The Future of Validation – Scrutiny at Stake?

_ecopa_ 12th ANNUAL WORKSHOP
MERCURE MADRID SANTO DOMINGO, 2011-11-11

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HISTORY of VALIDATION & ACCEPTANCE
Validation History: Amden I (1990)

**DEFINITION**
Validation is the process by which the reliability and relevance of a procedure are established for a particular purpose.

**PROCEDURE**

1. Test Development
2. Intra-laboratory assessment
3. Inter-laboratory assessment
4. Test database development
5. Independent Evaluation
6. Acceptance

- **number of test chemicals suggested**
  - (1) 5-10
  - (2) 20-50
  - (3) 10-20
  - (4) 200-250 (!!!!)
Validation History: Vouliagmeni (1990)

- **INDEPENDENT ASSESSMENT:**
  - Before regulatory authorities are asked to consider formal acceptance the published results of a validation study should be considered by one or more independent assessment panels (Peer Review Panels).

- **THESE PANELS SHOULD ASSESS:**
  - quality of design and conduct of study (test selection, laboratories involved, selection of test chemicals and quality of in vivo data)
  - quality of reporting, data analysis and conclusions
  - value of validated test in competition with other methods


Lessons learnt: Pre-validation (1995)

**Principle:**

In a cost-effective, sequential procedure starting with one laboratory and ending up with three laboratories and a mini-blind trial, test

- **Transferability** and needs for refinement (lab 1)
- **Reproducibility** (lab 1 + 2)
- **Performance** (incl. Prediction Model) (lab 1 + 2 +3)


- Reduced number of labs
- Reduced number of chemicals
- Improved study management
- Involvement of independent expert groups


no consensus reached on: "what is peer" ? & "which performance is acceptable " ?
- no Amden III report published
Validation and Acceptance: Harmonisation

CAAT & ERGATT - 1990 Amden I Workshop & Report
DG XI & FRAME - 1990 Vouliagmeni Workshop & Report
ECVAM & ERGATT - 1995 Amden II Workshop & Report
  - 1998 Amden III Workshop
ECVAM & DG XI - 1995 Statement ECVAM & ECB
ICCVAM - 1995 Workshop
  - 1997 Workshop Report
OECD - 1996 Solna Workshop
  - 2002 Stockholm Workshop
  - 2004 DIP Workshop Berlin
  - 2004 GD 34 Workshop Bethesda
  - 2005 Guidance Document No. 34 adopted

Final consensus on OECD GD 34: Bethesda 2004
Fifteen years after Amden I: GD 34 adopted (2005)

OECD GD 34: Modular Approach (ECVAM 2005)

<table>
<thead>
<tr>
<th>Test definition</th>
<th>yes</th>
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<tbody>
<tr>
<td>Within-lab. variability</td>
<td>yes</td>
</tr>
<tr>
<td>Transferability</td>
<td>yes</td>
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<tr>
<td>Between-lab. variability</td>
<td>yes</td>
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<tr>
<td>Predictive capacity</td>
<td>yes</td>
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<tr>
<td>Applicability domain</td>
<td>yes</td>
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<tr>
<td>Performance standards</td>
<td>yes</td>
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</tbody>
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- aids retrospective weight of evidence validation (meta-analysis of all data)
- aids identification of gaps and defining special studies to fill the gaps
- aids standardised, modular assessment of validity (Peer Review)
Development of a New OECD Test Guideline...

... is a process based on 100% consensus

at the OECD, majority agreements are impossible
In the Regulatory Context Validation is needed…

- …because OECD WNT would not even look at methods that have not been properly validated and independently reviewed

- … because the strategic combination of relevant information from a battery of in vitro tests is a much bigger challenge than looking into an animal model that provides the “full picture” in one test

- … because appropriate application of these techniques is more demanding of careful experimental design than ever, as the potential to generate incomplete and misleading data is great.

Because of that importance

In addition to strong commitments of Industry, the Commission funded the Validation Studies via ECVAM like

- phototoxicity
- skin corrosion
- skin irritation

finally resulting in OECD Test Guidelines 430, 431, 432, 435, 439
CURRENT support of VALIDATION

Funding of R&D and Validation of 3R Alternatives:
- Europe
- Germany
Research funding of 3R Alternatives in the EU

Allocation (Euro/annum)

- Italy
- Czech Rep.
- Hungary
- Norway
- Finland
- Austria
- Switzerland
- Slovakia
- Belgium
- Spain
- Netherlands
- UK
- Sweden
- France
- Denmark
- Germany

Devolder et al. 2008

Funding of 3R Alternatives in Germany

no validation

no validation
Funding of 3R Alternatives by BfR-ZEBET

Examples (of over 100 projects since 1990)
Funding of 3R Alternatives by BMBF

Since 1981

Total budget since ‘81: 100 million €

Total number of projects: > 360

Funding of R&D and Prevalidation

Joint projects (industrial partners!)

http://www.bmbf.de/de/1040.php

Funding of Alternatives by the European Union

- Cell-based technologies
- Integrated testing strategies
- -omics, bioinformatics & computational biology
- Computational modelling
- High throughput technique

NO FUNDING OF VALIDATION STUDIES

like

SMT within the 5th FRAMEWORK
The New EC Validation Procedures

- Proposal for a Validation Study to ECVAM (Presubmission)
- ECVAM involves regulators via MS-NSPC’s to check regulatory relevance PARERE (Preliminary Analysis of Regulatory Relevance)
- ECVAM involves stakeholders and users to assess usefulness via ESTAF (ECVAM STakeholder Advisory Forum)
- ECVAM sets priorities for Validation Studies (how??)
- ECVAM selects laboratories from a repository without involving MS-NCP’s (with priority on those that need no funding!)
EC forgot Importance of permanent Involvement of regulating SCIENTISTS in Validation !!

- Definition of Information Needs (suitable readouts / endpoints new Method)
- Selection of suitable Tests
- Selection of suitable Test Chemicals
- Participation in Method Peer Reviews
- Participation in international Consolidation Processes (e.g. OECD, ICH, ISO)
- Participation in Definition of Performance Standards

**Definition of Special Studies** to enlarge applicability domain (= enlarge regulatory acceptance in new areas than originally validated)
Regulators involved / not involved: Test Chemicals
(Example: *In Vitro* Skin Corrosion Tests)

ECVAM Validation Study

\[ \text{pH distribution} \]

\[ \text{acids + bases} = \text{minority} \]

replacement of \text{animals}

Corrositex

Company Submission to ICCVAM

\[ \text{pH distribution} \]

\[ \text{acids + bases} = \text{majority} \]

replacement of a \text{pH meter}

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DIR 2010/63/EU: MS contribution to validation

**DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL**

**of 22 September 2010**

on the protection of animals used for scientific purposes

**Article 47**

Alternative approaches

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.
DIR 2010/63/EU: MS contribution to validation

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.

5. Member States shall nominate a single point of contact to provide advice on the regulatory relevance and suitability of alternative approaches proposed for validation.

6. The Commission shall take appropriate action with a view to obtaining international acceptance of alternative approaches validated in the Union.

Commission call for Validation Laboratories

EUROPEAN COMMISSION
JOINT RESEARCH CENTRE
Institute for Health and Consumer Protection (ifpra)
Validation of Alternative Methods

Ispri, 5th October 2011
BfR/F03/36/bw Ares(2011)

Bundesministerium fuer Ernahrung, Landwirtschaft und Verbraucherschutz
Attn. Ms. Kluge
Rochusstrasse 1
D-53123 Bonn
Germany

Dear Dr. Kluge,

Directive 2010/63/EU on the protection of animals used for scientific purposes formally established the European Center for the Validation of Alternative Methods (ECVAM), hosted by the European Commission’s Joint Research Centre as the European Union Reference Laboratories (EURL) for Alternatives to Animal Testing. In support to this EURL, the Directive also requests that the Member States identify laboratories suitably qualified to carry out validation studies. As ECVAM is, inter alia, responsible for coordinating the validation of
Commission call for Validation Laboratories

validation studies. As ECVAM is, *inter alia*, responsible for coordinating the validation of alternative approaches at the European Union level, it herewith invites Member States to provide the coordinates of laboratories that should become part of a network of laboratories for the validation of alternative methods. Member States are not limited by the number of laboratories they would like to put forward.

ECVAM will establish an inventory of the nominated laboratories and will invite on a case by case basis those laboratories with the appropriate expertise and experience to participate in or to carry out validation studies. We expect a high interest and contribution from the assigned National expert laboratories. *If several laboratories are interested and capable to provide the requested contribution, those that can cover the biggest share of their own cost will be preferred.* In return, and to the extent possible, ECVAM will provide and make available the test chemicals to the participating laboratories and support the training of the participating laboratory personnel in the specific method.

- Current procedure circumvents nomination. The lab application questionnaires have to returned to EURL

He, who pays the piper calls the tune!

Does this also hold for Validation Studies?

YES

- Quality has its price
- Labs with established QC procedures will not do work for free
- A service contract including payment in exchange to delivered validation data is needed.
Personal Conclusion

- We are spending 100'ds of million € for investigating novel approaches, and at the same time do not spend a penny on validation of these approaches.
- I observe an increasing gulf between the (necessary and welcome!) novel approaches developed in basic science and regulatory information needs and expectations.
- In contrast to simple ring trials of analytical methods the validation of predictive methods to protect humans and environment is a highly scientific process.

EU Funding Programm Vision 2020

If we do not start to think about how to scientifically assess the new approaches for their validity and who will pay for it, the new roads that we are currently constructing will end nowhere.
Thanks
for your attention
and patience!

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