

Comments concerning revised texts published in Supplement 10.2

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the June 2019 session and published in Supplement 10.2.

When a text has been modified, this is indicated by horizontal or vertical lines in the margin of 10.2. The details given below complete this information, but are not necessarily exhaustive.

The following details can also be consulted in the [Knowledge database](#) under [View history](#).

GENERAL CHAPTERS

2.6.16. Tests for extraneous agents in viral vaccines for human use

Avian leucosis viruses. Deletion of the reference to general chapter 2.6.24 *Avian viral vaccines: tests for extraneous agents in seed lots*, further to the suppression of the chapter from the Ph. Eur.

5.2.4. Cell cultures for the production of vaccines for veterinary use

Cell cultures used for testing of vaccines. The particulars for these cells are described in the new general chapter 2.6.37. Thus any information has been deleted from 5.2.4 which is dedicated to cells used in production of veterinary vaccines.

Extraneous viruses. This section has been aligned with the revision of general chapter 5.2.5. *Management of extraneous agents in immunological veterinary medicinal products*. The scope of general chapter 5.2.5 has been widened and includes requirements for cell cultures for the production of veterinary vaccines, a risk management approach has been taken and the use of any method (culture or other) capable of detecting specified extraneous agents is permitted. As a result, the control of extraneous agents by culture methods according to the detailed method descriptions given in 5.2.4 has been replaced by a reference to 5.2.5.

Retroviruses. The following changes have been made for clarification purposes: addition of the terms 'endogenous', and 'extraneous', and restriction to 'mammalian cell lines'. In both related tables, the order of the tests has been changed to reproduce the order given in the text (editorial).

5.2.5. Management of extraneous agents in immunological veterinary medicinal products

Information on managing the presence of extraneous agents in immunological veterinary medicinal products (IVMPs) was previously spread across a number of Ph. Eur. texts (general monographs, several general chapters, and individual monographs for the control of the final product), but was not consistently reproduced for all the different products (e.g. avian and

mammalian products). This situation developed mainly for historical reasons, and the intention of this revision is to establish a harmonised approach to give greater clarity to users.

All of the existing requirements have been collated and harmonised, and have subsequently been compiled in this general chapter 5.2.5, which already included a suitable approach to risk management.

Consequently, this general chapter has been revised as outlined below, with the title changed to 'Management of extraneous agents in immunological veterinary products'.

Scope

The scope has been modified in order to:

- cover all materials (master seeds, substrates - eggs, cells, etc.), whereas previously only certain substances (sera, trypsin, etc.) were covered. This extension should allow manufacturers to test only when justified, and with fit-for-purpose testing methods, thereby reducing the overall number of tests performed on the final product.
- include the entire production process, from the sourcing of starting materials to the final product stage, in order to have a coherent and rational approach, and to avoid double testing or gaps in the testing strategy.
- restrict the text to living replicative extraneous agents, the purpose of which is to ensure safety with regard to this type of contaminant. Previously, this general chapter also included identification of an immune response to inactivated extraneous agents to address epidemiological or regulatory concerns. This has been deleted from the revised chapter as the focus has changed. Management of inactivated extraneous agents is covered by a statement in the general monograph *Vaccines for veterinary use (0062)*, under general provisions in the Production section.

Risk management

The section has been revised to give additional information on the impact of the manufacturing process on the management of extraneous agents.

Under Risk assessment (section 3-1), the term 'country of origin' has been replaced by 'region or country of origin' in order to additionally cover cases within defined regions that may include several countries, or parts of countries that are not defined by existing borders.

Under Risk control (section 3-2), requirements for final product testing have been introduced. A decision tree is given in Annex II as an example to illustrate the new approach, but is not meant to cover all possible cases.

The requirements regarding bacteria, fungi and mycoplasma were not repeated in this general chapter, and the related thresholds in both cases are provided in the general monographs *Vaccines for veterinary use (0062)* and *Immunosera for veterinary use (0030)* or specific monographs.

Control measures

The section has been revised and consists of 3 parts.

Section 4-1 focuses on starting materials, and requirements for donor animals used for the production of IVMPs is included in section 4-1-1-2-3.

Section 4-2 focuses on production, and section 4-2-2. Removal or inactivation of extraneous agents during production includes a summary of good manufacturing practice and information transferred from the general monograph *Vaccines for veterinary use (0062)*.

Section 4-3 is a new section on methods of detection of extraneous agents, and allows the use of new technologies, particularly *in vitro* methods, when appropriate. Section 4-3-1 focuses on general prerequisites and includes an introduction outlining the general principles and an updated approach to the requirements, with particular reference to *in vitro* tests and molecular methods. Section 4-3-2 focuses on test-specific information, and lists requirements for newly described methods (i.e. molecular methods), including a reference to the new general chapter 2.6.37. *Principles for the detection of extraneous viruses in IVMPs* using culture methods.

Annex

Annex I is a compilation of 2 lists, with the first being a list of extraneous agents of interest that consolidates the list of avian agents already published in the Ph. Eur. The second is the list of mammalian and fish agents which are currently outlined in the EMA guideline on requirements for the production and control of IVMPs (EMA/CVMP/IWP/206555/2010-Rev.1). Both lists have been updated recently and it has been agreed to have a single reference list within the Ph. Eur.

The list of avian agents comprises a general list of avian agents with additional lists for chickens, ducks, geese, turkeys and pigeons.

5.2.13. Healthy chicken flocks for the production of inactivated vaccines for veterinary use

Revised following the change in title of general chapter 5.2.5. (editorial).

GENERAL MONOGRAPHS

Immunosera for veterinary use (0030)

Batch tests, and Tests / Extraneous agents: These sections have been revised to take into account the modifications in the revised general chapter 5.2.5 as part of the new approach for extraneous agent testing. If PCR and egg inoculation methods give equivalent results, *in vitro* methods such as PCR are the preferred option and are therefore encouraged. Cell culture methods are described in the new general chapter 2.6.37 referred to in this general monograph.

Vaccines for veterinary use (0062)

The general monograph has been revised to:

– move the requirements regarding extraneous agents to the revised chapter 5.2.5 and, in doing this, update the approach to the testing for extraneous agents in immunological veterinary medicinal products; in particular a reference to risk management is included and the use of any suitable culture or other method capable of detecting specified extraneous agents is allowed; this is a move from a prescriptive to a scientifically sound and targeted approach, which has the advantage of being more flexible and uses proven, fit-for-purpose methods; this approach is expected to further define quality levels of immunological veterinary medicinal products and reduce the overall and in particular *in-vivo* tests performed;

- allow identification of live vaccines by any suitable method (instead of using an immunostaining/neutralisation test in cultures - cells or SPF eggs - with a monospecific antiserum or monoclonal antibodies) ;
- continue to allow the use of antibiotics during vaccine production, but request justification for such use.

A section-by-section breakdown of the revision is outlined below.

Production/General provisions (section 2). Reference to epizootic eradication programmes has been moved from general chapter 5.2.5, thereby allowing the test for specified extraneous agents to be deleted from individual monographs.

Starting material (section 2-1). Requirements regarding extraneous agent testing have been moved to revised general chapter 5.2.5.

Media used for seed culture preparation and for production (section 2-1-2). 'Country of origin' has been replaced by 'region or country of origin' in line with the wording published in general chapter 5.2.5. The use of antibiotics during vaccine production is still allowed (generally restricted to cell culture fluids and other media, egg inoculation and material harvested from tissues and embryonated eggs), but must be justified.

Seed lots/Absence of extraneous viruses (section 2-1-3-2-6). The detailed descriptions of the methodologies to follow when using culture methods (including expansion/preparation of the cells and virus seeds prior to testing) for extraneous agent testing have been replaced by general guidance; this is explained in the chapter 5.2.5 dedicated to the management of extraneous agents. This provides greater flexibility, but does not preclude the continued use of the current approach, provided the general principles described in the new approach are fulfilled and the updated list of extraneous agents proposed in Annex I of revised general chapter 5.2.5 is considered. The requirements are not repeated in individual monographs, as requirements given in general monographs apply to all products covered in their definition.

Substances (section 2-1-4). This section covers the substances used for the preparation of vaccines and refers to the basic requirements given in general chapter 5.2.5, or in the relevant monographs.

Preparation of the vaccine (section 2-3). The wording used has been clarified (editorial).

Identification (section 3-1). This section has been revised to allow the use of any suitable method for live vaccines. A similar exercise had already been carried out for inactivated vaccines (see revised text published in the 9th Edition of the Ph. Eur.). The same change has been made in the relevant revised individual monographs.

Extraneous agents (section 3-9). This has been revised to refer to general chapter 5.2.5 instead of having a prescriptive and detailed test method.

VACCINES FOR HUMAN USE

Influenza vaccine (live, nasal) (2772)

Avian leucosis viruses. Deletion of references to general chapter 2.6.24 *Avian viral vaccines: tests for extraneous agents in seed lots*, further to the suppression of the chapter from the Ph. Eur.

Yellow fever vaccine (live) (0537)

Avian leucosis viruses. Deletion of references to general chapter 2.6.24 *Avian viral vaccines: tests for extraneous agents in seed lots*, further to the suppression of the chapter from the Ph. Eur.

VACCINES FOR VETERINARY USE

Aujeszky's disease vaccine (inactivated) for pigs (0744)

Extraneous agents. The section Specified extraneous agents (section 3-4) has been deleted. Instead, a requirement that vaccines do not interfere with national disease eradication programmes has been added to the general monograph *Vaccines for veterinary use (0062)*.

Aujeszky's disease vaccine (live) for pigs for parenteral administration (0745)

Extraneous agents (section 3-4): protocol for testing in cell cultures deleted and reference to general chapter 5.2.5 added instead.

Avian infectious bronchitis vaccine (inactivated) (0959)

Extraneous agents. In line with general chapter 5.2.5, the section Seed lots/Extraneous agents (section 2-3) has been deleted. The related requirements figure in the general monograph *Vaccines for veterinary use (0062)*.

Avian infectious bronchitis vaccine (live) (0442)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents. In line with general chapter 5.2.5, revised as follows:

- Seed lots/Extraneous agents (section 2-3). Deleted as the requirements are given in the revised general monograph *Vaccines for veterinary use (0062)*.
- Extraneous agents (section 3-4). Revised to refer to general chapter 5.2.5.

Avian infectious bursal disease vaccine (inactivated) (0960)

Extraneous agents. In line with general chapter 5.2.5, the section Seed lots/Extraneous agents (section 2-3) has been deleted. The related requirements figure in the general monograph *Vaccines for veterinary use (0062)*.

Avian infectious bursal disease vaccine (live) (0587)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents. In line with general chapter 5.2.5, revised as follows:

- Seed lots/Extraneous agents (section 2-3). Deleted as the requirements are given in the revised general monograph *Vaccines for veterinary use (0062)*.
- Extraneous agents (section 3-4). Revised to refer to general chapter 5.2.5.

Avian infectious encephalomyelitis vaccine (live) (0588)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents. In line with general chapter 5.2.5, revised as follows:

- Seed lots/Extraneous agents (section 2-3). Deleted as the requirements are given in the revised general monograph *Vaccines for veterinary use (0062)*.
- Extraneous agents (section 3-4). Revised to refer to general chapter 5.2.5.

Avian infectious laryngotracheitis vaccine (live) (1068)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents. In line with general chapter 5.2.5, revised as follows:

- Seed lots/Extraneous agents (section 2-3). Deleted as the requirements are given in the revised general monograph *Vaccines for veterinary use (0062)*.
- Extraneous agents (section 3-4). Revised to refer to general chapter 5.2.5.

Avian paramyxovirus 3 vaccine (inactivated) for turkeys (1392)

Extraneous agents. In line with general chapter 5.2.5, the section Seed lots/Extraneous agents (section 2-3) has been deleted. The related requirements figure in the general monograph *Vaccines for veterinary use (0062)*.

Avian viral tenosynovitis vaccine (live) (1956)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents. In line with general chapter 5.2.5, revised as follows:

- Seed lots/Extraneous agents (section 2-3). Deleted as the requirements are given in the revised general monograph *Vaccines for veterinary use (0062)*.
- Extraneous agents (section 3-4). Revised to refer to general chapter 5.2.5.

Bovine parainfluenza virus vaccine (live) (1176)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents (section 3-4): protocol for testing in cell cultures deleted and reference to general chapter 5.2.5 added instead.

Bovine respiratory syncytial virus vaccine (live) (1177)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents (section 3-4): protocol for testing in cell cultures deleted and reference to general chapter 5.2.5 added instead.

Calf coronavirus diarrhoea vaccine (inactivated) (1953)

Extraneous agents. The section Specified extraneous agents (section 3-4) has been deleted, based on data provided by manufacturers. Instead a requirement that vaccines do not interfere with national disease eradication programmes has been added to the general monograph *Vaccines for veterinary use (0062)*.

Calf rotavirus diarrhoea vaccine (inactivated) (1954)

Extraneous agents. The section Specified extraneous agents (section 3-4) has been deleted, based on data provided by manufacturers. Instead, a requirement that vaccines do not interfere with national disease eradication programmes has been added to the general monograph *Vaccines for veterinary use (0062)*.

Canine adenovirus vaccine (live) (1951)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents (section 3-4): protocol for testing in cell cultures deleted and reference to general chapter 5.2.5 added instead.

Canine distemper vaccine (live) (0448)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents (section 3-4): protocol for testing in cell cultures deleted and reference to general chapter 5.2.5 added instead.

Canine parainfluenza virus vaccine (live) (1955)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents (section 3-4): protocol for testing in cell cultures deleted and reference to general chapter 5.2.5 added instead.

Canine parvovirus vaccine (live) (0964)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents (section 3-4): protocol for testing in cell cultures deleted and reference to general chapter 5.2.5 added instead.

Coccidiosis vaccine (live) for chickens (2326)

Extraneous agents. In line with general chapter 5.2.5, revised as follows:

- Seed lots/Extraneous agents (section 2-2-2). Deleted as the requirements are given in general monograph *Vaccines for veterinary use (0062)*.
- Freedom from extraneous agents (2-4-3) and Extraneous agents (section 3-4). Revised to refer to general chapter 5.2.5.

Distemper vaccine (live) for mustelids (0449)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents (section 3-4): protocol for testing in cell cultures deleted and reference to general chapter 5.2.5 added instead.

Duck plague vaccine (live) (1938)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents. In line with general chapter 5.2.5, revised as follows:

- Seed lots/Extraneous agents (section 2-3). Deleted as the requirements are given in the revised general monograph *Vaccines for veterinary use (0062)*.
- Extraneous agents (section 3-4). Revised to refer to general chapter 5.2.5.

Duck viral hepatitis type I vaccine (live) (1315)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents. In line with general chapter 5.2.5, revised as follows:

- Seed lots/Extraneous agents (section 2-3). Deleted as the requirements are given in the revised general monograph *Vaccines for veterinary use (0062)*.
- Extraneous agents (section 3-4). Revised to refer to general chapter 5.2.5.

Egg drop syndrome '76 vaccine (inactivated) (1202)

Extraneous agents. In line with general chapter 5.2.5, the section Seed lots/Extraneous agents (section 2-3) has been deleted. The related requirements figure in the general monograph *Vaccines for veterinary use (0062)*.

Feline calicivirosis vaccine (live) (1102)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents (section 3-4): protocol for testing in cell cultures deleted and reference to general chapter 5.2.5 added instead.

Feline infectious enteritis (feline panleucopenia) vaccine (live) (0251)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents (section 3-4): protocol for testing in cell cultures deleted and reference to general chapter 5.2.5 added instead.

Feline viral rhinotracheitis vaccine (live) (1206)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents (section 3-4): protocol for testing in cell cultures deleted and reference to general chapter 5.2.5 added instead.

Fowl-pox vaccine (live) (0649)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents. In line with general chapter 5.2.5, revised as follows:

- Seed lots/Extraneous agents (section 2-3). Deleted as the requirements are given in the revised general monograph *Vaccines for veterinary use (0062)*.
- Extraneous agents (section 3-4). Revised to refer to general chapter 5.2.5.

Infectious bovine rhinotracheitis vaccine (live) (0696)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents (section 3-4): protocol for testing in cell cultures deleted and reference to general chapter 5.2.5 added instead.

Infectious chicken anaemia vaccine (live) (2038)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents. In line with general chapter 5.2.5, revised as follows:

- Seed lots/Extraneous agents (section 2-3). Deleted as the requirements are given in the revised general monograph *Vaccines for veterinary use (0062)*.
- Extraneous agents (section 3-4). Revised to refer to general chapter 5.2.5.

Marek's disease vaccine (live) (0589)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents. In line with general chapter 5.2.5, revised as follows:

- Seed lots/Extraneous agents (section 2-3). Deleted as the requirements are given in the revised general monograph *Vaccines for veterinary use (0062)*.
- Extraneous agents (section 3-4). Revised to refer to general chapter 5.2.5.

Myxomatosis vaccine (live) for rabbits (1943)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents (section 3-4). The former test Specified extraneous agents, which was designed to detect rabbit haemorrhagic disease virus, has been deleted as myxomatosis vaccines are grown in cells, and therefore there is no risk of contamination with this virus. The test has been replaced by the section Extraneous agents, and refers to general chapter 5.2.5.

Newcastle disease vaccine (inactivated) (0870)

Extraneous agents. In line with general chapter 5.2.5, the section Seed lots/Extraneous agents (section 2-3) has been deleted. The related requirements figure in the general monograph *Vaccines for veterinary use (0062)*.

Newcastle disease vaccine (live) (0450)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents. In line with general chapter 5.2.5, revised as follows:

- Seed lots/Extraneous agents (section 2-3). Deleted as the requirements are given in the revised general monograph *Vaccines for veterinary use (0062)*.
- Extraneous agents (section 3-4). Revised to refer to general chapter 5.2.5.

Porcine parvovirus vaccine (inactivated) (0965)

Extraneous agents. The section Specified extraneous agents (section 3-4) has been deleted, based on data provided by manufacturers. Instead, a requirement that vaccines do not interfere with national disease eradication programmes has been added to the general monograph *Vaccines for veterinary use (0062)*.

Rabbit haemorrhagic disease vaccine (inactivated) (2325)

Extraneous agents. Preparation of the vaccine (section 2-1). updated to refer to general chapter 5.2.5, in which section 4-1-1-2-3.

- Seed lots/Extraneous agents (section 2-2). Deleted as the requirements are given in the general monograph *Vaccines for veterinary use (0062)*.
- Residual live virus (sections 2-4-1 and 3-3). Revised to make clear that healthy stocks must comply with the requirements described in section 4-1-1-2-3. Animals of general chapter 5.2.5.

Rabies vaccine (live, oral) for foxes and raccoon dogs (0746)

Substrate for virus propagation/Cell cultures (section 2-2-1). The second sentence has been deleted because when cell cultures comply with the requirements of general chapter 5.2.4, they are free from extraneous agents and therefore also free from rabies virus (editorial).

Extraneous agents (section 3-4): protocol for testing in cell cultures deleted and reference to general chapter 5.2.5 added instead.

Swine-fever vaccine (live, prepared in cell cultures), classical (0065)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents (section 3-4): protocol for testing in cell cultures deleted and reference to general chapter 5.2.5 added instead.

Turkey infectious rhinotracheitis vaccine (live) (2461)

Identification (section 3-1). Revised to allow the use of any suitable method.

Extraneous agents. In line with general chapter 5.2.5, revised as follows:

- Seed lots/Extraneous agents (section 2-3). Deleted as the requirements are given in the revised general monograph *Vaccines for veterinary use (0062)*.
- Extraneous agents (section 3-4). Revised to refer to general chapter 5.2.5.

MONOGRAPHS

Clomifene citrate (0997)

Content: section updated to indicate content of (Z)-isomer and test method moved from Tests to Assay accordingly.

Related substances: impurity specifications updated to reflect current quality of approved medicinal products on European market; explicit criterion for unspecified impurities introduced in line with requirements of general monograph *Substances for pharmaceutical use (2034)*.

(Z)-isomer: test replaced by a more suitable method using less toxic solvents and moved to Assay section.

Oxytetracycline dihydrate (0199)

Related substances: introduction of the newly established *Oxytetracycline for system suitability A CRS*.

Phenoxymethylpenicillin (0148)

Water: replacement of method B with method A of general chapter 2.5.12 (correction).

Phenoxymethylpenicillin potassium (0149)

Water: replacement of method B with method A of general chapter 2.5.12 (correction).

