3Rs in Safety Testing of Human and Veterinary Pharmaceuticals

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3Rs in safety testing in human pharmaceuticals

- Use of animal models implemented in period of observations of complex adverse effects
  - Thalidomide as teratogen, 1961: testing methods to be developed/established
- Animal studies are needed to support
  - Short – term and long-term use
  - Assessment of reproductive risks
  - Assessment of carcinogenic risks
- Animal studies have no value if underpowered → balance of too less or too many animals.
Animals models

- Safety studies during the development of a pharmaceutical product to establish maximum residue limits for safety of food to consumers,
- Safety and efficacy studies in the target species are conducted for pharmaceutical and immunological products
- For immunological products (mainly vaccines) for batch release
- Field studies in the target species
International Conference (now Council) on Harmonisation
EU-initiative of outreach of 3Rs

ICH started in 1989 in Paris

3Rs prominent on the agenda for nonclinical testing

- Harmonisation of reproductive toxicity testing designs to avoid duplication
- Evaluation of Carcinogenicity Study design to reduced the need (S1A) and decrease suffering of the animals (S1C) and the relevance of two species (S1B).
- Increase of animal use by introduction of Toxicokinetics, which was needed to improve Risk Assessment Strategies
Position paper on 3Rs published in 1997: Replacement of animal studies by in vitro models CPMP/SWP/728/95

Overview of possibilities for Reduction, Refinement and Replacement

Mainly focusing on evaluating single test methods as candidate replacement

Criteria for validation of single methods (referral to ECVAM)
## Use of animals for Regulatory Purposes

<table>
<thead>
<tr>
<th>2011 Experimental animals used in EU</th>
<th>%</th>
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<tbody>
<tr>
<td>Regulatory testing for human and veterinary medicinal products</td>
<td>4.4</td>
</tr>
<tr>
<td>Quality Batch Control testing of human medicinal products</td>
<td>10.9</td>
</tr>
<tr>
<td>Quality Batch Control testing of veterinary medicinal products</td>
<td>4.0</td>
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(Data derived from European Commission, 2013)
3Rs and vaccine batch release (European Pharmacopoeia)  
Progress in the reduction of animal testing

**Veterinary**

Deletion of safety tests:
- Safety in mice and guinea pigs (Abnormal toxicity test, LABST)
- Target Animal Batch Safety Test (TABST)

Potency Testing:
- Rabies vaccine (inactivated) for veterinary use
  → Replacement of mouse challenge by serology
3Rs and vaccine batch release (European Pharmacopoeia) Progress in the reduction of animal testing

**Human**

Deletion or Replacement of safety tests:

- Safety in mice and guinea pigs (Abnormal toxicity test) is deleted from the *Ph.Eur.*
- Limulus Amoebocyte Lysate –test and Monocyte Activation Test are introduced to replace the Rabbit Pyrogen Test

Reduction and Refinement in Potency Testing:

- Replacement of challenge tests, e.g. by serology
  - e.g. Vaccines against tetanus, diphtheria, rabies
JEG3Rs established in 2010

Common group for Human and Veterinary Medicines
Representation by SWP-h (Chair), SWP-v (vice-chair), QWP, BWP, IWP, VWP

September 2014
Guideline on Regulatory Acceptance of 3R (Replacement, Reduction, Refinement) Testing approaches

April 2016
Reflection paper providing an overview of the current regulatory testing requirements for veterinary medicinal products and opportunities for implementation of the 3Rs. (Draft)

November 2016
Reflection paper providing an overview of the current regulatory testing requirements for human medicinal products and opportunities for implementation of the 3Rs. (Draft)
VICH EU-initiative of 3Rs in safety testing (examples)

**Licensing:**
- Target Animal Safety - Examination of Live Veterinary Vaccines in Target Animals for Absence of Reversion to Virulence - VICH GL41 - July 2007

**Batch release:**
- Harmonisation of criteria to waive TABST for inactivated vaccines for veterinary use (VICH GL 50)

**Toxicity testing:**
- *Under discussion:* EU proposal for a tiered approach to genotoxicity testing with in vitro tests first - possibility to avoid in vivo tests where appropriate

However, progress at VICH level with 3Rs is sometimes behind EU level; e.g. the TABST which is reduced at VICH level is already deleted from the Ph.Eur.
Guideline on acceptance of 3Rs
EMA/CHMP/CVMP/JEG-3Rs/450091/2012 (October 3, 2014)

Criteria for regulatory acceptance of 3Rs testing approaches

1. Demonstration of method validation (e.g. by formal validation as described by EURL-ECVAM)

2. Demonstration that the new or substitute method or testing strategy provides new data that fill a recognised gap

3. Demonstration of adequate testing of medicinal products under real-life conditions
Procedure for submission of a proposal for regulatory acceptance of 3 R approaches

Assessment of the new 3R testing approaches will be performed according to the criteria in collaboration with 3Rs experts from CHMP and/or CVMP working parties.

The outcome of the assessment can entail following recommendations:

1. new 3R testing approaches is based on sufficient data and can be recommended
2. new 3R testing approaches needs real-life data collection period
3. new 3R testing approaches is rejected because it is immature.
ICH S1 Carcinogenicity testing
Potential waiver possible on the basis of prediction?

- Outcome chronic toxicity: if negative than carc. study likely to be negative
- Relation with pharmacological activity: relation with proliferative stimulation by pharmacology
- Evidence of hormonal activity?

→

- May lead to reduction of 40% of the required studies

Scheduled to be finished in 2020
ICH S5 Reproductive Toxicity testing
possible implementation of alternative approaches

Possible implementation of in vitro/ex vivo/in vivo alternative approaches

In vitro: mouse embryonic stem cell test
Ex vivo: rat whole embryonic culture
In vivo: zebrafish embryonic test

→

Qualification on the level of individual companies

May reduce the use of two species for Embryofetal Toxicity Studies

Scheduled to be finished in 2018/9
Wrap-up

EMA pro-active in 3R programs

• ICH and V-ICH initiatives
• JEG3Rs activities
• Current activities in ICH
  • Reprotox
  • Carcinogenicity