Regulatory acceptance of 3Rs testing methods for medicinal products – EMA perspective

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Outline

The JEG 3Rs
Regulatory acceptance of 3Rs at the EMA
ICH and 3Rs
Conclusions
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
Multidisciplinary drafting group under the JEG 3Rs

Draft guideline on regulatory acceptance of 3R (replacement, reduction, refinement) testing approaches

Document details

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Summary

In accordance with Directive 2010/63/EU, the principle of the 3Rs (replacement, reduction and refinement) needs to be considered when selecting testing approaches to be used for regulatory testing of human and veterinary medicinal products. A general overview is provided on animal use and current or future implementation of 3R testing approaches for quality, non-clinical (human) and safety and efficacy (veterinary) testing.
EMA Draft Guideline on regulatory acceptance of 3R testing approaches

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 testing approaches

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 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 testing approaches

- Criteria for regulatory acceptance

1. demonstration of method validation

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 testing approaches

1. Demonstration of method validation

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

The information needed and the criteria applied will depend on:

- regulatory and scientific rationale for the use of the method,
- type of method being evaluated (e.g. existing test, new method),
- proposed uses of the method (e.g. mechanistic, total or partial replacement, as part of a testing strategy),
- mechanistic basis for the test and its relationship to the effect(s) of concern,
- history of use of the test method, if any, within the scientific and regulatory communities
EMA Draft Guideline on regulatory acceptance of 3R testing approaches

Procedure

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 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
Overview of ICH Guidelines with 3R improvements

- 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
Overview of ICH Guidelines with 3R improvements

- 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
Regulatory Acceptance of 3R Test Methods

- The use of the SAWP method qualification process in collaboration with JEG 3Rs is recommended at EMA level through its draft GL on regulatory acceptance of 3R testing approaches.

- Initiatives to clearly define a process for regulatory acceptance of 3R methods used for regulatory decision making at the ICH level are not in place nevertheless the 3Rs are included in the drafting/revision of GLs.

- Regulatory science should be kept in pace with technological developments. Early involvement of regulators in international initiatives (e.g. EU IMI) is crucial to achieve progress in this rapidly evolving field.
Sonja Beken, PhD
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