FEDERAL INSTITUTE FOR RISK ASSESSMENT

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http://www.remanet.net/

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 } **VALIDATION**

(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

Balls et al. (1990) Report and Recommendations of an International Workshop on Promotion of the Regulatory Acceptance of Validated Non-animal Toxicity Test Procedures ATLA 18: 339-344, 1990

Lessions 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)

Curren RD, Southee JA, Spielmann H, Liebsch M, Fentem JH & Balls M (1995) The Role of Prevalidation in the Development, Validation and Acceptance of Alternative Methods. ATLA 23: 211 - 217

Lessions learnt: Amden II (1995)

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

M. Balls, B.J. Blaauboer, J.H. Fentem, L. Bruner, R.D. Combes, B. Ekwall, R.J. Fielder, A. Guillouzo, R.W. Lewis, D.P. Lovell, C.A. Reinhardt, G. Repetto, D. Sladowski, H. Spielmann and F. Zucco Practical Aspects of the Validation of Toxicity Test Procedures The Report and Recommendations of ECVAM Workshop 5, ATLA 23: 129 - 147, 1995

Lessions learnt ?: Amden III (1998)

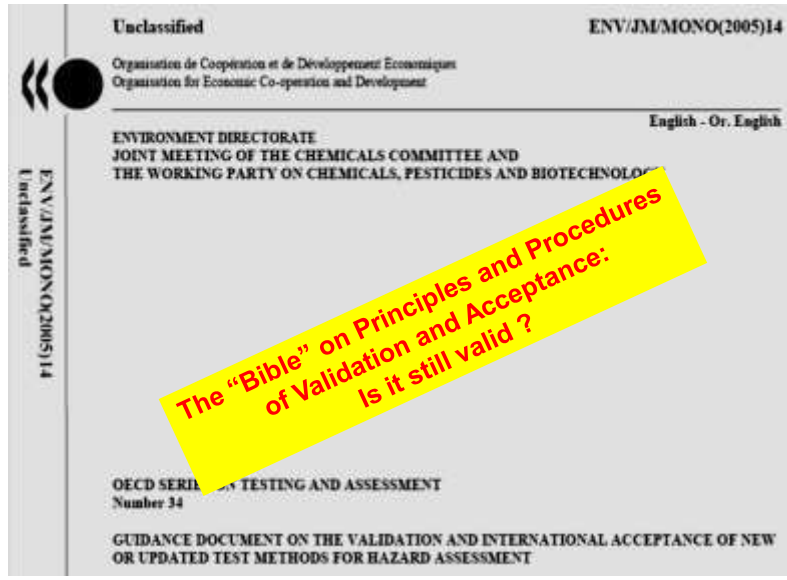
no consensus reached on: "what is peer" ?
& "which performance is acceptable " ?
- no Amden III report published

Validation and Acceptance: Harmonisation

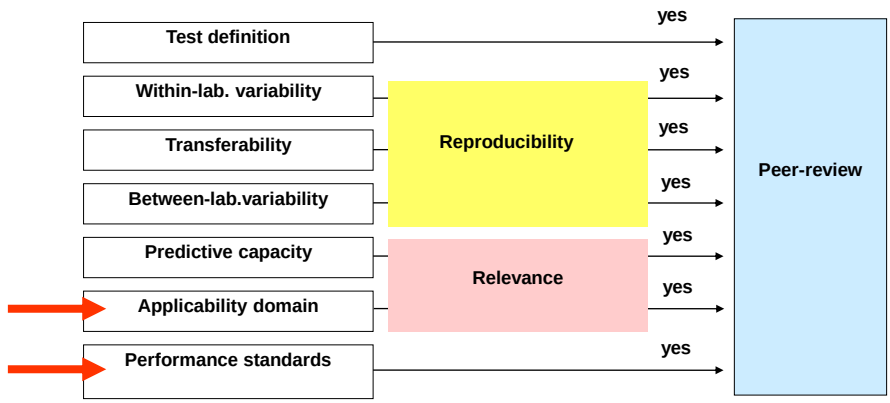
CAAT & ERGATT	- 1990	Amden I Workshop & Report
DG XI & FRAME	- 1990	Vouliagmeni Workshop & Report
ECVAM & ERGATT	- 1995	Amden II Workshop & Report
	- 1998	Amden III Workshop
ECVAM & DG XI	- 1995	Statement ECVAM & ECB
ICCVAM	- 1995	Workshop
	- 1997	Workshop Report
OECD	- 1996	Solna Workshop
	- 2002	Stockholm 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)

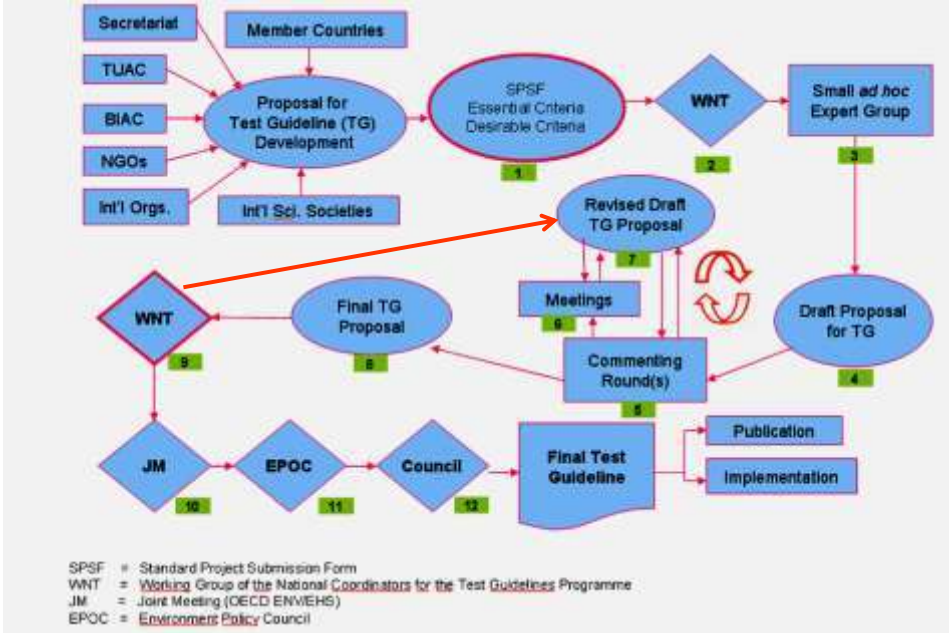


OECD GD 34: Modular Approach (ECVAM 2005)

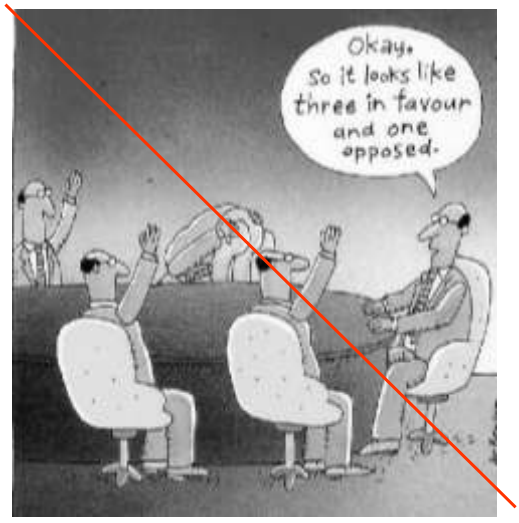


- aids retrospective **weight of evidence validation** (meta-anlyis of all data)
- aids **identification of gaps** and defining specials studies to fill the gaps
- aids standardised, **modular assessment of validity** (Peer Review)

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.

Sentence taken from a slide Phil Botham presented 2002 in Brussels

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

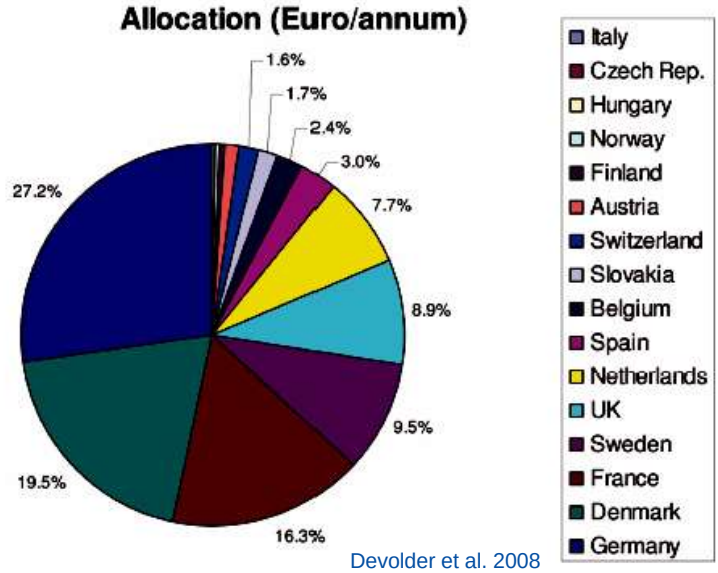
finally resulting in
OECD Test Guidelines 430, 431, 432, 435, 439

CURRENT support of VALIDATION

Funding of R&D and Validation of 3R Alternatives:

- Europe
- Germany

Research funding of 3R Alternatives in the EU



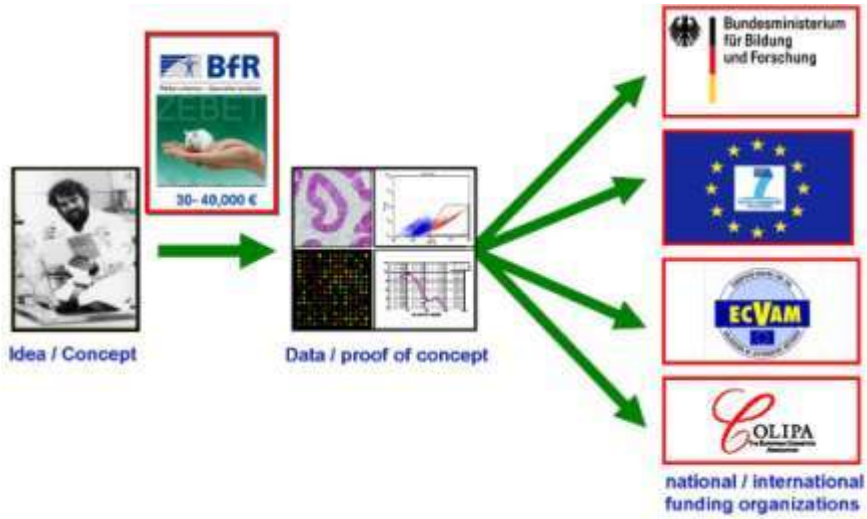
Devolder et al. 2008

Funding of 3R Alternatives in Germany

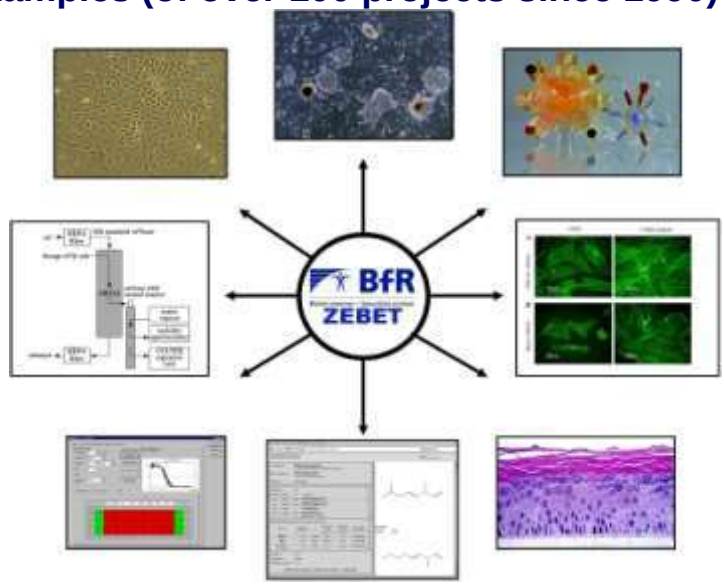
no validation

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

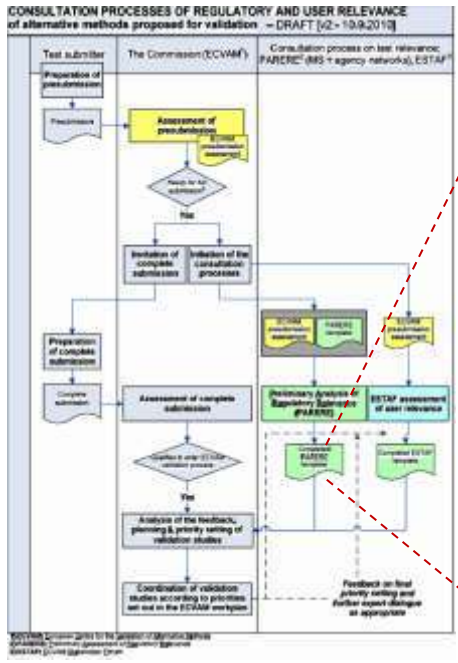
- Cell-based technologies
- Integrated testing strategies
- -omics, bioinformatics & computational biology
- Computational modelling
- High throughput technique

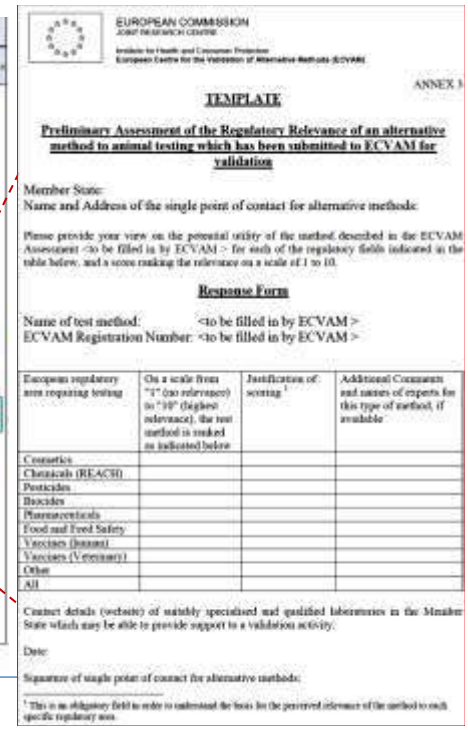
NO FUNDING OF VALIDATION-STUDIES
like
SMT within the 5th FRAMEWORK

FUTURE
of
VALIDATION
& ACCEPTANCE

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
  (**P**reliminary **A**nalysis of **R**egulatory **R**elevance)
- ECVAM involves stakeholders and users to assess usefulness via ESTAF
  (**E**CVAM **ST**akeholder **A**dvisory **F**orum)
- 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!)**





EUROPEAN COMMISSION

ANNEX 3

TEMPLATE

Preliminary Assessment of the Regulatory Relevance of an alternative method to animal testing which has been submitted to ECVAM for validation

Member State:
Name and Address of the single point of contact for alternative methods:

Please provide your view on the potential utility of the method described in the ECVAM Assessment <to be filled in by ECVAM> for each of the regulatory fields indicated in the table below, and a score ranking the relevance on a scale of 1 to 10.

Response Form

Name of test method: <to be filled in by ECVAM>
ECVAM Registration Number: <to be filled in by ECVAM>

European regulatory area requiring testing	On a scale from "1" (no relevance) to "10" (highest relevance), the test method is ranked as indicated below	Justification of scoring [1]	Additional Comments and names of experts for this type of method, if available
Cosmetics			
Chemicals (REACH)			
Pesticides			
Biocides			
Pharmaceuticals			
Food and Feed Safety			
Vaccines (human)			
Vaccines (Veterinary)			
Other			
All			

Contact details (website) of suitably specialised and qualified laboratories in the Member State which may be able to provide support to a validation activity:

Date:

Signature of single point of contact for alternative methods:

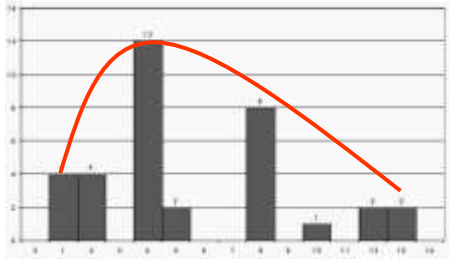
[1] This is an obligatory field in order to understand the basis for the perceived relevance of the method to each specific regulatory area.

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)

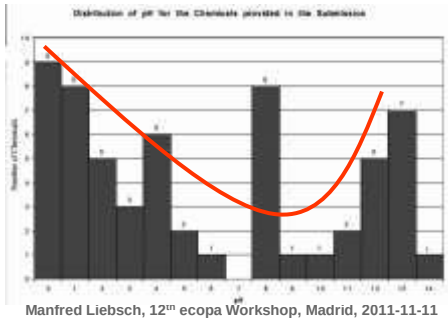
Regulators involved / not involved: Test Chemicals

(Example: *In Vitro* Skin Corrosion Tests)



ECVAM Validation Study
pH distribution
acids + bases = minority

replacement of **animals**



Corrositex
Company Submission
to ICCVAM
pH distribution
acids + bases = majority

replacement of a **pH meter**

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

Nomination Impossible !!

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

In conflict With National Funding !

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.

PARERE (dog without teeth)

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 (Ispra)
Validation of Alternative Methods

Ispra, 5th October 2011
IHCP/I03/JK/bw Ares(2011)

Bundesministerium fuer Ernaehrung,
Landwirtschaft and 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 Reserch Centre as the European Union Reference Laboratory (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.

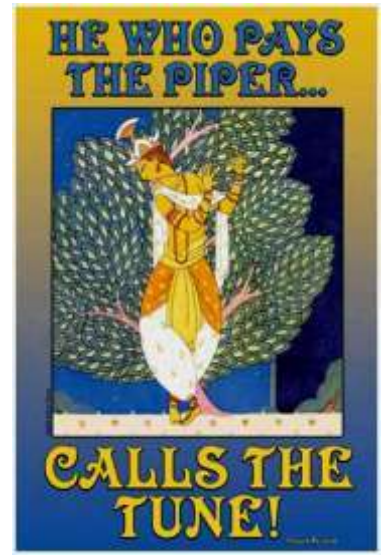
- Current procedure circumvents nomination. The lab application questionnaires have to returned to EURL

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.**



www.barewalls.com

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

FEDERAL INSTITUTE
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Thanks
for your attention
and patience !

Manfred Liebsch

BfR Unit 92: Alternative Methods to Animal Experiments – ZEBET

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