Federal Agency for Medicines and Health Products (FAMHP)

What can be done from regulatory side?

9th Annual ecopa Workshop
November 29-30, 2008, Brussels

Dr. Sonja BEKEN
Non-Clinical Assessor, Registration Department

29/11/2008

OVERVIEW OF PRESENTATION

Regulatory Background

Acceptance of 3R Methods for Non-Clinical Testing of Human Medicinal Products

ICH and the 3Rs: Recent Experiences

Input/Feedback Mechanisms

Conclusions

Regulatory Background

Acceptance of 3R Methods for Non-Clinical Testing of Human Medicinal Products

ICH and the 3Rs: Recent Experiences

Input/Feedback Mechanisms

Conclusions

Non-Clinical Guidelines, Recommendations by:

EU: EMEA (European Medicines Agency; www.emea.europa.eu)

Eudralex (The Rules Governing Medicinal Products in the EU; http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm)

USA: FDA (Food and Drug Administration ; www.fda.gov)

JAPAN: Japanese Ministry of Health and Welfare (www.mhlw.go.jp)

Ministry of Health, Labour and Welfare

厚生労働省

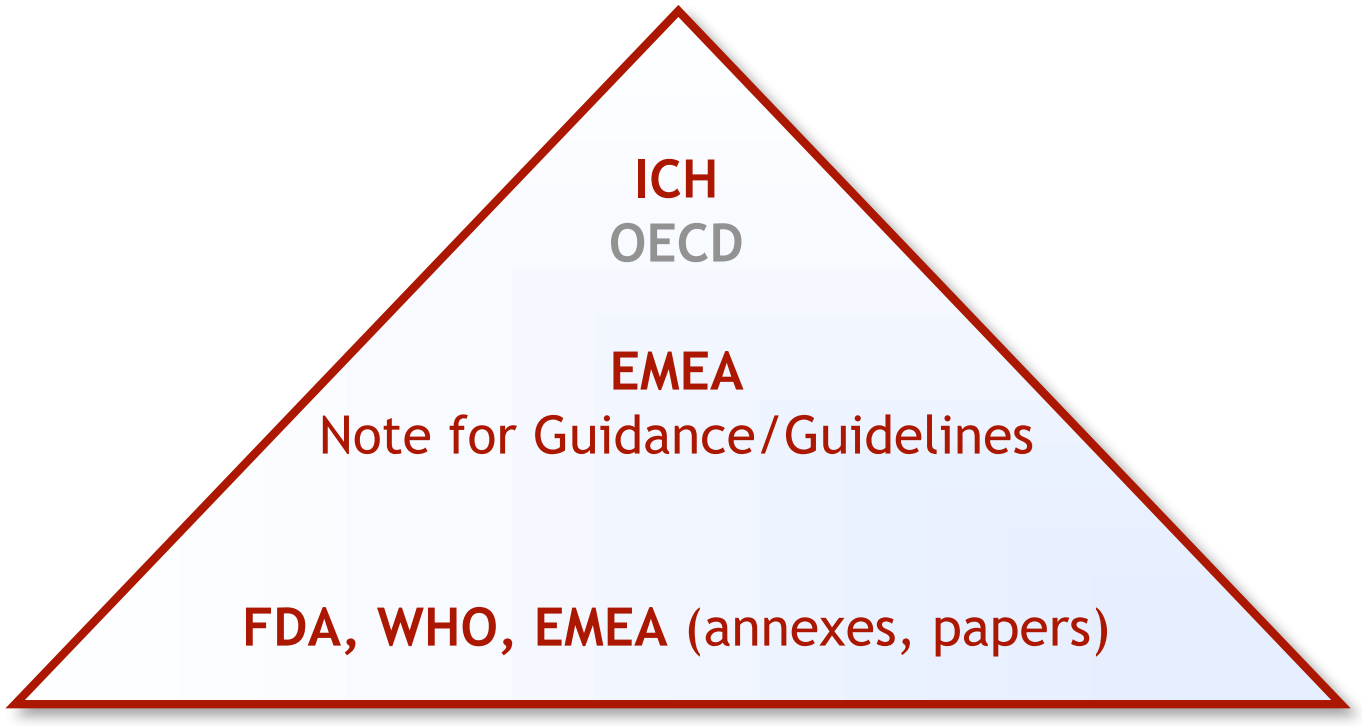
Non-Clinical Guidelines: Harmonisation

ICH: International Conference on Harmonisation (www.ich.org)

Mission:

- *To maintain a forum for a constructive **dialogue** between regulatory authorities and the pharmaceutical industry on the real and perceived differences in the technical requirements for product registration in the EU, USA and Japan;*
- *To contribute to the protection of public health from an international perspective;*
- *To monitor and update **harmonised technical requirements** leading to a greater mutual acceptance of research and development data;*
- *To avoid divergent future requirements through harmonisation of selected topics;*
- *To **facilitate the adoption** of new or improved technical research and development approaches;*
- *To facilitate the dissemination and communication of information on harmonised guidelines and their use.*

Non-Clinical Guidelines: Scientific Hierarchy



The Safety Working Party (SWP) of the CHMP

The SWP is established to provide recommendations to the CHMP on all matters relating directly or indirectly to non-clinical safety aspects.

These include:

- Support to **dossier evaluation** on non clinical safety related matters
- **Scientific advice** - general and product specific matters
- Contribution to the Scientific Advice Working Party of the CHMP
- Assessment of **non clinical safety findings raised post authorisation**
- **Preparation, review and update of guidelines**
- **Training**
- On request, advice, through the CHMP, to MRFG, HMPC, EC
- Liaison with interested parties (e.g. EFPIA, ECVAM, ABPI, ILSI)

Regulatory Background

Acceptance of 3R Methods for Non-Clinical Testing of Human Medicinal Products

ICH and the3Rs: Recent Experiences

Input/Feedback Mechanisms

Conclusions

CPMP Position Paper on Replacement of Animal Studies by *In Vitro* Models (CPMP/SWP/728/95 - adopted 1997)

EU level:

- Feasibility of replacing *in vivo* animal studies
- Procedure for validating *in vitro* tests
- Procedure for incorporating *in vitro* tests into the regulatory requirements
- Areas for which the acceptance of *in vitro* tests can be considered

Criteria of Acceptance of 3R Methods

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

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

- Pivotal (guideline-driven) studies:
  different routes of „formal (?)“ validation
  - “historically“ introduced 3R models: NO formal validation
  - transition from exploratory/mechanistic screening models to pivotal studies based on accumulating experiences (review of data bases)
  - targeted replacement of established animal study requires formal validation

Acceptance of 3R Approaches, the only Way Forward …

International level:

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

Implementation of new 3R methods should proceed via ICH process!!

- ICH mission includes commitment to take 3R aspects into consideration, but no formal criteria defined

Regulatory Background

Acceptance of 3R Methods for Non-Clinical Testing of Human Medicinal Products

ICH and the 3Rs: Recent Experiences

Input/Feedback Mechanisms

Conclusions

ICH and the 3Rs: Recent Experiences

- ICH Expert Working Group Meeting, Brussels, May 2007:
  1st ICH meeting with ICCVAM, ECVAM & JaCVAM; discussion on:
  - possibility of future collaboration
  - input of CVAMs when drafting new or revising existing guidelines?
  - input of CVAMs on defining acceptance criteria??

- Current ICH topics in relation to 3Rs:
  - S2, revision, genotoxicity testing
  - S6, update, non-clinical testing of biologicals
  - S9, new! Non-clinical testing of oncology products
  - M3, revision, non-clinical testing prior to clinical trials

Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals intended for Human Use (ICH S2 (R1))

- Revision of ICH S2A/B - Step 2 reached February 2008, Step 4 expected June 2010

- Why?
  - high rate of (false) positive findings in *in vitro* mammalian cell tests
  - consideration of new test methods:
    - *in vitro* micronucleus test
    - *in vivo* models applicable to a variety of tissues
    - use of rat blood for micronucleus evaluation
  - further implementation of 3R aspects

Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals intended for Human Use (ICH S2 (R1))

➢Application of the 3Rs

- ➢ No concurrent positive controls in every *in vivo* assay
- ➢ Genotoxicity testing is integrated into existing repeat dose toxicity studies
- ➢ Incorporation of 2 genotoxicity assays (different tissues) in one study using the same animals
- ➢ Reduction of "non-relevant" *in vitro* results → decrease in follow-up *in vivo* assays

Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (ICH S6)

- Update process only just started! Step 2 expected June/November 2009.

- Update on
  - Species selection
  - Study duration
  - Reproductive/developmental toxicity testing
  - Carcinogenicity testing
  - Immunogenicity testing

Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (ICH S6)

- Application of the 3Rs:
  - Enhanced Pre-&Post-Natal Development study design with overall assessment of all developmental toxicity endpoints in a single cohort of gestationally exposed animals:
    - Reduction of the need for 2 separate studies (EFD and PPND studies)
    - Reduction of animal numbers with one treated group and a control group
  - No need for fertility studies (inclusion of additional endpoints in repeat dose toxicity studies)
  - Use of only one relevant species for chronic toxicity studies – if circumstances can be defined when this would be sufficient
  - Recovery groups not required for all treatment groups
  - Only 2 repeat dose studies required for non-oncology products: FIH-supporting and 6-months chronic toxicity study
  - No need for two-year carcinogenicity studies
  - Use of a surrogate in order to avoid use of non-human primates e.g. for reproductive toxicity testing

Non-Clinical Evaluation of Anti-Cancer Pharmaceuticals (ICH S9)

- Step 2 probably November 2008

- Why?
  - New effective anticancer drugs sooner!
  - Phase I studies often in in cancer patients with advanced disease status
  - Clinical dose levels are at or close to adverse effect dose levels
  - Need for flexibility (type & timing) in design of non-clinical studies

- Scope:
  - All pharmaceuticals intended to treat patients with cancer (late stage or advanced disease), regardless of the route of administration, including both small molecules and biotechnology derived products

Non-Clinical Evaluation of Anti-Cancer Pharmaceuticals (ICH S9)

- Application of the 3Rs:
  - No need for a 6- or 9-month chronic toxicity study, 3-month data considered sufficient
  - No need for fertility studies (inclusion of additional endpoints in repeat dose toxicity studies)
  - No need for peri- and post-natal development studies
  - If embryofoetal development study is unambiguously positive, no confirmatory study in 2nd species is required
  - Inclusion of safety pharmacology endpoints in repeat dose toxicity studies
  - No need for non-rodent studies for initiation of clinical trials with cytotoxic pharmaceuticals

Non-Clinical Evaluation of Anti-Cancer Pharmaceuticals (ICH S9)

➢ Comparison of non-clinical programmes:

	New Chemical Entity	New Biotech. Product	New Oncologic Drug
Pharmacology			
Pharmacodynamics	+	+	+
Safety pharmacology	+	+	+[2]
Pharmacokinetics	+	+	+
Toxicology			
Acute toxicity	+	+	-
Repeat dose toxicity	+[1]	+[1]	+[3]
Reproductive toxicity	+	+	+[4]
Genotoxicity	+	(+)	+
Carcinogenicity	(+)	(+)	-
Local tolerance	(+)	+	-
Antigenicity/Immunotox.	+	+	(+)

1. including toxicokinetic and immunogenic measurements
2. performed as part of the repeat dose toxicity study
3. 3-month studies could be considered sufficient.
4. EF not essential for drugs targeting rapidly dividing cells, a positive result precludes further testing in 2nd species, no fertility or peri- & post-natal studies warranted.

Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals (ICH M3)

- Step 2 reached June 2008, Step 4 expected June 2009.

- Objective:
  - Recommendation of international standards for and promotion of harmonisation of non-clinical safety testing to support human clinical trials
  - Facilitation of timely conduct of clinical trials
  - Reduced the use of animals in accordance with the 3R principles

- New sections on:
  - Estimation of first dose in humans
  - Exploratory clinical trials
  - Paediatric clinical trials
  - Immunotoxicology
  - Phototoxicity
  - Non-clinical abuse liability
  - Non-clinical testing of fixed combination of drugs

Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals (ICH M3)

- Application of the 3Rs
  - No stand-alone single dose/acute toxicity test required
  - Reduced non-clinical programme for exploratory clinical trials
  - 6-month chronic toxicity studies
  - Timing reproductive/developmental toxicity testing

Regulatory Background

Acceptance of 3R Methods for Non-Clinical Testing of Human Medicinal Products

ICH and the 3Rs: Recent Experiences

Input/Feedback Mechanisms

Conclusions

Input/Feedback Mechanisms: Current Status

- Involvement in the regulatory-directed activities of EPAA
- EU initiatives in collaboration with pharmaceutical industry (e.g. concept paper on single dose/acute toxicity – EMEA/CHMP/SWP/302413/2008)
- Input in ICH related activities (e.g. interaction with CVAMs, revision/updating/drafting non-clinical guidelines)
- Recurrent interaction with EFPIA on 3R-related issues
- Planned dialogue with coordinators of relevant EU FP research projects
- Involvement of individual regulators in EU FP projects, IMI (EU), C-Path (FDA)
- Communications at scientific conferences (e.g. eSI)

Input/Feedback Mechanisms: Way Forward

- Need for a structural approach in order to
  - align early method development with (future) regulatory requirements
  - interact with ECVAM-driven validation exercises (prioritisation!)
  - identify critical non-clinical areas of concern for pharmaceuticals and upcoming new therapies
  - promote swift implementation of useful 3R methods

and thus …

Input/Feedback Mechanisms: Way Forward

- Need for a structural approach

and thus …

- Need for a specific 3R regulatory "task force" to serve a single contact point/watch dog to ensure
  - continuous input/feedback with stakeholders in the field of the 3Rs (academic research, pharmaceutical industry, EPAA, CVAMs, ecopa, …)
  - increased communication and formalised communication and interaction strategies with 3R stakeholders and other involved sectors (chemicals, cosmetics etc)
  - continuous, accurate, relevant and up-to-date 3R input in the regulatory process in balance with maximal protection of human health

Regulatory Background

Acceptance of 3R Methods for Non-Clinical Testing of Human Medicinal Products

ICH and the 3Rs: Recent Experiences

Input/Feedback Mechanisms

Conclusions

Conclusions

- Acceptance and implementation of 3R methods for regulatory non-clinical testing of pharmaceuticals occurs via multiple and flexible approaches in line with the range of specific objectives and regulatory requirements

- Implementation of 3R methods via ICH process has the highest impact and ongoing revisions/updating/drafting exercises all take the 3Rs into account as far as reasonably practicable

- Input/feedback mechanisms are in place but need to be much more elaborated and formalised in the near future

Thank you for your attention!

Questions???

The personal views expressed in this presentation do not necessarily reflect the views of the FAMHP or the EMEA.

Thanks to David Jones, Peter Kasper, Klaus Olejniczak & Jennifer Sims.