7 December 2017
EMA/CHMP/CVMP/3Rs/336802/2017
Committee for Medicinal Products for Veterinary Use (CVMP)

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

Applicable to veterinary vaccines from 01/01/2017

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.

The European Pharmacopoeia has introduced a number of measures via new or revised texts in the veterinary field to promote 3Rs. These requirements are published in the 9th edition and are in force from 01/01/2017.

Promotion of the move from final controls to verification of consistency of production:

Further to the introduction of the consistency of production concept in the context of the 3Rs in the General Notices (Supplement 8.2), this concept has also been included in the general monograph Vaccines for veterinary use (0062) and in the three following vaccine-specific monographs: Canine

[1] 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 (L 276/33).

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

leptospirosis vaccine (inactivated) (0447), Bovine leptospirosis vaccine (inactivated) (1939) and Infectious bovine rhinotracheitis vaccine (inactivated) (2674).

Promotion of the move from final controls to upstream quality controls:

The introduction of a reference to the new general chapter setting requirements for Healthy Chicken flocks for the production of inactivated vaccines for veterinary use (5.2.13) will provide guarantees with regard to extraneous agents contamination, making the test for specified extraneous agents performed on each final product obsolete for the eight following specific monographs: Equine influenza vaccine (inactivated) (0249), Newcastle disease vaccine (inactivated) (0870), Avian infectious bronchitis vaccine (inactivated) (0959), Avian infectious bursal disease vaccine (inactivated) (0960), Porcine influenza vaccine (inactivated) (0963), Egg drop syndrome '76 vaccine (inactivated) (1202), Avian paramyxovirus 3 vaccine (inactivated) (1392) and Feline chlamydiosis vaccine (inactivated) (2324).

Promotion of in-vitro testing (3Rs) for the control of inactivated veterinary vaccines:

Approximately 40 inactivated vaccine-specific monographs and the general monograph Vaccines for veterinary use (0062) were adopted including the following changes:

(a)* revision of the requirements for identification: reference to the antibody induction test has been removed for all inactivated vaccines, which allows the user to identify the antigen(s) by any suitable method.

(b)* revision of inactivation testing of all the inactivated veterinary vaccines to give conditions that allow omission of the second inactivation test.

Promotion of natural housing conditions to avoid animal stress:

When compatible with the described test, solitary housing of laying hens and young chickens has been replaced by housing in small groups in the following monograph: *Infectious chicken anaemia vaccine (live) (2038).*

**** (a) and (b) apply to***: Avian infectious bronchitis vaccine (inactivated) (0959), Avian infectious bursal disease vaccine (inactivated) (0960), Avian paramyxovirus 3 vaccine (inactivated) for turkeys (1392), Egg drop syndrome '76 vaccine (inactivated) (1202), Newcastle disease vaccine (inactivated) (0870), Mycoplasma gallisepticum vaccine (inactivated) (1942), Feline chlamydiosis vaccine (inactivated) (2324), Feline calicivirosis vaccine (inactivated) (1101), Feline infectious enteritis (feline panleucopenia) vaccine (inactivated) (0794), Feline leukaemia vaccine (inactivated) (1321), Feline viral rhinotracheitis vaccine (inactivated) (1207), Equine influenza vaccine (inactivated) (0249), Equine herpesvirus vaccine (inactivated) (1613), Bovine viral diarrhoea vaccine (inactivated) (1952) , Calf coronavirus diarrhoea vaccine (inactivated) (1953), Calf rotavirus diarrhoea vaccine (inactivated) (1954), Porcine influenza vaccine (inactivated) (0963), Aujeszky's disease vaccine (inactivated) for pigs (0744), Porcine parvovirosis vaccine (inactivated) (0965), Porcine enzootic pneumonia vaccine (inactivated) (2448), Rabies vaccine (inactivated) for veterinary use (0451), Canine adenovirus vaccine (inactivated) (1298), Canine parvovirosis vaccine (inactivated) (0795), Rabbit haemorrhagic disease vaccine (inactivated) (2325).

(a) only applies to: Fowl cholera vaccine (inactivated) (1945), Salmonella Enteritidis vaccine (inactivated) for chickens (1947), Salmonella Typhimurium vaccine (inactivated) for chickens (2361), Furunculosis vaccine (inactivated, oil-adjuvanted, injectable) for salmonids (1521), Vibriosis (cold-

water) vaccine (inactivated) for salmonids (1580), Vibriosis vaccine (inactivated) for salmonids (1581), Yersiniosis vaccine (inactivated) for salmonids (1950), Neonatal piglet colibacillosis vaccine (inactivated) (0962), Swine erysipelas vaccine (inactivated) (0064), Foot-and-mouth disease (ruminants) vaccine (inactivated) (0063), Mannheimia vaccine (inactivated) for cattle (1944), Neonatal ruminant colibacillosis vaccine (inactivated) (0961), Mannheimia vaccine (inactivated) for sheep (1946), Pasteurella vaccine (inactivated) for sheep (2072).

For more information:
http://pharmeuropa.edqm.eu/home/menupage/English/Useful%20Information/Supplementcomments90_E.pdf

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[2]. 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.

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