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Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Review and update of EMA guidelines to implement best practice with regard to 3Rs (replacement, reduction and refinement) in regulatory testing of medicinal products – report on actions taken

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The status of the EMA guidelines, updated to implement best practise of 3Rs, referred to in this document is correct at the time of publication.

Keywords	Best practise, 3Rs, guidelines, regulatory testing

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1. Introduction

In February 2014, CHMP and CVMP published a joint concept paper announcing a review and update of EMA guidelines to implement best practice with regard to 3Rs (replacement, reduction and refinement) in regulatory testing of medicinal products (EMA/CHMP/CVMP/JEG-3Rs/704685/2012).

As background, it should be noted that the purpose of this review was not to reconsider established testing requirements but, rather, to ensure that EMA guidelines do not make reference to animal tests that are no longer considered appropriate.

The purpose of the current document is to provide an update on the work undertaken and the guidelines that have been or will be updated as a result of this review.

2. Guidelines reviewed

As stated in the concept paper, the guidelines reviewed were those overseen by the joint CHMP/CVMP Quality Working Party (QWP), the CHMP Biologicals Working Party (BWP), the CHMP Vaccines Working Party (VWP), CHMP Safety Working Party (SWP-H), the Biosimilar Medicinal Products Working Party (BMWP), the Committee for Advanced Therapies (CAT), the CVMP Immunologicals Working Party (IWP), the CVMP Safety Working Party (SWP-V) and the CVMP Efficacy Working Party (EWP-V).

3. Outcome of the review

3.1. Statements highlighting the need to consider 3Rs

As indicated in the concept paper, there is a desire to include a statement highlighting the need to consider 3Rs in all relevant guidelines. However, it was agreed that guidelines would not be updated if the only intended change was the addition of such a statement. Relevant statements will be added to these guidelines when they are next opened up for a more general revision.

The use of a standard statement for inclusion in section 3 (Legal basis) in all relevant EMA guidelines was considered. However it was acknowledged that some flexibility should be maintained as, in some cases, there may be particular concerns that warrant a modified statement. The following 3Rs statement was agreed as a default option:

'In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and Directive 2010/63/EU on protection of animals used for scientific purposes, the 3R principles (replacement, reduction and refinement) should be applied to regulatory testing of medicinal products.'

3.2. Guidelines amended/to be amended

3.2.1. Guidelines overseen by the joint CHMP/CVMP Quality Working Party (QWP)

The QWP, having reviewed its guidelines (including ICH and VICH guidelines), noted that most quality control tests are physical, physicochemical or are pharmaceutical technical procedures, and that very few animal tests are required for quality testing of pharmaceuticals.

The QWP concluded that at present all CHMP/CVMP quality guidelines related to chemical active substances and derived medicinal products are consistent with best practice in relation to 3Rs.

3.2.2. Guidelines overseen by the CHMP Biologicals Working Party (BWP)

The BWP agreed and has updated the following three guidelines:

1. The CHMP Guideline on development, production, characterisation and specifications for monoclonal antibodies and related products (EMA/CHMP/BWP/532517/2008):
    - Reference to the use of ascites fluid for production of monoclonal antibodies has been removed.
    - In relation to testing biological activity, the original guideline allowed use of either *in vitro* or *in vivo* assays without implying a preference. The relevant text has been amended to favour *in vitro* assays.
    - A 3Rs statement has been added.
2. The CHMP Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer (EMA/CHMP/BWP/271475/2006-Rev.1):
    - In relation to potency testing, the original guideline allowed use of either *in vitro* or *in vivo* assays. The relevant text has been amended to favour *in vitro* assays.
    - A 3Rs statement has been added.
3. The CHMP Guideline for guidance on production and quality control of animal immunoglobulins and immunosera for human use (EMA/CHMP/BWP/3354/1999-Rev.1):
    - In relation to potency testing, the original guidance already stated that it would be desirable to avoid the use of animals by using in vitro methods. The relevant section of the guidance has been further strengthened.
    - A 3Rs statement has been added.

3.2.3. Guidelines overseen by the CHMP Biosimilar medicinal products working party (BMWP)

Since 2011, specific consideration of 3Rs principles have been implemented in the drafting of new guidelines and in the revision of older ones, including the overarching guideline “Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1)”. Although relevant statements in the latter revised guideline override older product-specific guidelines, also the outdated statements in the older guidelines will be revised to include the stepwise approach for evaluation of the similarity of the biosimilar and the reference product which means that analytical studies and *in vitro* pharmaco-toxicological studies should be conducted first and a decision then made as to the extent of what, if any, *in vivo* work in animal studies will be required.

The following guidelines have been updated:

- The Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins (EMEA/CHMP/BMWP/118264/2007-Rev.1);
- Guideline on similar medicinal products containing somatropin (Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues) (EMEA/CHMP/BMWP/94528/2005);
- Guideline on Similar biological medicinal products containing recombinant erythropoietins (EMEA/CHMP/BMWP/301636/08).

Revision is ongoing in the BMWP work plan for the following:

- Reflection paper on similar biological medicinal products containing recombinant interferon alpha (EMEA/CHMP/BMWP/102046/2006);
- Guideline on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor (EMEA/CHMP/BMWP/31329/2005).

3.2.4. Guidelines overseen by the Committee for Advanced Therapies (CAT)

The CAT, having reviewed its guidelines, did not identify guidelines for which 3Rs principles updates are necessary. A stepwise and risk-based approach is recommended for Advanced Therapy Medicinal Products (ATMPs) giving preference to *in vitro* models. If an animal model is necessary, only a relevant one should be performed.

3.2.5. Guidelines overseen by the CHMP Safety Working Party (SWP-H)

A number of ICH (safety) guidelines are currently under revision or finalised with specific consideration of 3Rs principles, including:

1. ICH S1: Revision of the Rodent Carcinogenicity Studies for Human Pharmaceuticals Guideline
    - A new testing paradigm under evaluation based on weight-of-evidence assessment of carcinogenic potential would restrict the need for a 2-year rat carcinogenicity study.
2. ICH S3A: Q&As on Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure (Focus on Microsampling) - *Finalised*
    - Facilitation of microsampling techniques in order to reduce/eliminate TK satellite animals use and sample volumes.
3. ICH S5(R3): Revision on Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility
    - Aspects under consideration include evaluation of novel *in vitro* ex-vivo or non-mammalian in-vivo assay(s) for embryo-foetal development (EFD) testing within an integrated testing strategy and potential to replace one *in vivo* species testing in limited circumstances.
4. ICH S9: Q&As on Nonclinical Evaluation for Anticancer Pharmaceuticals
    - Aspects under consideration include clarification of the scope which may result in further decrease of the conduct of toxicology animal studies.
5. ICH S11: NEW Guideline on Nonclinical Safety Testing in Support of Development of Paediatric Medicines
    - Better guidance on the need for juvenile animal studies to avoid unnecessary testing.

In addition, the following guideline is planned for revision:

6. ICH S7B: Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation)
    - Aspects under consideration will be advances in the science and methods as currently discussed in the Comprehensive *In Vitro* Pro-arrhythmia Assessment (CIPA) initiative.

3.2.6. Guidelines overseen by the CHMP Vaccines Working Party (VWP)

Guidelines overseen by VWP, including ICH guidelines, did not identify guidelines where 3Rs updates would be necessary at this time.

3.2.7. Guidelines overseen by the CVMP Immunologicals Working Party (IWP)

The IWP agreed and implemented revisions of the following guidelines:

1. The CVMP Guideline on data requirements for removing the target animal batch safety test for immunological veterinary medicinal products in the EU (EMA/CVMP/IWP/810769/2011).
    - Since the target animal batch safety test is no longer required by the Ph. Eur., this guideline paper is considered obsolete and this is now clearly reflected on the EMA website.
2. The CVMP Guideline on the procedure to be followed when a batch of a vaccine finished product is suspected to be contaminated with bovine viral diarrhoea (BVD) virus (EMEA/CVMP/IWP/205351/2006).
    - Reference to the possible use of an *in vivo* test has been removed.

In relation to VICH guidance, it was noted that following finalisation of VICH GL50R: harmonization of criteria to waive target animal batch safety testing for inactivated vaccines for veterinary use (EMA/CVMP/VICH/582610/2009, updated and came into force on 01/05/2018), VICH has now published a parallel draft guideline relating to live vaccines (VICH GL55 Harmonisation of criteria to waive target animal batch safety testing for live vaccines for veterinary use, EMA/CVMP/VICH/313610/2013). The work was led by the EU regulators and came into force in May 2018.

The majority of animal tests required for regulatory testing of IVMPs are established in the Ph. Eur. Revision of 3Rs aspects of monographs is ongoing at the Ph. Eur. level and the use of alternatives is already possible if appropriate validation has been carried out.

3.2.8. Guidelines overseen by the CVMP Safety Working Party (SWP-V)

Guidelines overseen by SWP-V were considered to already be in line with best practice in relation to 3Rs and consequently no updates are considered necessary at this time.

The following was noted in relation to VICH guidelines:

- VICH GL23(R): Studies to evaluate the safety of residues of veterinary drugs in human food: genotoxicity testing (EMA/CVMP/VICH/526/2000) includes a default requirement for a stand-alone *in vivo* test. Following a recommendation from the EU regulators VICH is discussing whether this default requirement should be maintained and, if so, if it could be integrated into another *in vivo* test in order to reduce the number of animals used;
- VICH GL22: Studies to evaluate the safety of residues of veterinary drugs in human food: reproduction testing (CVMP/VICH/525/00-FINAL) includes a requirement for a multigeneration reproduction toxicity study. Following a recommendation from the EU regulators, the VICH is discussing whether the Extended One Generation Reproductive Toxicity Study (EOGRTS) could be considered as an alternative to the multigeneration study.

It was noted that both VICH and SWP-V routinely consider 3Rs when developing guidance.

3.2.9. Guidelines overseen by the CVMP Efficacy Working Party (EWP-V)

Noting that the animal species used are the target species for the products concerned, the EWP-V considered that the majority of its guidelines are in compliance with the 3Rs principles. However, it was considered that the following guidelines, would benefit from a general review to ensure they integrate recommendations with current best practice in 3Rs. Revision of these guidelines was incorporated into the EWP-V work plans, and work on the revisions was either completed or is currently ongoing:

- Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market (EMA/CVMP/EWP/117899/2004–Rev.1). - *Finalised*
- The guideline on veterinary medicinal products for fluid therapy in case of diarrhoea (7AE14a);
- The guideline on anticoccidials used for the therapy of coccidiosis in chickens, turkey and geese (7AE15a);
- The CVMP guideline for the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/99-FINAL);
- The CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-Rev.2).

In addition, the wording of relevant paragraphs in the CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005) will be reviewed in order to integrate best practice in 3Rs, once ongoing work on the development of a combination guideline by the VICH has been completed.

While a detailed review of VICH guidelines was not undertaken, the working party noted that consideration of 3Rs in relation to the following guidelines would be recommended:

- VICH Topic GL 7: Efficacy requirements for anthelmintics: overall guidelines (CVMP/VICH/832/99-corr);
- VICH Topic GL 19: Efficacy of anthelmintics: specific recommendations for canines (CVMP/VICH/835/99-FINAL);
- VICH Topic GL 20: Efficacy of anthelmintics: Specific recommendations for feline (CVMP/VICH/545/00-FINAL).