Removing obstacles on the way to implement 3R methods in toxicology: regulator’s point of view

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Disclaimer

The views and opinions expressed in the following presentation are personal and should not be attributed to the Belgian Federal Agency for Medicines and Health Products or to the European Medicines Agency.
Introduction

Current preclinical testing paradigm was established 30 years ago

70% of human toxicity in clinical trials is predicted by preclinical studies (Olson et al 2000, Regul. Toxicol. Pharmacol 32; 56-67). More recent review by Tamaki et al 2013 (J. Toxicol. Sci. 38; 581-598) demonstrates that 48% of human ADRs are predicted in non-clinical testing

Classical paradigm based on descriptive toxicology, not MOA-based
Main drivers for change

Better prediction of human relevant effects – efficacy and safety

Animal welfare considerations – 3Rs
Major reasons for drug attrition

Kola and Landis, 2004
Nature Review Drug Discovery 3; 711-715

Hay et al, 2014,
Nature Biotechnology 21; 40-541

Hornberg et al 2014
Drug Discovery Today 19; 1131-1136

Most noted safety reasons for withdrawal of marketed drugs:
• Liver toxicity
• Cardiovascular toxicity
• CNS effects

Suspended programmes:
395 phase 3
95 NDA

Article 4 clearly states that:

Member States shall ensure that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used instead of a procedure.

Member States shall ensure that the number of animals used in projects is reduced to a minimum without compromising the objectives of the project.

Member States shall ensure refinement of breeding, accommodation and care, and of methods used in procedures, eliminating or reducing to the minimum any possible pain, suffering, distress or lasting harm to the animals.

Article 13 states that:

1. Without prejudice to national legislation prohibiting certain types of methods, Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognised under the legislation of the Union.

2. In choosing between procedures, those which to the greatest extent meet the following requirements shall be selected:
   (a) use the minimum number of animals;
   (b) involve animals with the lowest capacity to experience pain, suffering, distress or lasting harm;
   (c) cause the least pain, suffering, distress or lasting harm; and are most likely to provide satisfactory results.
Joint *ad hoc* Expert Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products - JEG 3Rs

Created in 2010/2011 to

*provide advice and recommendations to CVMP and CHMP on all matters relating to the use of animals in the testing of medicines for regulatory purposes*

**Membership:**

- experts from existing committees and WPs for which animal testing is relevant and observers from EURL ECVAM and EDQM
- Chair: Dr Sonja Beken
- Vice Chair: Dr Ellen-Margrethe Vestergaard

**Two one-day meetings per year**

JEG 3Rs – recent/ongoing activities

- Concept paper on review and update of EMA guidelines to implement best practice with regard to 3Rs in regulatory testing of medicinal products (EMA/CHMP/CVMP/JEG-3Rs/704685/2012)
- Reviewing existing guidance with recommendations to WPs to consider revisions where appropriate
- Development of guidance relating to gaining acceptance for 3Rs testing paradigms (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)
- Pilot project to review batch testing requirements for individual products and highlight possible shortcomings directly to MAHs
- Guidance on transferring quality control methods validated in collaborative trials to a product/lab specific context (CHMP/CVMP/JEG-3Rs/94304/2014)
- PARERE – coordination of EMA responses to requests form EURL ECVAM on potential regulatory relevance of test approaches
- Assessor’s training on 3Rs
Enhanced exploratory drug safety testing to reduce attrition
(Hornberg et al 2014, Drug Discovery Today 19; 1137-1144)
Technological progress – stem cells

EBiSC
European Bank for induced pluripotent Stem Cells

EPAA Stem cell project

The European Partnership for Alternative Approaches to Animal Testing

SC4SM
Stem Cells for Safer Medicines

ESNATS
The ESNATS project has received funding from the European Community’s Seventh Framework Programme (FP7/2007-2013) under grant agreement n° HEALTH-F5-2006-201619

ScrTox
STEM CELLS FOR RELEVANT EFFICIENT EXTENDED AND NORMALIZED TOXICOLOGY
Technological progress – organ-on-chip
Better prediction – a lot of projects

1. To identify and validate an improved panel of in vitro “best practice assays” for predicting DILI in the human population.

2. To explore and understand the relationship between in vitro assay signals and DILI in vivo, in preclinical test species and in man.

3. To develop and validate novel Systems Modeling approaches that integrate multiple preclinical data types to improve prediction of DILI in man.

4. To enhance shared understanding, between academia, pharma and regulatory agencies, of the value and limitations of new and existing approaches for DILI hazard identification and risk assessment.

MIP-DILI

Mechanism-Based Integrated Systems for the Prediction of Drug-Induced Liver Injury

WP1: Compound and Assay Selection
WP2: Established in vitro systems
WP3: Novel in vitro systems
WP4: Bioanalysis, Toxicological Function & Phenotype
WP5: Systems Analysis, Biomathematical & ADMET Modelling
WP6: Communication & Dissemination

Outcomes MIP-DILI
Better prediction – synergy

**eTOX**
Database of pharmaceutical industry legacy toxicology reports and public toxicology data
- In silico toxicity modelling
- All types of toxicity

**STEM CELLS FOR SAFER MEDICINES & STEM-BANCC**
- Production of hepatocytes from embryonic stem cells

**SAFER AND FASTER EVIDENCE-BASED TRANSLATION**
- Qualification of new specific and sensitive safety biomarkers for drug-induced kidney, liver and vascular injury

**INTERNATIONAL SERIOUS ADVERSE EVENT CONSORTIUM (iSAEC)**
- Identification of DNA-variants for predicting the risk of drug toxicity

**PREDICT-IV**
- Development of non-animal preclinical safety screens

**VIRTUAL LIVER**
- Development of a dynamic model that represents, rather than fully replicates, human liver

**MIP-DILI**

**SAFE-T**

**SC4SM StemBANCC**

**EFPIA**

**EMA**

**Virtual liver**

**FDA**

**Improved validated assays**

**Virtual liver**
Moving beyond discovery towards regulatory acceptance of novel methods

**Early tox / compound screening:**
in-house validation by companies, NO regulatory involvement

**Exploratory/mechanistic studies for regulatory decision-making:**
regulatory acceptance based upon demonstrated scientific validity

**Pivotal (guideline-driven) studies:**
formal regulatory acceptance, different modalities:
- historically introduced in vitro models
- transition from exploratory/mechanistic screening models to pivotal studies based on accumulating experiences (review of databases)
- targeted replacement of established animal study by in silico or in vitro model(s) requires “formal” validation
Guideline describes:

- regulatory acceptance
- a new procedure for submission and evaluation of a proposal for regulatory acceptance of 3R testing approaches for use in the development and quality control during production of human and veterinary medicinal products.
- scientific and technical criteria for regulatory acceptance of 3R testing approaches (incl. Safe Harbour)
- pathways for regulatory acceptance of 3R testing approaches
EMA Draft Guideline on regulatory acceptance of 3R (Replacement, Reduction, Refinement) testing approaches

- Regulatory acceptance
  - the incorporation of a new 3R testing approach into a regulatory testing guideline
  - on a case-by-case basis: the acceptance by regulatory authorities of new approaches not (yet) incorporated in testing guidelines but used for regulatory decision making
  - regulatory guidelines concerned: those related to the quality or non-clinical (safety and residues) requirements for human or veterinary medicinal products and regulatory guidelines related to clinical requirements for veterinary medicinal products
EMA Draft Guideline on regulatory acceptance of 3R (Replacement, Reduction, Refinement) testing approaches

Criteria for regulatory acceptance

1. demonstration of method validation (protocol, reliability, relevance)

2. demonstration that the new or substitute method or testing strategy provides either new data that fill a recognised gap or data that are at least as useful as, and preferably better than those obtained using existing methods.

3. demonstration of adequate testing of medicinal products under real-life conditions (human and veterinary) which can be generated through the safe harbour process.
EMA Draft Guideline on regulatory acceptance of 3R (Replacement, Reduction, Refinement) testing approaches

- **Procedure**

  1. Submission of proposal to the EMA in accordance with the procedure described in the **Guideline on Qualification of Novel Methodologies for Drug Development** (EMA/CHMP/SAWP/72894/2008 Rev. 1).

     For veterinary medicinal products only, proposal submission is to be in accordance with existing scientific CVMP guidance for companies requesting scientific advice.
EMA Draft Guideline on regulatory acceptance of 3R (Replacement, Reduction, Refinement) testing approaches

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1. Assessment in accordance with criteria as defined in collaboration with relevant 3R experts from CHMP and/or CVMP working parties.

2. Recommendations:
   - new 3R testing approaches is based on sufficient data and can be recommended for regulatory acceptance to the relevant working parties.
   - new 3R testing approaches needs real-life data collection period under safe harbour provisions.
   - new 3R testing approaches is rejected because it is immature.
EMA Draft Guideline on regulatory acceptance of 3R (Replacement, Reduction, Refinement) testing approaches

Added value of a process for regulatory acceptance at the EU level:

- Regulatory acceptance process at EMA level encompasses more than ICH S-related topics
- Proposals intended to be submitted to the (V)ICH can be thoroughly prepared at the EU level
- EMA regulatory acceptance process needed for topics that are subjected to EMA guidelines
Quick overview of ICH Guidelines either revised or under revision

- M3 (R2), Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals
- S1 Regulatory notice on changes to core guideline on rodent carcinogenicity testing of pharmaceuticals
- S2 (R1), Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
- S3, Toxicokinetics: A guidance for assessing systemic exposure in toxicology studies
- S5, Detection of toxicity to reproduction for medicinal products and toxicity to male fertility
- S9, Non-clinical Evaluation for Anticancer Pharmaceuticals
- S6 (R1), Addendum to ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
- S10, Photosafety evaluation of pharmaceuticals
- S11, Non-clinical Safety Testing in Support of Development of Paediatric Medicines
Case study 1: Non-clinical development of biosimilars

**In vitro studies**
- binding studies (e.g. receptors, antigens, enzymes)
- cell-based assays (signal transduction & functional activity)

may be more specific and sensitive than *in vivo* comparability studies
→ considered fundamental

Appropriate # batches of product representative for clinical use.

**In vivo studies**
- designed to maximise the information obtained (PD/PK/Tox)
- relevant species

High species-specificity of some biosimilars triggered discussion on appropriateness of non-clinical *in vivo* studies

→ A step-wise approach is proposed
Biosimilars entering the clinic without animal studies in the EU

In vivo testing of biosimilar candidates

<table>
<thead>
<tr>
<th>Component</th>
<th>PK/PD</th>
<th>Immune</th>
<th>Toxicology’1)</th>
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<tr>
<td>Pharmacopeial</td>
<td>Testing formally required for a few</td>
<td>Predictable</td>
<td>Adverse</td>
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<tr>
<td>type</td>
<td>substances but models likely too</td>
<td></td>
<td>effects of</td>
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<tr>
<td></td>
<td>insensitive to detect minute differences</td>
<td></td>
<td>active</td>
</tr>
<tr>
<td></td>
<td>May be informative but:</td>
<td>Unpredictable</td>
<td>substance</td>
</tr>
<tr>
<td></td>
<td>• likely superseded by human PK/PD</td>
<td></td>
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<tr>
<td></td>
<td>data; • only in rare specific cases</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>animal data relevant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacopeial</td>
<td>May be informative but:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>type</td>
<td>• strongly depends on the model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacopeial</td>
<td>likely superseded by more sensitive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>type</td>
<td>functional in vitro data; • may be</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacopeial</td>
<td>superseded by human PD data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>type</td>
<td>The ability of animal models to predict</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacopeial</td>
<td>a response in humans has been limited</td>
<td></td>
<td></td>
</tr>
<tr>
<td>type</td>
<td>= exaggerated pharmacology</td>
<td></td>
<td></td>
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<tr>
<td>Pharmacopeial</td>
<td>Functional comparison by more sensitive</td>
<td></td>
<td></td>
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<tr>
<td>type</td>
<td>in vitro assays obviates the need</td>
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<tr>
<td>Pharmacopeial</td>
<td>Comparison of safety cannot be achieved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>type</td>
<td>with animal studies that do not predict</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacopeial</td>
<td>these safety aspects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>type</td>
<td>• high unlikelihood of occurrences</td>
<td></td>
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<tr>
<td>Pharmacopeial</td>
<td>• limited predictive value of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>type</td>
<td>potential spurious findings</td>
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<td></td>
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<tr>
<td>Pharmacopeial</td>
<td>In vivo testing may be informative if</td>
<td></td>
<td></td>
</tr>
<tr>
<td>type</td>
<td>no or limited other data exist</td>
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</tr>
<tr>
<td>Pharmacopeial</td>
<td>(literature; other products, etc.)</td>
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</tbody>
</table>

Relevance for biosimilars

Comparison likely for information purposes only and likely not decisive for biosimilar comparability exercise

In vivo testing of no value

In vivo studies of no value

Only required when information is lacking. Testing may be undertaken also in a species regarded as non-relevant for the active substance
Case study 2: Novel testing approaches for embryofoetal development testing, the long and winding road of regulatory acceptance...
What precedes regulatory discussions:

The Practical Application of Three Validated *In Vitro* Embryotoxicity Tests

The Report and Recommendations of an ECVAM/ZEBET Workshop (ECVAM Workshop 57)\(^1\)

Horst Spielmann,\(^1\) Andrea Seiler,\(^1\) Susanne Bremer,\(^2\) Lars Hareng,\(^2\) Thomas Hartung,\(^2\) Hans Ahr,\(^3\) Elaine Faustman,\(^4\) Ulla Haas,\(^5\) Graeme J. Moffat,\(^6\) Heinz Nau,\(^7\) Philippe Vanparys,\(^8\) Aldert Piersma,\(^9\) Juan Riego Sintes\(^10\) and Jane Stuart\(^11\)
ICH Workshop, Tallinn, June 2010:

*In Vitro* Models for Reproduction Toxicity Workshop – Use?

Workshop held as part of an assessment of whether the S5(R2) Guideline on Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility needed to be revised.

It was agreed that no further work needed to be undertaken on the topic at the current time at the ICH level.

More work needed on:

- Enhancing applicability of mEST for risk assessment
- rat vs rabbit comparison
- Establish robustness of *in vitro* approaches with more pharmaceuticals in different labs
Follow-up on reproductive toxicity testing

Objectives:

- to bring scientific information about new in vitro technologies for reproductive and developmental toxicology testing to FDA
- to provide a forum for scientists from FDA, academia, and industry to discuss how these new technologies could eventually be integrated into FDA's regulatory paradigm.

discussion on:

- Value of rodent versus non-rodent species (rat or rabbit) in the evaluation of human pharmaceuticals for their effects on embryo-foetal development: what data are needed?
- Value of 3R methods to detect crucial developmental effects? What type of data is available? Can recommendations be given for further evaluation of these in vitro methods?
- mEST: various endpoints, various protocols!
- Other 3R models used: zebrafish, whole rat embryo culture
2011- 2014:
HESI Developmental and Reproductive Toxicology (DART) Technical Committee (US) will conduct a cross pharma survey to collect data regarding the relative value of non-rodent vs rodent in signal detection of developmental toxicity and the influence on human risk assessment

⇒ ILSI HESI DART 2nd species working group: database compilation and analysis
Follow up by ICH

Progress report presented at Safety Brainstorming Meeting, 10-15/11/2012, San Diego, US

Points addressed:
- Update on the activities of the HESI DART 2nd Species Working Group
- Applicability of 3R methods: additional data requirements
- A stepwise approach to an integrated testing strategy for embryofoetal development

Follow up by ICH

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Follow up by ICH

Proposal at Safety Brainstorming Meeting, 9-17/11/2013, Osaka, Japan

- Need to develop a new strategy for EFD testing
- Stepwise approach!
  - Data gathering to evaluate 3R methods to replace one species for developmental toxicity testing
  - Participation to and follow-up of the outcome of the HESI DART 2nd species working group: recommendations for primary species selection
  - Design and real life evaluation of a integrated testing strategy → phased approach!
  - Generate a reference list of reproductive toxicants that the ITS need to be able to identify
  - Provide recommendations on how to revise the ICH S5 guidance
ICH SC endorsement of Concept Paper - March 2015

Final Concept Paper
S5(R3): Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility
dated 9 February 2015
_Endorsed by the ICH Steering Committee on 27 March 2015_

Type of Harmonisation Action Proposed

Revision of the ICH S5 (R2) Guideline as defined in the “Revised ICH Procedures” (2011), section “3. Revision Procedure”\(^1\).
Revision ICH S5(R2)

Issues to be resolved

• Agreement on appropriate multiples above human exposure or other endpoints that could be used for dose selection

First F2F Meeting of the Expert Working Group, June 2015, Fukuoka, Japan

limited circumstances under which such a testing strategy would be considered
Some interesting brainstorming ....

Animal Free Safety Testing of New Medicines

Thursday May 23 2013
Centraal Museum
Agnietenstraat 3
3512 XA Utrecht

Key question addressed by 2 expert panels with members from industry, regulatory authorities and academia: What will drug development look like if we stop using animals for safety testing?
Some interesting brainstorming ....

Future Nonclinical Safety Testing – Regulatory & Industry views

EFPIA PDC / EMA Non-clinical Assessors brainstorming workshop
April 9th 2014, Vienna, Austria

Key Question:
The Nonclinical Regulatory Landscape: Can we reduce the number of guidelines? What type of data are really needed?

Since the Directive 75/318 is the number of guidelines continuously growing. Seldom guidelines are withdrawn (except for acute toxicity). Is it possible to rethink our testing paradigms?
So ... is this the future?

Regulatory science clearly needs to be kept in pace with technological developments. Early involvement of regulators in international initiatives (e.g. EU IMI, EU FPs, etc) is crucial to achieve progress in this rapidly evolving field.

Past and current regulatory revision efforts have been mostly reformatting of the existing non-clinical requirements (excl. biosimilars). Although this has entailed improvements both with respect to predictive power as with regards to the 3Rs there is still room for improvement.

Regulatory non-clinical testing should be moved forward to mechanistic based safety and efficacy testing – quid upgrading exploratory safety testing. This will necessitate close interaction by multiple stakeholders to ensure qualification of fit-for-purpose methods and science-driven, mechanism-based testing strategies.
“I have a dream.”

-Martin Luther King Jr.

“It always seems impossible until it’s done.”

-Nelson Mandela
1918-2013
Thank you for your attention!

Sonja Beken, PhD
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Vice-Chair SWP (EMA)
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