and KeratinoSens™ will be adopted in 2014, the draft TG on the human Cell Line Activation Test (h-CLAT) is under commenting at OECD level and the draft Guidance Document on IATA on skin sensitisation (including illustrative examples of IATA) will be finalised by 2015. However efforts from many engaged parties need to be sustained to ensure success.
- EURL ECVAM also presented an overview and its work on Integrated Approaches to Testing and Assessment (IATA). EURL ECVAM participated at the OECD level in the development of a Guidance Document for an IATA on skin irritation and corrosion (approved at the WNT in April 2014 and declassified by the OECD in July 2014) and is leading the current development of an IATA on skin sensitisation.

Actions:

(i) PARERE and ESTAF members should provide comments on the draft EURL ECVAM strategy on fish toxicity bioconcentration/bioaccumulation (already circulated) by 31 July 2014.

(ii) PARERE and ESTAF members should provide comments on the draft EURL ECVAM strategy on acute systemic toxicity (already circulated) by 31 July 2014.

(iii) EURL ECVAM will make available on CIRCABC all documents and presentations related to the items discussed at the meeting.

7. Any Other Business

ESTIV asked how the use of animals in the biomedical research area was being addressed, and how this topic could be best tackled. EURL ECVAM's primary activities addressing animal testing in the research field are the EURL ECVAM Search Guide and DB-ALM, that serve to make researchers aware of alternative approaches that could serve their purpose and which provide detailed information on them to allow their implementation by new users. This issue is also being addressed by various entities in the EU and beyond through different means. It was agreed that the biomedical research area could be a topic for discussion at a future meeting. The current state-of-play would be covered extensively at the World Congress in Prague (August 2014) and the outcome could help inform these discussions.

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Annex I

Joint PARERE-ESTAF Meeting

5th & 6th June 2014, Hotel Hilton Garden Inn, Somma Lombardo, Italy

Agenda

5th June 2014			
Item	**Time**	**Description**	**Format**
	14:00-14:30	Welcome and introductions (tour de table)	
1	**14:30-14:50**	Overview on recent EURL ECVAM activities *M. Whelan*	Presentation Discussion
2	**14:50-15:30**	Updates related to the EURL ECVAM validation workflow *V. Zuang*	Presentation Discussion
	15:30-16:00	*Coffee break*	
3	**16:00-17:00**	Q&A (360°) on validation and acceptance	Discussion
4	**17:00-17:30**	EU Network of Validation Laboratories (EU-NETVAL) *S.Coecke*	Presentation Discussion
5	**17:30-18:00**	Update on EURL ECVAM dissemination activities*A. Janusch-Roi*	Presentation Discussion
	18:00	Close of Day 1	
	19:30	*Dinner*	

6th June 2014			
Item	**Time**	**Description**	**Format**
6	**09:00-10:00**	EURL ECVAM strategy on toxicokinetics *J. Bessems*	Presentation Discussion
7	**10:00-10:45**	EURL ECVAM strategy on acute systemic toxicity *P. Prieto*	Presentation Discussion
	10:45-11:15	*Coffee break*	
8	**11:15-12:00**	EURL ECVAM strategy on fish toxicity *M. Halder*	Presentation Discussion

9	**12:00-13:00**	Integrated Approaches to Testing and Assessment (IATA) *J. Barroso*	Presentation Discussion
10	**13:00-13:30**	AOB	Discussion
	13:30	Meeting close	