EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3 October 2014
EMA/CHMP/CVMP/JEG-3Rs/450091/2012
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

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

Draft

Draft Agreed by JEG 3Rs	**March 2014**
Draft agreed by SWP, SWP-V, BWP, IWP and EWP-V	By July 2014
Adoption by CVMP for release for consultation	11 September 2014
Adoption by CHMP for release for consultation	24 September 2014
Start of consultation	3 October 2014
End of consultation (deadline for comments)	31 December 2014

This guideline replaces the Position on Replacement of Animal Studies by *in vitro* Models (CPMP/SWP/728/95).

Comments should be provided using this template. The completed comments form should be sent to JEG-3Rs@ema.europa.eu

Keywords	***3Rs, regulatory acceptance, testing approaches, non-clinical, quality, human medicinal products, veterinary medicinal products, qualification, validation, replacement, reduction, refinement,***

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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

Table of contents

Executive 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. Regulatory acceptance is defined and guidance is given on the scientific and technical criteria for regulatory acceptance of 3R testing approaches, including a process for collection of real-life data (safe harbour). Pathways for regulatory acceptance of 3R testing approaches are described and a new procedure for submission and evaluation of a proposal for regulatory acceptance of 3R testing approaches is described.

1. Introduction

Regulatory testing of medicinal products for human and veterinary use is carried out to support first administration of a new medicinal product to humans or to the target animal species, before carrying out clinical trials in larger populations and before marketing authorisation and to control quality during production of the medicinal product.

To comply with Directives 2001/83/EC [1] and 2001/82/EC [2] and their associated Guidelines, quality and non-clinical1 testing often requires the use of laboratory animals. Ethical and animal welfare considerations require that animal use is limited as much as possible. In this respect, Directive 2010/63/EU [3] on the protection of animals used for scientific purposes, which is fully applicable to regulatory testing of human and veterinary medicinal products2, unambiguously fosters the application of the principle of the 3Rs (Replacement, Reduction and Refinement) when considering choice of methods to be used.

Various large scale international initiatives and organisations (e.g. EDQM, EPAA, EURL ECVAM, ICCVAM/NICEATM, JACVAM, OECD) are involved either directly or indirectly in the development, validation and dissemination of 3R testing approaches. In addition some initiatives attempt to foster cross-sectorial regulatory acceptance.

The application of all 3Rs is currently embedded in the drafting process of non-clinical regulatory guidance both at the European and at (V)ICH level. In addition, EDQM upholds the principles of Directive 2010/63/EU in the development of European Pharmacopoeia monographs and through its Biological Standardisation Programme, which aims to validate novel 3R testing methods for inclusion in the European Pharmacopoeia.

With respect to non-clinical testing requirements for human and veterinary medicinal products, over the past years, new *in vitro* methods have been accepted for regulatory use via multiple and flexible approaches, either as pivotal, supportive or as exploratory mechanistic studies, wherever applicable.

Whilst replacement of animal studies remains the ultimate goal, focus needs to include the application of all 3Rs. As such, approaches aiming at reducing or refining animal studies are routinely implemented in regulatory guidelines, where applicable. The recently approved ICH guidelines, ICH M3(R2) and ICH S2(R1) are good examples in this respect.

[1] Referred to as safety testing in marketing authorisation applications for veterinary medicinal products
[2] With the exception of clinical trials for veterinary medicinal products, which are specifically excluded from the scope of the directive

Although regulatory acceptance of 3R testing approaches is currently possible, a formal regulatory acceptance process has been lacking and implementation of new test methods in routine regulatory testing has sometimes proven problematic. The availability of a defined acceptance process is expected to foster the regulatory agreement to new 3R testing approaches and thereby stimulate innovation which may even result in increased predictivity of regulatory testing.

2. Scope

This guideline describes the process 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. Furthermore, scientific and technical criteria for validation of 3R testing approaches are presented and pathways for regulatory acceptance of 3R testing approaches are described.

This 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 European Pharmacopoeia monographs.

3. Legal basis and guidelines

This guideline has to be read in conjunction with:

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version: 05/10/2009) [1].
- Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (consolidated version: 18/7/2009) [2].
- Directive 2010/63/EU on the protection of animals used for scientific purposes on 3 June 2010 [3].
- Qualification of novel methodologies for drug development: guidance to applicants (EMA/CHMP/SAWP/72894/2008 Rev. 1).

4. Replacement, reduction and refinement of *in vivo* studies

The 3Rs of humane technique have been defined by Russell and Burch (1959) with replacement meaning "the substitution for conscious living higher animals of insentient material". Reduction means "reduction in the numbers of animals used to obtain information of a given amount and precision". Refinement means "any decrease in the incidence or severity of inhumane procedures applied to those animals which still have to be used".

Directive 2010/63/EU on the protection of animals used for scientific purposes of 3 June 2010 [3] fully endorses the principle of replacement, reduction and refinement by stating in article 4 that:

1. 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 procedure3.

[3] A 'procedure' means any use, invasive or non-invasive, of an animal for experimental or other scientific purposes, with known or unknown outcome, or educational purposes, which may cause the animal a level of pain, suffering, distress or

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

3. 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.

The choice of methods is to be implemented according to article 13 which 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.

5. Application of the 3Rs during drug development

In the context of drug development and production, laboratory animal studies are mainly used for two purposes: (1) for non-clinical/safety testing during development of new human/veterinary medicinal products and (2) for quality batch control as part of the manufacturing process. While animal tests are still required some progress has been made in implementing 3Rs.

The number of animals used for experimental and other scientific purposes in the EU Member States is reported by the European Commission on a 3 yearly basis4. The latest report (European Commission, 2013) provides an overview of the number of animals used in the Member States for experimental purposes for 2011. As such, regulatory safety studies for human and veterinary medicinal products account for approximately 4.4% of the total number of experimental animals used. Animal use for quality batch control testing of human and veterinary medicinal products account, respectively for 10.9% and 4% of experimental animals.

A tabulated overview of the current regulatory testing requirements for human and veterinary medicinal products and opportunities for implementation of the 3Rs is under development and will be published separately.

lasting harm equivalent to, or higher than, that caused by the introduction of a needle in accordance with the good veterinary practice [10].

[4] http://ec.europa.eu/environment/chemicals/lab_animals/reports_en.htm

6. Regulatory acceptance of 3R testing approaches

6.1. Definition of regulatory acceptance

In the scope of this paper regulatory acceptance of a new 3R testing approach can in general be defined by its incorporation into a regulatory testing guideline. It may also include 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.

The process and decision of acceptance for incorporation in a regulatory guideline is usually carried out by a working group of experts involved in drafting a new guideline/document or updating an existing one (EMA or (V)ICH).

Regulatory guidelines concerned are those related to the quality or non-clinical (safety and residues) requirements for human or veterinary medicinal products. In addition, regulatory guidelines related to clinical requirements for veterinary medicinal products are concerned.

6.2. 3R testing approaches

The modification of existing testing approaches to achieve refinement, reduction and replacement of laboratory animal use and, if possible, at the same time increase predictive power of regulatory testing is expected to occur at different levels. These levels range from discrete modifications of existing testing approaches (e.g. reduction of the top concentration used in *in vitro* genotoxicity testing in ICH S2R, [4]) to the implementation of a completely new approach in regulatory toxicology (e.g. Toxicity Testing in the 21st century; [5]).

6.3. Criteria for regulatory acceptance of 3R testing approaches

Following criteria should be fulfilled before consideration of a 3R testing approach 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 (see 6.3.4).

6.3.1. Method validation

Demonstration of scientific validity is considered a prerequisite for regulatory acceptance of 3R testing approaches. This implies that the criteria and scientific principles for test method validation need to be fulfilled, including:

1. defined test methodology/standard protocol with clear defined/scientifically sound endpoints
2. reliability
3. relevance

However, the amount of information needed and the criteria applied to a new method will depend on a number of factors, including:

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

Different routes of method validation are acceptable including formal validation by recognised institutions such as the VAMs and EDQM (see below). Formal validation generally directly implies the intention to seek regulatory acceptance.

6.3.2. Regulatory acceptance following formal validation

Examples of formal validation processes for 3R test methods are described by the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) and by the EDQM.

EURL ECVAM's validation criteria are comparable to the criteria subsequently defined by the (US) Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the OECD [6-10]. The evolution of a regulatory test is subdivided in five stages that reflect the sequence of steps to be performed for a prospective validation exercise: evaluation of candidate method" (to see if suitable/ready for validation), pre-validation (protocol refinement, transfer and performance), validation, independent peer review and regulatory acceptance (new or updated OECD guidelines).

In a prospective validation study, an inter-laboratory blind trial (involving at least three laboratories) is conducted to assess whether tests can be shown to be relevant and reliable for one or more specific purposes. This inter-laboratory trial is followed by data analysis and an evaluation of the outcome of the study in comparison with predefined performance criteria.

The modular approach to the EURL ECVAM principles on test validity allows for flexibility by breaking down the various stages in validation into independent modules and defining for each module the information needed for assessing test validity. This allows for retrospective validation studies to be conducted [10, 11] or for a combination of retrospective and prospective studies.

At the level of the EDQM, the Biological Standardisation program (BSP) aims at validating new methods for the quality control of biological medicinal products with the goal of including them in European Pharmacopoeia monographs. It is overseen by a steering committee consisting of the chairs of the relevant European Pharmacopoeia groups of experts, representatives from the relevant EMA working parties, co-opted scientific experts and an observer from the WHO. The program takes methods of interest which have been validated on a local scale (single laboratory/limited products) and proceeds with a wider generic validation to demonstrate the potential applicability in other laboratories and with other similar products on the market. Similar to the EURL ECVAM procedure the process involves multiple phases including preparatory method refinement, small scale transfer studies and finally large scale international collaborative studies with manufacturers and national control laboratories. The study reports are presented to the relevant European Pharmacopoeia expert group for consideration for inclusion of the method in the European Pharmacopoeia and are made publicly available.

6.3.3. Alternative routes of regulatory acceptance

3R testing approaches that have sufficient demonstration of scientific validity according to the criteria described (see 6.3.1) but have not been assessed in a formal validation process can however also be included in regulatory guidelines/documents wherever possible. In this case the data are evaluated on a case–by-case basis by National Control Authorities and/or relevant Working Parties, or Expert Working Groups.

Examples of such testing methods include the hERG assay recommended in the integrated testing strategy in the ICH S7B Guidance on the non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals [12] and the reconstructed skin models for phototoxicity testing recommended in ICH S10 Guidance on Photosafety Evaluation of Pharmaceuticals [13].

6.3.4. Data collection through the safe harbour concept

The safe harbour is defined as a period of voluntary submission of data obtained by using a new 3R testing approach in parallel with data generated using existing methods. Data generated with the new 3R testing approaches will not be used as part of the regulatory decision making process and should be evaluated independently and solely for the purpose of evaluation of the novel 3R testing approaches for possible future regulatory acceptance. This will allow data on the 3R testing approaches to be gathered before consideration for regulatory acceptance.

The real-life data generated through the safe harbour agreement will be submitted (see 6.4) for review and decision making on the regulatory acceptability of the proposed new 3R testing approaches based on the assessment of the submitted data.

6.4. A Procedure for submission of a proposal for regulatory acceptance of 3R approaches

Proposals for regulatory acceptance of 3R testing approaches may be submitted to the EMA in accordance with the procedure described in the Guideline on Qualification of Novel Methodologies for Drug Development (see EMA/CHMP/SAWP/72894/2008 Rev. 1). Proposals that relate to approaches that are intended for use in testing veterinary medicinal products only may be submitted in accordance with existing scientific CVMP guidance for companies requesting scientific advice (EMA/CVMP/172329/2004-Rev.3). The CVMP Scientific Advice Working Party would then liaise with other working parties as necessary.

Assessment of the new 3R testing approaches will be performed according to the criteria as defined in 6.3 in collaboration with the relevant 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 for regulatory acceptance to the relevant working parties,
2. new 3R testing approaches needs real-life data collection period under safe harbour provisions (see 6.3.1),
3. new 3R testing approaches is rejected because it is immature.

When applicable, real-life data generated through the safe harbour concept will need to be submitted for review and decision making on the regulatory acceptability of the proposed new 3R testing approaches based on the assessment of the submitted data.

References

1. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version : 05/10/2009)
2. Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (Official Journal L 311, 28/11/2001 p. 1 - 66). (consolidated version : 18/7/2009)
3. Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (Official Journal L 276/33).
4. Note for Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals intended for Human Use (EMEA/CHMP/ICH/126642/2008).
5. Committee on Toxicity Testing and Assessment of Environmental Agents, National Research Council (2007). Toxicity Testing in the 21st century: A vision and a Strategy. The National Academies Press, USA.
6. Balls M, Blaauboer BJ, Fentem JH, Bruner L, Combes RD, Ekwall B, Fielder RJ, Guillouzo A, Lewis RW, Lovell DP, Reinhardt CA, Repetto G, Sladowski D, Spielmann H & Zucco, F (1995) Practical aspects of the validation of toxicity test procedures. The report and recommendations of ECVAM workshop 5. ATLA 23: 129-147.
7. Balls M & Karcher W (1995) The validation of alternative test methods. ATLA 23: 884-886.
8. NIH (1997). Validation and Regulatory Acceptance of Toxicological Test Methods. A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods. NIH Publication 97-3981, 105pp. Research Triangle Park, NC, USA: NIEHS.
9. NIH (1999). Evaluation of the Validation Status of Toxicological Methods: General Guidelines for Submissions to ICCVAM (Revised, October 1999). NIH Publication 99-4496, 44pp. Research Triangle Park, NC, USA: NIEHS.
10. OECD (2005). Guidance document on the validation and international acceptance of new or updated test methods for hazard assessment. OECD Testing Series and Assessment Number 34. ENV/JM/MONO(2005)14, pp 96, Paris, France: OECD.
11. Hartung T, Bremer S, Casati S, Coecke S, Corvi R, Fortaner S, Gribaldo L, Halder M, Hoffmann S, Janusch Roi A, Prieto P, Sabbioni E, Scott L, Worth A and Zuang V (2004). A Modular Approach to the ECVAM Principles on Test Validity. ATLA 32, 467–472.
12. Note for Guidance on the Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (CPMP/ICH/423/02).
13. ICH Guideline S10 on photosafety evaluation of pharmaceuticals (EMA/CHMP/ICH/752211/2012).