

The new approach to extraneous agent testing in immunological veterinary medicinal products (IVMPs) in the European Pharmacopoeia as of 1 July 2020

What has changed and why

In June 2019, the European Pharmacopoeia Commission adopted the following texts:

- The revision of the general monographs *Vaccines for veterinary use (0062)* and *Immunosera for veterinary use (0030)*, the general chapters (5.2.5 *Management of extraneous agents in IVMPs* and 5.2.4 *Cell cultures for the production of vaccines for veterinary use*) and around 40 vaccine specific monographs¹
- The addition of a new chapter 2.6.37 *Principles for the detection of extraneous viruses in IVMPs using culture methods*
- and the deletions of chapters 2.6.24 *Avian viral vaccines: tests for extraneous agents in seed lots* and 2.6.25 *Avian live virus vaccines: tests for extraneous agents in batches of finished product*.

These changes have come into force on the 1 July 2020.

The aim of these changes is to introduce a harmonised approach within the European Pharmacopoeia (Ph. Eur.) to managing the presence of extraneous agents in IVMPs. This is set within the wider context of evolution of manufacturing practices within the veterinary vaccine industry and reflects the use by manufacturers of newer technologies which has led to the use of a risk management approach to quality aspects of vaccines. It also reflects and builds on the changes to EU guidance notes concerning the management of IVMPs (e.g. guideline on requirements for the production and control of IVMPs (EMA/CVMP/IWP/206555/2010- Rev.1)).

Prior to this revision, information on managing the risk of extraneous agents was spread across several chapters as well as general and individual monographs and required a prescriptive approach focusing on starting materials and extensive testing of the final product with a limited risk management approach to handling substances of animal origin in chapter 5.2.5. *Substances of animal origin for the production of IVMPs*. There were also different levels of information for different types of products (e.g. avian and mammalian products). All of the existing requirements have been collated, reorganised and harmonised by this revision, providing greater clarity for users.

This revision extends this approach to all materials of animal origin (including master seeds and substrates) and the entire production process allowing a more focused approach to the management of extraneous agents which is based on risk identification and assessment. The

¹ Concerns monographs: 50213, 1177, 1955, 1176, 649, 1956, 1206, 2461, 696, 450, 65, 1938, 964, 251,1943, 589, 449, 448, 745, 1068, 2326, 1102, 587, 442, 1315, 588, 2038, 1951, 1392, 1954, 1953, 870, 965, 2325, 1202, 744, 960, 959

risk of extraneous agent contamination across the whole production process is assessed, thereby allowing risk identification and targeted testing. Manufacturers may now develop a coherent risk management strategy across the production process employing a fit-for-purpose testing approach. This can reduce the overall number of tests performed during production and on the final product by a process of risk reduction (e.g. sourcing of raw materials, manufacturing standards) and risk identification, thereby focusing testing on risk areas using fit-for-purpose tests. This approach, as well as the adoption of newer technologies for testing such as PCR, will lead to a reduction in the number of animals used for routine testing. Overall, these changes should result in safer, state of the art products with cost benefits for manufacturers.

Chapter 5.2.5. Management of extraneous agents in IVMPs

As chapter 5.2.5 (previously *Substances of animal origin for the production of IVMPs*) already included a risk identification and assessment approach for substances of animal origin, it formed the basis for extending this approach to the management of extraneous agents not only in substances of animal origin but also in all starting materials (including seeds and substrates), throughout the entire production process and in the final product. The emphasis of the chapter has been restricted to live replicative agents only.

The section on control measures has been revised and consists of three parts.

Part 1 focuses on raw materials encompassing seed materials, substrates and substances and also summarises requirements for donor animals used for the production of IVMPs. When considering the risks related to the source and origin of materials, it is accepted that risk from disease may be more appropriately assessed across a region rather than within the borders of a country and therefore the term “country of origin” has been replaced with “region or country of origin”.

Part 2 focuses on the production process and includes information previously found in monograph 0062.

Part 3 is a new section focusing on the methods of detection of extraneous agents and introduces wider use of new technologies particularly in vitro methods (e.g. NAT) where appropriate. It also includes information on tests and requirements for described methods.

This revised chapter also includes **two annexes**.

Annex I brings specific lists of extraneous agents to be tested in mammalian, fish and avian vaccines together in one place. The lists also comprise extraneous agents occurring in rodents; material of these species may be used during the production of IVMPs. Prior to this, the mammalian and fish requirements were only available within the guideline on requirements for the production and control of IVMPs (EMA/CVMP/IWP/206555/2010 Rev.1). The lists are advisory based on current knowledge but are not exhaustive. All lists have been updated prior to publication and it has been agreed that the Ph. Eur. will act as a single reference list. The lists will be reviewed on a regular basis to ensure that they reflect evolving disease agents.

Annex II illustrates the new targeted approach giving an example of a decision tree to support targeted testing. Arguments to support a decision not to test for a particular extraneous agent must be submitted to the competent authority which alone has the authority to decide on the suitability of a particular case.

The chapter also contains requirements collated from other chapters and monographs (0030, 0062, 5.2.4) which have been deleted from their original locations to avoid duplication and discrepancies.

Monograph 0062 Vaccines for veterinary use

The overall approach has been revised to be less prescriptive and to encompass a more flexible targeted approach using fit-for-purpose methods to underpin the quality of veterinary vaccines. The detailed description of methodologies for extraneous agents testing of virus seed lots which included the expansion and preparation of virus seeds for testing is no longer in 0062; This information has been replaced by more general guidance in order to introduce greater suitability and more flexibility which is now described in chapter 5.2.5. It does not preclude the continued use of previously described testing methods (still available in the archives of the Ph. Eur.) provided the principles described in the updated requirements are met.

Where appropriate information has been rationalised with other revised chapters and if it is present in other chapters it has not been repeated here.

Reference to epizootic eradication programmes has been moved to the general provisions of this monograph from general chapter 5.2.5. Consequently, this test has been removed from specific monographs thereby contributing to the reduction in animal testing.

In line with the changes to chapter 5.2.5, the term “country of origin” has been replaced with “region or country of origin”.

The use of antibiotics during vaccine production (generally restricted to cell cultures fluids and other media, media, egg inoculation and material harvested from tissues and embryonated eggs) is accepted but justification for such use is now requested.

The identification of live vaccines has been widened to allow use of any suitable method instead of prescribing tests in cultures, cells or SPF eggs. This may lead to a reduction in use of embryonated eggs which could be considered as reduction in numbers of animals used in routine testing.

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

This chapter has been revised in the light of the new approach and the extension of scope of chapter 5.2.5. Detailed methodology for detection of extraneous agents by culture methods has been deleted. The requirement that the cells have to be free of extraneous viruses remains but a cross reference is given to chapter 5.2.5 regarding how to establish freedom from extraneous viruses.

Some changes have been made to the retrovirus section for clarification.

Chapter 2.6.37 Principles for the detection of extraneous viruses in IVMPs by using culture methods

This new chapter represents a move away from a prescriptive set of detailed testing methods to a more flexible, scientifically sound targeted approach, using test methods that have been shown to be fit-for-purpose. The detailed descriptions of how to detect extraneous agents using culture methods have been replaced by general principles and examples of parameters to be taken into account when considering a suitable test method. The chapter also introduces newer technologies such as PCR that can be used instead of, or in addition to existing methods

for highlighting the presence of a targeted EA after amplification by culture. Use of newer technologies which deliver greater sensitivity and involve in vitro methods is encouraged. If an in vitro method such as PCR gives an equivalent result when compared to an in vivo method such as embryonated egg inoculation or a cell culture, then the in vitro method is the preferred option. The chapter will be updated to include reference to high-throughput sequencing technology which will be published in supplement 10.3 (implementation date 1 January 2021).

Monograph 0030 Immunosera for veterinary use

The testing sections of this monograph have been revised to take account of the modifications in chapter 5.2.5 as part of the new approach to extraneous testing.

Chapter 2.6.24 Avian viral vaccines: tests for extraneous agents in seed lots and Chapter 2.6.25 Avian live virus vaccines: tests for extraneous agents in batches of finished product - deleted from the Ph. Eur.

These chapters were adopted by the Pharmacopoeia Commission in 2003 and introduced into the 5th Edition of the European Pharmacopoeia. They outlined a rationale for the testing of master and working seed lots as well as a set of abridged tests to be carried out on the final product.

The introduction of the new approach of risk identification and risk assessment means that a targeted testing strategy can be employed throughout the production of a vaccine, from starting material to final product, using fit-for-purpose methods which are scientifically sound. The new chapter 2.6.37 describes the principles of testing and examples of parameters to be taken into account when selecting fit-for-purpose methods. It allows flexibility in selecting (a) suitable testing method/s and therefore chapters 2.6.24 and 2.6.25 have been deleted from the Ph. Eur. These chapters, including the detailed methodology will remain in the Ph. Eur. archives for information.

Chapter 5.2.13. Healthy chicken flocks for the production of inactivated vaccines for veterinary use was the subject of a minor revision to reflect the change in the title of chapter 5.2.5.

To ensure consistency with the approach outlined above the following individual monographs have been revised and adopted by the EP Commission (164th session – June 2020) : 0065, 0251, 0442, 0448, 0449, 0450, 0587, 0588, 0589, 0649, 0696, 0744, 0745, 0746, 0870, 0959, 0960, 0964, 0965, 1068, 1102, 1176, 1177, 1202, 1206, 1315, 1392, 1938, 1943, 1951, 1953, 1954, 1955, 1956, 2038, 2325, 2326 and 2461.