Update on EMA and ICH activities

Dr. Sonja Beken
SWP, EMA (Vice-Chair)
JEG 3Rs, EMA (Chair)

famhp

.be

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

Outline

Introduction

JEG 3Rs and the Draft EMA Guideline on Regulatory acceptance of 3R testing approaches

ICH initiatives on regulatory acceptance of 3Rs

Case study

Conclusions

New (*in vitro*) tools for drug development

New testing approaches should satisfy validation criteria:

- defined test methodology/standard protocol with clear defined/scientifically sound endpoints
- reliability
- relevance

New test methods or strategies should provide 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

New methods should be followed up for their „real-life" performance

Regulatory acceptance process should be harmonised both at regional (e.g. EMA) and at global (ICH) level

Joint *ad hoc* Expert Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products - JEG 3Rs

A **joint CHMP/CVMP expert group** set up to provide advice to the Committees on 3Rs topics relevant to the testing of medicines for regulatory purposes

Made up of experts from CHMP/CVMP and all EMA working parties for which testing in animals is relevant, plus observers from EURL ECVAM and EDQM

Chair: Sonja Beken (SWP)

Vice chair: Ellen-Margrethe Vestergaard (CVMP)

Meets twice a year

Joint Expert Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products - JEG 3Rs

Aims include:

- Identifying opportunities for implementation of 3Rs
- Coordinating, facilitating and prioritising EMA activities within the 3Rs arena
- Establishing strong ties with EDQM and EURL ECVAM
- Contribute to development of guidelines in which 3Rs issues are applicable in collaboration with relevant Working Parties

More information available at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CVMP/people_listing_000094.jsp&mid=WC0b01ac05803a9d6d

EMA Draft Guideline on regulatory acceptance of 3R (Replacement, Reduction, Refinement) testing approaches

- Multidisciplinary drafting group under the JEG 3Rs (Joint ad hoc Expert Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products)

- Guideline applies only to testing approaches that are subject to regulatory guidance for human and veterinary medicinal products which are used to support regulatory applications (e.g. clinical trial applications, marketing authorisation applications) and does not cover the process by which 3R improvements are included in the Ph. Eur. Monographs.

EMA Draft Guideline on regulatory acceptance of 3R (Replacement, Reduction, Refinement) testing approaches

- Guideline describes
  - regulatory acceptance
  - a new procedure for submission and evaluation of a proposal for regulatory acceptance of 3R (Replacement, Reduction and Refinement) 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
- Link with Guideline on Qualification of Novel methodologies for Drug Development (EMEA/CHMP/SAWP/72894/2008_Corr1)

EMA Draft Guideline on regulatory acceptance of 3R (Replacement, Reduction, Refinement) testing approaches

Relates to regulatory acceptance at the EU level

→ a global process is needed!

- A regional implementation of new 3R methods is mostly not feasible taking into account existing ICH S-regulations

- Various initiative/institutions are involved with developing 3R testing approaches with little or no coordination and no driver to introduce the results into the regulatory environment

- The implementation of technically validated assays or assays with a long history of use does not guarantee optimal performance in the regulatory environment

ICH
harmonisation for better health

Need for:

- Monitoring and evaluating scientific and technological developments on an ongoing basis → improve predictivity of non-clinical safety testing by the implementation of innovative approaches into regulatory requirements

- Formalisation of the current ad hoc process to identify safety topics within ICH and thus to create a clear contact/entry point for institutions/initiatives that are involved with developing new testing approaches

- ICH SC Meeting – Fukuoka – June 2012: EFPIA proposal for a Pre-S Procedure → request by the SC to draft a formal Concept Paper
- ICH SC Meeting – San Diego – November 2012: Presentation of concept paper, renamed into Safety Brainstorming Group
- Endorsement of the group, with another name change by the ICH SC on 1 February 2013: Safety Topic Recommendation Working Group (STRWG)
- **However,** after approval of the concept paper by the ICH Steering Committee one of the 6 ICH founding parties indicated that after internal deliberation they had a different view on the proposed concept → **no progress!**

- In June 2013 the Steering Committee had agreed that all **ICH regions and observers will submit topics to be considered for new ICH guidelines, revision of guidelines, Q&A documents**

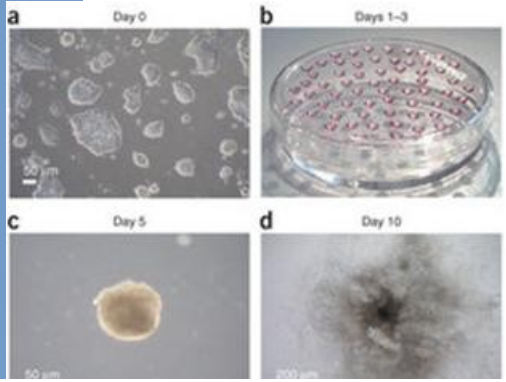
- Proposals on non-clinical topics were submitted, discussed and prioritised in the November 2013 ICH Meeting (Osaka, Japan) during a **Safety Brainstorming Meeting**

- At the same meeting the ICH SC has further prioritized and selected an number of topics for preparation of Concept Papers by January 2014

- Concept Papers will be discussed at the **ICH Meeting in June 2014 (Minneapolis, US)**

Novel testing approaches for embryofoetal development testing, the long and winding road of regulatory acceptance…

What precedes the regulatory discussions:



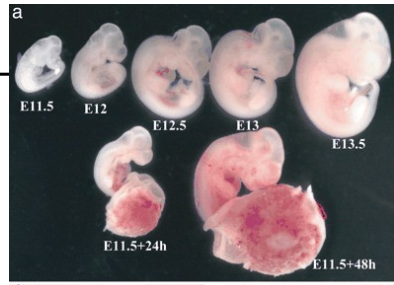
www.ReProTect.eu

ATLA **34**, 527–538, 2006

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 DIA Workshop; 10-11/10/2011

DART Testing Strategies for Human Pharmaceuticals: Animal Models vs In-Vitro Approaches

DIA
www.diahome.org

Event #11116
10–11 October 2011
Hotel Holiday Inn, Leiden, The Netherlands

discussion on:

- Value of rodent versus non-rodent species (rat or rabbit) in the evaluation human pharmaceuticals for their effects on embryo-foetal developmental: 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

Follow-up FDA Workshop; 16/04/2013

Public Workshop on Reproductive and Developmental Toxicology: From In Vivo to In Vitro, April 16, 2012, White Oak Campus, Silver Spring US

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

HESI DART 2nd species Workgroup:

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

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

Follow up by ICH

ICH Meeting, 1-5/6/2014, Minneapolis, US

Way forward:
to be decided on the basis of concept paper on the revision of ICH S5(R1)

Regulatory Acceptance of 3R Test Methods

The use of the SAWP method qualification process in collaboration with JEG 3Rs is recommended at EMA level

Initiatives to clearly define a process for regulatory acceptance of 3R methods used for regulatory decision makin at the ICH level are not in place

A global approach (ie ICH) is the preferred option, if applicable

Early interaction of regulators with large scale initiatives (e.g. EU IMI, EU FPs, etc) is encouraged

thank you for your attention

Sonja Beken, PhD
Coordinator Non-Clinical Assessors
Chair JEG 3Rs (EMA)
Vice-Chair SWP (EMA)
DG PRE Autorisation, Division Assessors

FAMHP
Place Victor Horta 40/40
1060 Bruxelles
tel.: +32 2 524 80 00
e-mail sonja.beken@fagg-afmps.be

www.afmps.be

Your medicines and health products, our concern

famhp

.be