28 January 2022
EMA/CVMP/IWP/206555/2010-Rev.2
Committee for Veterinary Medicinal Products (CVMP)

Guideline on requirements for the production and control of immunological veterinary medicinal products

Draft

Draft revised guideline agreed by Immunologicals Working Party (IWP)	June 2015
Adoption by CVMP for release for consultation	9 July 2015
End of consultation (deadline for comments)	31 January 2016
Revised draft guideline agreed by IWP	19 October 2016
Adopted by CVMP	8 December 2016
Date for coming into effect	May 2017
Draft revised guideline agreed by IWP	18 November 2021
Adoption by CVMP for release for consultation	19 January 2022
End of consultation (deadline for comments)	28 March 2022

This guideline supersedes the 'Guideline on requirements for the production and control of immunological veterinary medicinal products' (EMA/CVMP/IWP/206555/2010 Rev. 1).

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Guideline on requirements for the production and control of immunological veterinary medicinal products

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Executive summary

This document provides information on items to be considered for the production and control of all immunological veterinary medicinal products (IVMPs).

The guideline outlines important items related to the quality, safety and efficacy parts of the marketing authorisation dossier that are not sufficiently defined in the requirements of Annex I of Regulation (EU) 2019/6 on veterinary medicinal products and in the Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 repealing Directive 2001/82/EC and in the European Pharmacopoeia (Ph. Eur.). Therefore, compliance with this guideline (and the abovementioned regulatory documents) provides an assurance that the IVMP will be considered satisfactory by all the Member States.

I. Introduction

The guideline is intended to supplement Regulation (EU) 2019/6, the European Pharmacopoeia, in particular Ph. Eur. 0062 Vaccines for veterinary use, and relevant VICH guidelines.

Annex I of Regulation (EU) 2019/6 contain administrative details that need to accompany an application for a marketing authorisation of veterinary medicinal product.

Annex II of Regulation (EU) 2019/6 provides details on the technical data to be provided by the applicants for marketing authorisations of veterinary medicinal products. In particular, it details the technical documentation necessary for demonstrating the quality, safety and efficacy for the different types of products. Section IIIb details data set requirements for quality, safety and efficacy for IVMPs.

This guideline intends to clarify the requirements that are not covered by these. Principles of GMP are covered by specific guidance and by Directive 91/412/EC and are out of the scope of this guideline but they should be kept in mind in order to understand the rationale behind the requirements of this guideline.

All IVMPs shall normally comply with this guideline.

Compliance with the guidelines provides an assurance that the research and development work undertaken will be considered valid by all Member States. Nevertheless, in order not to place undue constraints on scientific research, an alternative approach to the one described in a guideline may be used, if it can be shown that this is justified.

Reductions in the requirements that may be acceptable are provided in specific guidelines:
- "Guideline on data requirements for applications for immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6" (EMA/CVMP/59531/2020)
- "Guideline on data requirements for authorisation of immunological veterinary medicinal products under exceptional circumstances" (EMA/CVMP/IWP/299554/2021)

Specific requirements for the production and control of immunosera and colostrum substitutes are attached as Annex 1 to this guideline.

Freedom from extraneous agents (EA) is a high priority for any medicinal product. For any IVMP placed on the market in the EU, the requirement to test IVMPs for potential infectious contaminants is specified in Regulation (EU) 2019/6 and in Ph. Eur. general and specific monographs.

The approach to demonstrate freedom from extraneous agents as part of the production and control of IVMPs for IVMPs is attached as Annex 2 to this guideline.

Guidance on safety and efficacy requirements in the application for marketing authorisation for fish vaccines is outlined in "Guideline on the design of studies to evaluate the safety and efficacy of fish vaccines" (EMA/CVMP/IWP/206555/2010).

II. Quality

1. Devices

1.1. Definition

Annex II of Regulation (EU) 2019/6, Section IIIb, Part 2A, 1. Qualitative and quantitative composition states that:

"Those data in point (1) shall be supplemented by any relevant data concerning…, together with details of devices with which the IVMP will be used or administered and which will be delivered with the medicinal product. If the device is not delivered together with the IVMP, relevant information about the device shall be provided, where necessary for the assessment of the product."

For the purpose of this guideline, devices are defined as equipment used for the proper administration of IVMPs and which may influence the safety and efficacy of the product (e.g. devices for spray, intranasal, eye drop, intracutaneous, intrafollicular, *in ovo* administration).

1.2. Data requirements

As the use of a device can have an impact on the safety and efficacy of the IVMP, all the necessary data should be provided:

- A precise description of the device including an analysis of the possible influence on safety and efficacy of the IVMP.
- A detailed description of the sterilisation or disinfection of the device.
- A detailed description of the handling of the device.
- A clear statement of whether the device is delivered together with the IVMP or not
- A clear indication of the sources accessible in each Member State if the device is not delivered with the IVMP.

To avoid the use of inappropriate devices not evaluated in the safety and efficacy trials, the product information should indicate the type of device that should be used when administering the IVMP, and describe the physical and biological prerequisites and specifications of the device [e.g. volume of the delivered dose, pattern of distribution in skin, location of administration (intracutaneous, subcutaneous, and intradermal), pressure of the device, droplet size, etc.].

2. Starting materials and control during the manufacturing process

2.1. Absence of extraneous agents

When the Regulation (EU) 2019/6 and the Ph. Eur. refer to the testing of potential contaminants, Annex 2 (The approach to demonstrate freedom from extraneous agents as part of the production and control of immunological veterinary medicinal products) to this guideline should be taken into account.

2.2. Antibiotics

Antibiotics used during the production of an IVMP should be justified and in compliance with the restrictions of the Ph. Eur. 0062 Vaccines for veterinary use.

The addition of antibiotics during the manufacturing process is normally restricted to cell culture fluids and other media, egg inocula and material harvested from tissues and embryonated eggs.

Antibiotics used in the production of IVMPs may be present in the finished product. It is therefore recommended that for IVMPs intended for food producing species, antibiotics for which maximum residue limits (MRLs) have been established in the relevant species should be used (i.e. the antibiotics should be listed in table 1 of the annex to Commission Regulation (EU) 37/2010 for the relevant species). If an antibiotic not listed in table 1 of the annex to Commission Regulation (EU) 37/2010 is used, then the applicant should address the consumer safety implications arising from its potential presence in the finished product. Applicants should note that residues of antibiotics not included in table 1 of Commission Regulation (EU) 37/2010, found at residue control, would be considered as violative residue findings.

The number of antibiotics used has to be justified. The maximum concentration level of antibiotics used during the production should be defined. The level of remaining antibiotic content in the finished product should be indicated in the dossier and can be based on calculation.

2.3. Preservatives

In selecting a preservative system, the applicant should consider

- the effectiveness against potential microbial contaminants;
- possible interaction with the formulation or container (for example, thiomersal is ineffective in sera, and can bind to sulphydryl (SH) groups and polymeric material);
- the potential pharmacological and toxicological effects on the target animal species, at the dose rates appropriate to the veterinary medicinal product;
- any MRLs which have been fixed for the preservative substance(s), if appropriate;
- possible effects on testing of the IVMP, for example tests on cell cultures or mammalian species.

Long term experience with the use of the preservative in numerous similar products (e.g. thiomersal, formaldehyde) can be regarded as sufficient justification. The test procedures and microorganisms employed for demonstrating preservative efficacy should be as outlined in the Ph. Eur. 5.1.3. Efficacy of antimicrobial preservation. The range of microorganisms chosen for the testing should reflect the potential risk. As the Ph. Eur. allows some flexibility in the experimental conditions and range of microorganisms, the materials and methods for testing, if different from the ones listed in Ph. Eur.

5.1.3., should be described in appropriate detail by the applicant who must also validate the method to "ensure that any residual antimicrobial activity of the product is eliminated by dilution, filtration or by the use of a specific inactivator" in the recovery operation. The maintenance of the quantity of preservative (or the preservative efficacy, if justified) throughout the period of the IVMP shelf life should be demonstrated.

2.4. Solvents

2.4.1. Definition

Annex II of Regulation (EU) 2019/6, Section I, I.2.2.(7) states that: "For biological veterinary medicinal products, including immunologicals, information on solvents needed for making the final product preparation shall be included in the dossier. A biological veterinary medicinal product is regarded as one product even when more than one solvent is required so that different preparations of the final product can be prepared, which may be for administration by different routes or methods of administration." The solvent does not contain any active substance.

2.4.2. Data requirements

The data for production and control should follow the principles for IVMPs (Annex II, Section IIIb), where applicable. The dossier should provide the relevant data especially for:

- Qualitative and quantitative composition;
- Description of the manufacturing method;
- Production and control of starting materials;
- Control tests during the manufacturing process;
- Control of the finished product;
- Sterility;
- Virucidal/bactericidal effect on the active substance by using the solvent to prepare the active substance prior to titration;
- Stability tests;
- Starting materials used for the production of IVMPs for food producing species should comply with the current MRL legislation.

The IVMP for which the solvent is intended for should be fully tested for safety and efficacy. Provided the relevant studies are performed with the final product prepared with the solvent, no separate studies on the solvent concerning safety and efficacy are required.

2.5. Purity of antigen harvest for inactivated vaccines produced on eggs (bioburden)

For micro-organism grown in eggs, each batch of clarified harvest shall be tested for the amount of bacteria present and the value obtained shall be included on the batch test protocol. In general, it is stated that the production (harvest) process should ensure that the bioburden is as low as possible. Reduction of the bioburden and the validation of the inactivation procedures shall be considered not only for the vaccine antigen but also for the amount of bioburden present in the bulk prior to inactivation.

The maximum bioburden should be defined by the applicant, based on data from validation of inactivation and safety studies and it should be controlled in each harvest or bulk as an in-process control.

2.6. Inactivation

Annex II of Regulation (EU) 2019/6 states under Section IIIb, Part 2D Control tests during the manufacturing process: "For inactivated or detoxified vaccines, inactivation or detoxification shall be tested during each production run as soon as possible after the end of the inactivation or detoxification process and after neutralisation if this occurs, but before the next step of production." According to Ph. Eur. 0062, the test can be also performed "after subsequent process steps enhancing the sensitivity of the test (e.g. concentration step)."

It is considered that a single test to confirm complete inactivation carried out at the stage after inactivation when detection of any residual live antigen is most likely should give sufficient assurance of complete inactivation and compliance with the pharmacopoeial standard.

Validation of the inactivation process of IVMPs is subjected to the provision of data showing complete inactivation of the micro-organism. To this aim, according to Ph. Eur. 0062, Vaccines for veterinary use, data on inactivation kinetics should be obtained using the selected method of inactivation. However, a clear indication is only given concerning the time required for inactivation which, normally, should not exceed 67% of the duration of the inactivation process. It is considered that extrapolation of inactivation kinetics results (during a 1-step process) to higher pre-inactivation titres than those used in the corresponding validation studies is not permitted. The maximum titre of the micro-organism capable to be inactivated by the selected method of inactivation should be then established based on the actual data obtained from inactivation kinetics studies.

2.7. Samples

Representative samples of all seed materials (e.g. subsequent passages), reagents, in-process materials and finished product shall be supplied to the competent authorities, on request.

3. Control on the finished product

The control tests on the finished product mentioned in the Annex II of Regulation (EU) 2019/6 under Section IIIb, Part 2E shall normally be performed on each batch or sub-batch of IVMP produced. In the case of sub-batches which differ only due to their processing after bulk blending, for example in their filling session or vial size, some tests may be carried out on the final bulk or on one of the sub-batches, if justified.

It should be demonstrated that the subsequent procedure does not result in differences in test results and the results obtained from tests on the final bulk can be reproduced on the sub-batch(es) of the finished product. For example, it may be expected that tests of potency of inactivated IVMPs could be done on the final bulk. On the other hand, tests for sterility must be carried out on each sub-batch.

3.1. Batch titre or potency

For a live IVMP, the titration of the active substance shall be validated according to the principles of the VICH GL1 "*Guideline on validation of analytical procedures: definition and terminology*" and VICH GL 2 "*Validation of analytical procedures: methodology*". An inactivated IVMP shall be shown to be of satisfactory potency using validated methods.

3.2. Preservatives – Identification and assay of excipients components

Tests for the concentrations of preservatives shall be carried out to show that these are in conformity with the limits set for the product. The concentration of preservative at release can be higher than at the end of the shelf life if the efficacy of the preservative has been demonstrated with the lower concentration. The composition of the product shall indicate the lower concentration of the preservative.

3.3. Batch protocols

The batch protocols should be based on the templates issued by the European Commission and the European Directorate for the Quality of Medicines (EDQM) at the time the batch was produced.

4. Stability tests

Stability testing shall be carried out as specified in Regulation /EU) 2019/6 and in the Ph. Eur. 0062 Vaccines for veterinary use on not fewer than three representative consecutive batches. The three consecutive production runs may be carried out on a pilot scale, providing this mimics the full-scale production described in the application. The sterility of the IVMPs has to be proven at the end of the shelf life. This can be achieved by sterility testing or alternatives (e.g. test for container/closure integrity). Where bulk material is to be stored before formulation and final manufacturing, stability data should be provided.

III. Safety and efficacy tests

Animal welfare concerns should be taken into consideration in compliance with Directive 2010/63/EC when designing studies to test the safety and efficacy of IVMPs. Aspects to be considered include:

- Personnel conducting the studies should be appropriately trained to detect signs of illness as well as behavioral changes in the test animals.
- The method used to identify vaccinated and controls animals should involve the least harmful technique for the animals in the study.
- The number of animals in the vaccinated and control groups should be sufficient to obtain statistically significant and clinically reliable results. However, for vaccination-challenge studies, the possibility of reducing the number of control non-vaccinated animals should be investigated as these animals will suffer disease and associated distress.
- Mortality as an evaluation parameter in vaccination-challenge studies should be avoided whenever possible; humane endpoints have to be respected. Moribund animals should be humanely killed.

Annex 1 - Additional items, specific requirements for the production and control of immunosera and colostrum substitutes

This annex is intended to provide additional guidance on the type of data, which should be included in applications for marketing authorisations for immunosera and colostrum substitutes. It is intended to supplement Regulation (EU) 2019/6 and the general guideline.

The annex has not been prepared to give guidance for applications for products containing monoclonal antibodies and may not be applicable to such products.

DEFINITIONS

The definitions in the Ph. Eur. 0030 Immunosera for veterinary use apply together with the following additional definition:

Immunoserum – a veterinary medicinal product containing for example, polyclonal antibodies, or immunoglobulin fractions, or antibodies produced in eggs and used to provide passive immunity, through its immunoglobulin content.

Colostrum substitute – a veterinary medicinal product for administration by the oral route to new-born animals to provide passive immunity, through its immunoglobulin content. It contains, for example, polyclonal antibodies, or immunoglobulin fractions, or antibodies produced in eggs.

Donor animal – an animal, which is kept for the production of immunoserum or colostrum or antibodies produced in eggs.

The donor animals may or may not have been actively immunised to boost the concentration of immunoglobulins to one or more specific antigens.

1. Starting materials

Preparation of the material containing the active ingredient

1.1 Donor animals

Donor animals should comply with the Ph. Eur. 0030 Immunosera for veterinary use.

Detailed information must be provided of the testing regime used to monitor the health status of the animals and this must include information on the test methods used and their validation.

1.2 Immunising antigen

Immunising antigen should comply with the Ph. Eur. 0030 Immunosera for veterinary use.

Wherever possible, the immunising antigen used should be a product with a marketing authorisation granted in the relevant Member State, in accordance with the requirements of Regulation (EU) 2019/6.

When an authorised product is used, it will be sufficient, in the dossier provided in support of the application for a marketing authorisation for the immunoserum or colostrum substitute, to provide brief details of the immunising antigen (e.g. name, licence number, holder of the marketing authorisation, manufacturer(s) and the SPC).

Where the immunising antigen is not an authorised product, the principles and the format of Regulation (EU) 2019/6 and this guideline can be used as a guide for this.

For live organisms, for inoculation into a donor animal, information should also be provided on the safety of the organisms for the donor animal and it may be necessary to provide information on the rate of clearance of the organism from the material to be collected from the donor (e.g. where there may be a long lasting infection or a short time from immunisation to collection of material).

2. Finished product – batch testing for sterility

The product shall be shown to meet the requirements of the Ph. Eur. 2.6.1. Sterility and 2.6.7.Mycoplasmas unless it is a colostrum substitute to be administered orally, in which case it may contain not more than one saprophytic organism per dose.

Annex 2 - The approach to demonstrate freedom from extraneous agents as part of the production and control of immunological veterinary medicinal products

Freedom from extraneous agents is a high priority for any medicinal product. For any IVMP placed on the market in the EU, the requirement to test IVMPs for potential infectious contaminants is specified in Regulation (EU) 2019/6 and in the European Pharmacopoeia (Ph. Eur.) (Monographs 0062 and 0030, general chapters 5.2.4, 5.2.5 and 2.6.37).

Prevention of potential contamination through extraneous agent testing embraces the entire production process, from starting materials to the final product. This includes reliable sourcing and testing of starting materials; standardised, controlled production processes using Good Manufacturing Practices (GMP) in order to assure consistent production; and, tests confirming the quality of starting and in-process materials as well as the final product.

Therefore, the management of potential contamination also comprises all components of animal or human origin such as seed materials, substrates for production (e.g. cell substrates, embryonated eggs, animals), ingredients in culture media, other substances, in-process materials and the final product, as specified in the Ph. Eur. and relevant EMA guidelines. The Ph. Eur. approach for management of EAs which is elaborated in monographs and general chapters has changed from a prescriptive approach, mainly relying on extensive laboratory testing, to a scientifically sound and targeted risk-based approach. It is restricted to living replicative EAs and includes a reference to risk management including risk assessment and risk control.

Cell seeds must not be contaminated by extraneous viruses (Ph. Eur. 5.2.4). Batches of substances of animal origin if found contaminated are either discarded or reprocessed and shown to be satisfactory (Ph. Eur. 5.2.5).

This annex is applicable to all IVMPs.

For Transmissible Spongiform Encephalopathies (TSEs), Ph. Eur. general chapter 5.2.8 and the most recent version of the TSE Note for Guidance apply (Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products - EMA/410/01) are applicable.

As indicated in the Ph. Eur., consideration has to be given to the species of origin of the test material and the target species for the product. In addition, the applicant must also take into account:

1. the animal diseases occurring in the region or country of origin of the animals from which the material is obtained, including emerging or re-emerging diseases - in this context, this annex should be read in conjunction with the Clarification note on the requirements for the starting materials of biological origin (EMEA/CVMP/439633/2007),
2. the nature of the material, and
3. for cell cultures, their permissivity to extraneous agents from other species than the species of origin of the cells and the target species of the vaccine, if the cells have been maintained in the presence of substances of animal origin of other species, unless these substances were subjected to appropriate virus inactivation procedures.

Reference lists of extraneous agents, which may be present in the material of animal origin are provided in Ph. Eur. chapter 5.2.5, Annex I, should be considered as part of the risk assessment when considering which testing for extraneous agents is appropriate. The lists provided in Annex I do not

preclude additional agents from being considered, if necessary, and in agreement with the competent authority.

The presence of an agent on the list does not mean that a test for this agent must be carried out. However, for not carrying out a test for a specific agent, the applicant must provide justification according to the steps mentioned below.

For appropriate testing for extraneous agents, the following steps should be accomplished:

Step 1: Justification for not carrying out a test for a specific agent

The types of justification that can be given include:

a) Disease/agent did not occur in country/geographical area of origin at the time of isolation/recovery of the material supported by convincing official data (e.g. OIE's status in the applicable time period, literature information); continuous traceability to support the absence of contamination by this agent during subsequent processing of the material (e.g. preparation, culture, etc.).

b) Disease/agent does not occur in herd of origin (i.e. specific pathogen free (SPF) status). Animals used for the production of IVMPs are free from specified pathogens, as appropriate to both source and target species. If animals from a flock free from specified pathogens are used, supporting documentary evidence must be provided for the SPF status of the herd. SPF certificate indicating the methods of control used and showing that the herd is free of the respective extraneous agent has to be provided.

c) Substance in question cannot be contaminated with this agent, e.g. agent does not cross placenta or does not produce viraemia. Adequate justification must be provided.

d) The need for testing might not be relevant when an extraneous agent cannot grow in some systems or under some specific conditions, e.g. the extraneous agent does not grow in cell culture or does not grow in the absence of trypsin.

e) Where applicable, the agent can be inactivated using a validated method. Alternatively, a demonstration that the extraneous agent is removed by the production process may be acceptable as well, including an adequate justification.

f) For active substances derived by recombinant DNA techniques, the presence of extraneous agents from the species of origin or the target species can often be excluded because of the implemented biotechnological processes. Testing for extraneous agents may therefore not be necessary. In cases of partial or complete omission of testing, a risk assessment must be made, including the materials of animal origin that were/are used to produce the rDNA-derived active substance, and a thorough justification must be provided.

g) For finfish: disease/agent does not occur in the source and target fish species involved. Available literature or expert view to support this should be provided.

Step 2: Implementation of tests for the detection of extraneous agents

The extraneous agents to be tested are those, which could not be excluded after implementation of step 1. For detection of extraneous agents in IVMPs highly sensitive methods should be used. *In vitro* methods have to be used, if available.

The suitability of test methods used to detect extraneous agents is an essential prerequisite. The following aspects are identified as key criteria for test suitability: defined method, sensitivity,

specificity, repeatability of the method and need for positive and negative controls. It is not possible to describe all suitable methods and therefore any method that fulfils the requirements described in this chapter may be used. The results of the analysis are acceptable if the method has been demonstrated to provide adequate sensitivity and specificity for the detection of the targeted extraneous agent.

The parameters used to show suitability should be chosen based on the purpose of the assay. Proven testing and production experience are good tools to justify the suitability of test methods. For cell culture methods, it is important to check the quality of the cell culture and to verify that the cell culture is viable and able to allow the multiplication of extraneous agents. The agents used as positive controls may be those to be tested or other suitable agents.

Highly sensitive methods are preferred. In general, molecular methods are suitable, although the results of these techniques require appropriate interpretation and further investigation may be necessary. For example, if a positive signal from nucleic acid amplification technique (NAT) detection methods is obtained, other in vitro methods are used to verify and document the absence of viability of possible contaminants.

For the detection of viruses, appropriate methods for virus isolation and identification can be used and criteria established, e.g. cytopathic effect, haemadsorption, immunostaining, etc (Ph. Eur. 2.6.37). Their suitability for the detection of field (wild) strains of specified agents should be known.

Testing for bacteria and fungi is performed in accordance with general chapter 2.6.1. For bacteria and fungi that are not detectable by the sterility test (e.g. intracellular pathogens), other suitable methods are used, e.g. NAT (2.6.21. Vaccines must be free of mycoplasmas and mycobacteria. The tests for mycoplasmas (Ph. Eur. 2.6.7) and mycobacteria (Ph. Eur. 2.6.2) are considered suitable and sufficient to show absence of mycoplasmas and mycobacteria in IVMPs. These tests should be implemented on a case-by-case basis, whenever relevant. A thorough justification must be provided for the complete or partial omission of these testing.

Exceptionally, in the absence of any available in vitro test method, the use of in vivo tests methods is regarded as acceptable providing the risk assessment justifies the need for the test. Detection of an agent may also be based on detection of corresponding antibodies. In this case, appropriate serological methods should be used.

General principles that apply to culture methods for the isolation and detection of extraneous viruses in all materials used during the manufacture of IVMPs) at all stages of the process, up to and including the final product are described in Ph. Eur. 2.6.37.

The document "Questions and Answers on management of extraneous agents in immunological veterinary medicinal products" (EMA/CVMP/IWP/669993/2019) addresses comments and concerns on the revised risk management approach to the potential for EA contamination on areas concerning the authorisation of IVMPs and to provide clarification on these aspects.