



REGULATORY ACCEPTANCE OF ALTERNATIVE APPROACHES



**EPAA WORKSHOP
18-19 June 2007 - Centre Borschette, Brussels**

Day One: DRIVERS FOR ACCEPTANCE: UNDERSTANDING SECTORAL REQUIREMENTS

Introduction

Developing and validating alternative methods for regulatory testing purposes can only make sense if at the end of the process regulatory authorities accept it is used for registration or authorisation of a product or compound.

This important issue was given a high priority by the EPAA, with an action on identifying barriers to acceptance and developing an action plan to overcome them. Setting up a working group specifically dedicated to validation and regulatory acceptance of 3Rs approaches shows also the importance of these matters, which are closely interlinked.

The workshop of 18 and 19 June in Brussels was a first attempt to understand sector specific acceptance criteria within a given regulatory framework. Based on case studies, participants identified barriers and possible way forward for overcoming these. This workshop addressed more specifically the pharmaceutical and biologicals, as well as the cosmetics and agrochemicals needs. Future work will also cover the needs of the chemical sector.

This summary reflects the main conclusions from a very open discussion, which sets the tone for a regular dialogue between regulators, industry/researchers and policy makers.

The 2007 EPAA annual conference will provide an opportunity to present these outputs and discuss them with a wider audience, including international trading partners.

Link to presentation

Different sectors – different criteria?

Regulatory requirements can be different from sector to sector, depending on the specific aspects of the relevant legal framework. Also, in some sectors, the use of specific test methods is subject to regulation, in others to guidance.

Pharmaceuticals International guidelines (ICH/VICH)

Guidelines on testing for key areas of non-clinical safety testing for pharmaceuticals have been agreed by regulatory authorities from Europe, Japan and USA within the **ICH** (human medicines) or **VICH** (veterinary medicines), which are agreed by regulatory authorities from Europe, Japan and USA. There are few EU specific guidelines (e.g. photosafety). Implementation of regionally developed 3R methods will for most cases be impossible. A1997 **EMA** Position Paper on Replacement of Animal Studies by In Vitro Models (CPMP/SWP/728/95) addresses the feasibility of

replacement, procedures for validation and regulatory acceptance. It also sets areas for which the acceptance of in vitro tests can be considered. This non-legally binding position paper has never been applied and **CHMP** considerations on this issue are now put at the disposal of interested parties.

The ICH mission includes a commitment to take 3R aspects into consideration, but no formal criteria were defined. However, in May 2007 an ICH working group comprising representatives from validation bodies of the three regions (**ECVAM**, **ICCVAM** and **JaCVAM**) met to explore ways to collaborate in the future, to ensure that input of these bodies is sought when drafting new or revising guidelines.

The robustness of a 3R method has to be scientifically justified. The peer review is part of this process of guaranteeing scientific robustness. If a method were to be used in a regulatory context this robustness would have to be demonstrated to regulatory authorities.

Refinement and Reduction in regulatory carcinogenicity studies

6 month transgenic mouse models (p53, TgrasH2, Tg-AC, XPA-Knock out / in vitro SHE assay) was proposed to replace 2-year mouse bioassay. ILSI HESI carried out a collaborative validation study (with involvement of regulators from the 3 ICH regions) to define protocol and set of positive/negative compounds. The new model was mentioned as potential option in revised ICH S2 guideline and after evaluation of the study included in the EU specific recommendations for selected models.

Replacement of phototoxicity in vivo testing

The in vitro 3T3 NRU PT is recognised to replace animal phototoxicity test. The formal validation process (driven by the cosmetics and chemical sectors) resulted in OECD guidance TG432. This recommendation was taken up by the pharmaceutical sector and implemented in 2002 in an EU Photosafety guideline which recommends using the in vitro model. No ICH guidance was adopted yet.

Refinement and reduction in genotoxicity testing

This approach is being included in ICH guidelines. The revision process is carried out based on data provided by industry in the 3 ICH regions. This approach may have impact on other sectors:

- Integration of genotoxicity endpoint in general toxicity studies (no stand-alone acute in vivo MN

test needed)

- Integration of multiple endpoints/multiple tissues into one study
- Avoidance of irrelevant positive results in mammalian cell tests removes the need for additional follow-up animal studies

Acceptance and implementation of 3Rs can be achieved by different procedures, to best respond to specific purposes and requirements.

International processes, like ICH/VICH, which will integrate in the future also specific 3Rs expertise, seem to be the best mechanism and can constitute a model for other sectors. Cross-sectoral dialogue, like the one initiated through EPAA, is also an opportunity to share best practice and should be further encouraged. Finally, information on existing 3Rs approaches and ongoing research in this field has to be shared more widely.

[Link to presentation](#)

Cosmetics **SCCP opinion before amendment to regulation**

The SCCP intervenes with regard to the modification of lists of ingredients authorised, banned or restricted. It will assess alternative methods used in relation to cosmetic ingredients safety assessment. Modifications of the relevant annexes will be based upon an opinion of the SCCP.

The criteria for acceptance applied by the SCCP are of scientific nature:

- A method must be first validated in the context of the evaluation of chemicals safety or equivalent,
- It must have passed [ESAC](#) or [OECD](#) review
- It has to be useful for QRA and applicable for cosmetics ingredients (validation therefore should be performed on cosmetic ingredients, which is not always the case or demonstrated applicability)

Terms like "satisfactory" methods or "equivalent" methods as discussed in [REACH](#) do not exist in cosmetic regulations or guidance documents. ECVAM sees "equivalence" in the context of "me too"-alternatives.

Deadlines imposed by the Cosmetics Directive 76/768/EEC as amended by Directive 2003/15/EC, with a first set of bans by 2009 and total ban of safety tests involving use of animals by 2013, are considered as quite a challenge for getting sufficient number of available and validated replacement methods.

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Agrochemicals **Validated and non-validated methods – interpretation of test**

The relevant Directive on plant protection products 91/414/EC is currently under review. The new rules could be adopted towards the end of 2008 and enter into force by mid 2010.

Similarly to pharmaceuticals, there is no formal process or strictly defined criteria for acceptance. Regulators will accept methods with finalised validation or OECD

review process. However, non-validated methods will also be taken up if they satisfactorily predict a hazard.

Some methods developed in another sector could in theory be adapted to the needs of the agro-chemical sector. However, in this particular area, impurities, metabolites and residues constitute an additional difficulty for full extrapolation. Besides securing human safety, environmental risk assessment constitutes another hotspot, which requires extensive use of animals.

The existence of methods is not sufficient: experience has to be developed on how to interpret results that are generated. Also in case of high prediction of false negatives, regulators would have tendency to over-predict the hazard. Here more collaboration with other sectors can be very useful in order to determine the interpretation of data.

Solutions for better implementation of 3Rs in regulatory testing include optimisation of already accepted testing methods (more results from one study), transgenic mouse models should be used more often. Cross-sector collaboration is needed with the purpose of exchange of information about existing methods and support to development of guidance for interpretation of results from different alternatives available.

Guidance in agrochemical field

Guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under council directive 91/414/EEC

Guidance document on dermal absorption: Clear steps and cut-off values

[Link to presentation](#)

Biologicals **Product specific validation before publication in Pharmacopoeia monographs**

In the field of quality assurance of biological medical products (e.g. vaccines and hormones and blood products), validation and regulatory acceptance follow a strictly defined path.

The EDQM Biological Standardisation Programme is dedicated to development of 3Rs in this sector. It comprises validation through collaborative studies with involvement of industry, regulators and control laboratories. Following successful validation, alternative methods are proposed to the European Pharmacopoeia Commission to be included in the European Pharmacopoeia.

It has to be highlighted that alternative methods for quality check of biologicals have to be validated for each product by the manufacturer. This is due to variations in manufacturing process of biological medicines.

Product specific validation for biologicals

In the case of Newcastle Disease vaccine, a collaborative validation of an in-vitro method was done by the Biological Standardisation Programme of the EDQM and necessary new reagents are now available in large quantities. However, the test is not widely used yet since it still needs to be individually validated for each product.

Diphtheria vaccine: implementation of 3Rs

Method A: intradermal challenge test in Guinea-pigs
Method B: lethal challenge test in guinea-pigs
Method C: determination of antibodies in guinea-pigs (blood sampling)

Methods A or B are used 1) During the development of a vaccine, to assay batches produced to validate the production; 2) Wherever revalidation is needed following a significant change in the manufacturing process

Method A or B may also be used for the routine assay of batches of vaccine, but in the interests of animal welfare, method C is used wherever possible

Method C may be used after verification of the suitability of the method for the product. For this purpose, a suitable number of batches (usually 3) are testing using method C and methods A and B

There are still regional differences in acceptance of alternatives or waivers: while an abnormal toxicity test was definitely abandoned in Europe, it is still required in other regions by WHO or FDA.

The availability of sufficient number of reagents is also an important criterion for general acceptance of a test.

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Do liability issues play a role?

Concerns regarding the use of 3Rs have been raised in various EPAA workshops, both from the point of view of liability and the precautionary principle.

Liability has various facets -- product liability, regulatory liability, commercial liability -- and that the combined

effect might also be relevant to regulatory acceptance and uptake.

The precautionary principle serves as a guiding principle in regulations. Since traditional animal testing is widely seen as the gold standard, this approach is still privileged, which holds true for both regulators and industry.

The discussion has shown, however, that scientific robustness of the method is the key criterion for acceptance and eventually determines liability.

The formal process of the type of validation and need for publication might be driven by other considerations (full validation path and product specific validation for biologicals or extrapolation of methods used in other sectors based on interpretation of results (agrochemicals)).

The interpretation of the character of EU guidance/guidelines was also debated. Unlike regulations or directives, guidelines at EU level do not have a strictly binding character. However, they reflect a consensus statement of authorities, often in cooperation with stakeholders, and any deviation from this guidance must therefore be clearly justified. De facto, guidelines gain an implicitly a binding character. For reasons of transparency, a revision of guidelines should be preferred in case an alternative is accepted and/or recommended.

Flexible versus mandatory regulatory requirements with regard to the use of specific methods were discussed. Regardless of the nature of requirements, it was concluded that "one size does not fit all" and that a case-by-case approach is appropriate.

Where there is flexibility, the use of the best available method/technology gives highest assurance with regard to liability. Therefore liability questions are inevitably linked to the state of scientific and technical knowledge, and the debate about "best science" and toxicology paradigms.

To provide access to an international market, the overall "best level of acceptance" directs the choice of methods.

Day Two:

BARRIERS TO ACCEPTANCE – CASE STUDIES AND WAY FORWARD

Case Study 1: Pyrogenicity tests

T. Hartung (ECVAM) presented the case study of novel in vitro pyrogenicity tests.

Although the Limulus amoebocyte lysate assay substitutes for about 90% of the classical rabbit pyrogenicity test, this method has several limitations and in practice is not a full in vitro substitute (false positives)

Following validation of the five novel pyrogen tests and endorsement by ESAC in March 2006, work at European Pharmacopoeia's "Blood Product Group" (BPG) is ongoing to develop one general method that fulfils the regulatory needs for pharmaceuticals.

Work at ISO is also ongoing with a view to address testing for medical devices.

T. Hartung pointed out that some companies are not supportive of a new method that is more sensitive since it could block or hinder products from going faster into the market.

The representative of EDQM explained that the BPG including national EU, US, WHO and industry experts had recently concluded that more studies on the validity of in vitro pyrogenicity tests are needed before recommending in the Pharmacopoeia to pass from rabbit to the in vitro method. Due to liability concerns there was little support by the US experts for such replacement. Moreover, even at EU level, not all Member States were supportive, whilst for adoption of European Pharmacopoeia monographs unanimity of all 36 current Member States is needed.

[Link to presentation](#)

Case Study 2: CFU GM

L. Gribaldo (ECVAM) presented as case study the validation and ongoing acceptance of the in vitro CFU-GM assay for myelotoxicity/haematotoxicity. Although not a replacement method since studies in mice are still necessary, this method can deliver useful information primarily for early R&D screening and pre-clinical testing of anti-cancer drugs: if they show myelotoxicity they would be discarded and avoid further animal testing (reduction). Comments from the audience suggested that regulatory acceptance of the assay could be facilitated if it would be clearer which regulatory animal study the in vitro assay would be able to refine/reduce/replace (anti-cancer drugs protocols for pre-clinical studies are different from those for pharmaceuticals).

It was pointed out that there would be a high interest if the assay would be optimised to enable potency evaluation or rank ordering of compounds pre-screened therefore allowing use at an early stage such as the lead optimisation phase. A participant from EMEA suggested that in parallel to

evaluation of the validated assay by EMEA, the optimised protocol could be given to EFPIA for in use evaluation by the pharmaceutical industry. It was recommended that in addition to involvement of regulators, the end users from industry should be involved in the validation modules of new methods.

Furthermore, it was suggested that a mechanism should be established to make the competent authorities in the Member States who are responsible for implementing Directive 86/609 aware of: a) the roadmap of ECVAM validation – methods ongoing validation and b) the new validated methods that are available and their profile /applicability domain.

[Link to presentation](#)

Case study 3: Embryo-toxicity

T. Hartung presented the results of the validation study of three in vitro embryotoxicity tests on behalf of S. Bremmer (ECVAM). A post-validation workshop was organised by ECVAM to support the regulatory acceptance and application of the validated methods and its recommendations were used to set up the ReProTect project funded by FP6. The improved (human) Embryonic Stem cells Test (EST) has been recently proposed as further support for reduction of the 2nd species for regulatory developmental toxicity testing of industrial chemicals. Participants mentioned that the test was not suitable for pharmaceuticals.

It was underlined that the new test cannot be used to assess teratogenicity (later effects). Whilst it can satisfy the needs of existing chemicals testing under REACH, more risk analysis may be needed in the case of new substances.

[Link to presentation](#)

Case study 4: Transgenic mice

C. Ponsar (GSK) summarised in a presentation the long steps, including fundamental research, taken since 1991 for replacing oral polio vaccines quality testing (neurovirulence test) on monkeys by transgenic mice testing. In 2006 the European Pharmacopoeia approved the use of transgenic mice testing as an alternative to testing on monkeys. The limitations and advantages of the new method were explained. It has been highlighted that the EDQM introduced a new control strategy for the neurovirulence safety test with the test performed only once by the manufacturer with a close supervision from the National Control Authority. The method has been further suggested to be used to build a new reduced testing scheme for batch release of other well known vaccines based on GMP related consistency of vaccines production.

The EDQM representative explained that in the scientific and regulatory community testing on

monkeys is still considered as the “gold standard” due to history of good experience in spotting problematic vaccines in the past, being an easier technique and offering materials that the manufacturer can fix and present as evidence in case of future inspections. It was explained that the liability and political dimensions of the issue impact the acceptance of the new method, since the WHO would like to continue its global polio eradication programme without adverse human effects caused by vaccines produced in the EU but used mainly in developing countries.

The EDQM representative mentioned that under the current regulation, changing the batch quality control testing would be treated as “type II variation” for which pharmaceutical companies have to submit new studies supporting the safety of their product, even when the manufacturing process has not been changed. It was therefore recommended that since this process is currently under review by the EU (DG Enterprise, Pharmaceuticals Unit) there was opportunity for EPAA suggestions to facilitate future uptake of the alternative methods.

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Roundtable discussion:

How to promote acceptance and upcoming methods?

Communication within industry (e.g. sharing of in house practices in drug companies) and between industry and regulators was identified as key to allow applying more and earlier in vitro technologies that could reduce animal studies.

In addition to regulatory testing, application of alternative methods could have a greater impact when addressing gaps of knowledge (in mechanistic, early R&D studies).

It was reported that testing for disease models in pharma industry accounts for 80% of animals used while regulatory testing accounts for 20%. Therefore, establishing a cross sector central inventory of existing methods that companies or ethical committee advisors could consult would have a large impact.

The cross sector platform offered by EPAA could be used to share on a voluntary basis the cumulative knowledge of companies and host a forum of safety assessors.

Whilst the legislative pressure is different for the various sectors represented in the EPAA, the common objectives of EPAA could help the development and acceptance of alternatives. For example, substance information exchange is needed under REACH but pharma companies could also be welcome to join the relevant consortia and contribute information.

Computational toxicity approaches, ITS and literature data are already considered by national regulators but there is need for further education and training especially in areas where gaps of knowledge exist (e.g. residues, impurities or metabolites for agrochemicals).

Common challenge: securing maximum safety

1. Regulators and industry are facing common challenges with regard to the need of ensuring human safety and applying alternative methods whenever feasible and according to the legislation in each sector.
2. Industry and regulators still rely on animal testing as despite some individual failures, animal tests generally depict well human toxicity, offer more confidence and trust, built on longer in use experience.
3. The first key question to be addressed is "what information is needed from the regulatory tests, can animal testing provide this information, and what is the potential for a 3Rs approach?"

More information and dialogue between all parties and sectors

4. Scientific criteria are the main drivers for acceptance of a method: robustness of data, suitability for a given purpose, validation carried out on relevant set of substances, demonstrated applicability.
5. Precautionary principle or liability issues do not necessarily play any decisive role in regulatory acceptance. Lack of methods or lack of sufficient information about its scientific robustness is a barrier.
6. Liability considerations, especially in a broader sense (product liability, regulatory liability, commercial liability, etc;), may, however, form a hurdle for acceptance for some approaches.
7. The approach towards acceptance should be more structured, ranging from dialogue on regulatory needs and information on what new testing approaches can bring, to understanding processes necessary for implementation of new tests in a sector.
8. Information about existing methods should be enhanced. There is no systematic and cross-sectoral source of information.
9. Cross-sector dialogue can improve understanding of specific features of different approaches. EPAA can facilitate such broad dialogue at EU level. At national level, the UK Interdepartmental Group on the 3Rs, chaired by the Home Office might be a good practice example to promote.

Building confidence in approaches

10. Validation and acceptance need to go hand-in-hand. Early dialogue and collaboration between industry, other relevant stakeholders and authorities will allow a better understanding of the needs.

11. Level of confidence in a method is very important: in addition to a regulatory module (involvement of regulators) at the beginning and at the end of the validation process, applicability of methods should be revisited with regulators at regular intervals to consolidate the relevance of the approach.
12. The so-called "assay proliferation syndrome" and confusion caused to regulators by too many new methods are to be addressed. Guidance on the profile of new methods is needed, and will help the regulators make useful choices, preserve human safety and their own liability.
13. Communication, training, information exchange, bringing of new actors together under the auspices of EPAA, including testing laboratories and end users would be essential.
14. A question remains: can regulators refuse a regulatory accepted method on the basis that there are now other methods which are based on better science and ethics? Authorities in charge of the different sectors should provide guidance on this aspect.
15. Overall, we seek to increase the predictivity of the test systems, using the best science, the best strategies and methods, and whenever possible introducing the 3Rs approaches.

Other aspects

16. In addition to costs associated with the introduction of new methods, the sector specificity and needs should be considered. It is not necessary for a method to be applicable in all sectors.
17. Continuity of supply of tests systems and reagents in sufficient quantity could be an important criterion to uptake, but also potential condition for acceptance of a test especially for large-scale products.

International dimension

18. The international dimension is very important: there are advantages as well as difficulties due to the lengthy decision-making process of international acceptance bodies.
19. EU policy to enhance the use of alternative approaches should be promoted globally. Mechanisms such as ICH/VICH involving regulators, policy makers and industry should be seen as best practice example.
20. Liaising with research institutes in the USA or China, which advise their local authorities, would indirectly result in educating the latter to accept alternatives.
21. The international dimension has already to be taken into consideration at the level of

validation. International cooperation on validation is to be reinforced.

22. Additionally, EU experts within global companies should try to share knowledge with their colleagues from US or other countries within the same company.

23. The EU should maintain alternative approaches on the agenda of the regulatory dialogue with its trading partners.

**EPAA Workshop on
Regulatory Acceptance of 3 R methods and strategies
Brussels, 18 and 19 June 2007**

FINAL PROGRAMME

Day One: 18 June 2007

Session chaired by Cornelis Brekelmans, DG Enterprise

1. General Introduction on the objectives of the Workshop - Magda Chlebus, EFPIA
2. Identification of requirements for acceptance for regulatory safety testing
 - Biologicals - Jean-Marc Spieser, EDQM
 - Pharmaceuticals - Peter Kasper, EMEA Safety Working Party
 - Cosmetics - Vera Rogiers, EU Scientific Committee for Consumer Products
 - Agrochemicals - Sonja Jeram, Institute of Public Health, Slovenia
3. How and when to integrate regulators in the development of 3 Rs methods and strategies and in the validation process.
 - ECVAM modular validation and conclusions of workshop on post-validation – Laura Gribaldo, ECVAM
 - Proposals identified by EPAA working group on validation and acceptance (WG5) - Odile de Silva, L'Oréal

Session chaired by Julia Scheel, Henkel

4. Implementation of 3Rs in regulation and decision-making: How do liability issues affect acceptance and uptake of 3R methods? – Peter Bogaert, Covington and Burling LLP
5. Discussion

Day Two: 19 June 2007

Session chaired by Odile de Silva, L'Oréal

6. Implementation of 3Rs in regulation and decision-making Case studies
 - Pyrogenicity tests – Thomas Hartung, ECVAM
 - Embryo-toxicity – Susanne Bremer, ECVAM
 - CFU GM – Laura Gribaldo, ECVAM
 - Transgenic Mouse – Cécile Ponsar, GSK Biologicals
7. What are the key actions in order to promote acceptance and upcoming methods?
8. Conclusions - Cornelis Brekelmans & Odile de Silva

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Glossary of terms

CHMP	Committee for Medicinal Products for Human Use (Part of the EMEA)
ECVAM	European Centre for the Validation of Alternative Methods
EDQM	European Directorate for the Quality of Medicines of the Council of Europe
EMA	European Medicines Agency for the Evaluation of Medicinal Products now called European Medicines Agency
ESAC	ECVAM Scientific Advisory Committee
FDA	Food and Drug Administration (US)
ICCVAM	Interagency coordinating Committee on the Validation of Alternative Methods
ICH & VICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use & International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
ICH guidelines	Guidelines adopted by the three ICH regions – EU, US and Japan
JaCVAM	Japanese Centre for the Validation of Alternative Methods
OECD	Organisation for Economic Cooperation and Development
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SCCP	Scientific Committee on Consumer Products (European Commission – DG Health and Consumer Protection)
WHO	World Health Organisation
EPAA	European Partnership for Alternative Approaches to Animal Testing
3Rs	Replacement, Reduction, Refinement
ILSI HESI	ILSI Health and Environmental Sciences Institute
GMP	Good Manufacturing Practice
ITS	Intelligent Testing Strategies