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Committee for Medicinal Products for Human Use (CHMP)

Recommendation to marketing authorisation holders, highlighting recent updates for reduction, refinement and replacement (3Rs) methods described in the European Pharmacopoeia

Applicable to human vaccines against hepatitis A

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 reduce, refine and replace 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[1], 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.

Description of an *in vitro* method based on the outcome of a collaborative study 'Validation of a new ELISA method for *in vitro* potency testing of hepatitis A vaccines'[2] has been introduced as method A in the Ph. Eur. general chapter 2.7.14, Assay of Hepatitis A vaccine. The assay details are included as an example of an immunochemical method that has been found suitable. The revision was published in Ph. Eur. supplement 8.5 and is in force from 07/2015.

[1] Available at http://ec.europa.eu/environment/chemicals/lab_animals/home_en.htm
[2] Morgeaux, S. et al. Validation of a new ELISA method for in vitro potency testing of hepatitis A vaccines. Pharmeur Bio Sci Notes 2013 (1): 64-92. http://pharmeuropa.edqm.eu/home/

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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.

Therefore, in order to comply with the provisions of Directive 2010/63/EU 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)