EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 December 2017
EMA/CHMP/CVMP/3Rs/614768/2017-corr[1]
Committee for Medicinal Products for Human Use (CHMP)

Recommendation to marketing authorisation holders, highlighting recent measures in the human field to promote replacement, reduction, and refinement (3Rs) measures described in the European Pharmacopoeia

Applicable to human vaccines from 01/01/2018

In accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Council of Europe), tests performed in animals must be carried out in such a way as to use the minimum number of animals and to cause the least pain, suffering, distress or lasting harm. The European Pharmacopeia (Ph.Eur.) has, over the years, applied these principles by implementing alternative tests and assays that replace, reduce and refine animal use.

In the EU, after 1 January 2013, the date when Directive 2010/63/EU on the protection of animals used for scientific purposes[2], replacing earlier Directive from 1986, took full effect, the use of animals in testing of medicinal products has clearly become more regulated.

Article 13 of the above-mentioned directive states that “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”.

Article 13 also requires that, if it is necessary to use animal tests, the method which to the greatest extent reduces the number of animals, causes the least pain, suffering, distress or lasting harm and is most likely to provide satisfactory results, shall be selected.

The European Pharmacopoeia has introduced a number of measures via new or revised texts in the human field to promote 3Rs. These requirements are published in Supplement 9.3 and are in force from 01/01/2018.

[1] Correction in title of document
[2] Available at http://ec.europa.eu/environment/chemicals/lab_animals/home_en.htm

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

Revisions to general chapters on Tests for extraneous agents in viral vaccines for human use (2.6.16) and Cell substrates for the production of vaccines for human use (5.2.3).

In the revised general chapter 2.6.16, Tests for extraneous agents in viral vaccines for human use, the testing strategy as regards extraneous agents is to be established based on a risk assessment and the list of tests must be adapted depending on the extraneous agents that have the potential to contaminate the product. Molecular biology methods may be considered for the detection of specific viruses, while broad molecular methods may be considered for broad detection of viruses.

As part of the revisions to general text 2.6.16 and the revision to general chapter 5.2.3 Cell substrates for the production of vaccines for human use, the tests in adult mice and guinea pigs are deleted. In addition, the tests in suckling mice and control eggs are to be used only if a risk assessment indicates that the tests provide risk mitigation.

For more information: https://www.edqm.eu/en/alternatives-animal-testing

Within the framework of pharmaceutical legislation, monographs including general monographs and general chapters of the Ph. Eur. have legal force with regard to the quality part of the dossier[3]. As a consequence, if the Ph. Eur. includes a method more compliant with the objectives of the 3Rs than that used by Marketing Authorisation Holders (MAHs), the competent authorities responsible for granting approval of animal testing under Directive 2010/63/EU are obliged to require the more animal friendly Ph. Eur. method to be used.

A new Ph.Eur general chapter 5.2.14, coming into force on the 1st January 2018 "Substitution of in vivo method(s) by in vitro method(s) for the quality control of vaccines" provides guidance to facilitate the implementation of *in vitro* methods as substitutes for existing in vivo methods, in cases where a typical one-to-one assay comparison is not appropriate for reasons unrelated to the suitability of one or more in vitro methods.

Therefore, in order to comply with the provisions of Directive 2010/63/EU and Ph.Eur and to secure an undisrupted supply of medicinal products to the European Market, MAHs should take all necessary actions to introduce 3Rs Ph. Eur. methods including submission of variations to marketing authorisations as appropriate.

[3] Status of EMEA scientific guidelines and European Pharmacopoeia monographs and chapters in the regulatory framework applicable to medicinal products (EMEA/42371/2008)