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

Draft

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This guideline replaces the following guidance documents:

General requirements for the production and control of live mammalian bacterial and viral vaccines for veterinary use 7BIm1a

General requirements for the production and control of inactivated mammalian bacterial and viral vaccines for veterinary use 7BIm2a

Specific requirements for the production and control of avian live and inactivated viral and bacterial vaccines 7BIm3a

Specific requirements for the production and control of bovine live and inactivated viral and bacterial vaccines 7BIm4a

Specific requirements for the production and control of pig live and inactivated viral and bacterial vaccines 7BIm5a

Specific requirements for the production and control of ovine and caprine live and inactivated viral and bacterial vaccines 7BIm6a

Specific requirements for the production and control of live and inactivated vaccines intended for fish 7BIm9a

Table of extraneous agents to be tested for in relation to the general and species-specific guidelines on production and control of mammalian veterinary vaccines 7BIm10a

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Specific requirements for the production and control of immunosera and colostrum substitutes 7BIm12a

Specific requirements for the production and control of live and inactivated vaccines for cats and dogs 7BIm13a

Note for guidance Inclusion of antimicrobial preservatives in immunological veterinary medicinal products 7BIm14a

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

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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 clearly defined in the requirements of the existing texts (Directive 2001/82/EC as amended, Directive 2009/9/EC and the European Pharmacopoeia). Therefore compliance with this guideline (and with previous mentioned texts) provides an assurance that the IVMP will be considered satisfactory by all the Member States.

Introduction (background)

The guideline is intended to supplement Directive 2001/82/EC as amended, the texts of the European Pharmacopoeia (Ph. Eur.) and must also be read in conjunction with the principles of the GMP Directive (91/412/EC) and the related GMP guidelines. This guideline intends to clarify the requirements that are not covered by the previous texts.

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 the 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 a specific guideline “Guideline on data requirements for immunological veterinary medicinal products intended for minor use or minor species/limited markets”.

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

I Quality

1. Devices

1.1. Definition

Directive 2001/82/EC as amended by Directive 2009/9/EC, Annex I, Title II, Part 1.A, 1. Qualitative particulars states that:

“These particulars ……., together with details 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

A precise description of the device including an analysis of the possible influence on safety and efficacy of the IVMP administered with the device should be provided.

A detailed description of the sterilisation or disinfection of the device should be provided.

A detailed description of the handling of the device should be provided.

A clear statement of whether the device is delivered together with the IVMP or not should be provided. If not delivered with the immunological veterinary medicinal product a clear indication of the sources accessible in each Member State should be provided.

To avoid the use of similar devices not evaluated in the safety and efficacy trials, the product information should include a statement of the device that should be used when administering the IVMP, and a description of the device and its handling.

2. Starting materials and control during the manufacturing process

2.1. Absence of extraneous agents

When the Directive 2001/82/EC as amended and the Ph. Eur. refer to the testing of potential contaminants, the table of extraneous agents should be taken into account.

2.2. Antibiotics

Antibiotics used during the production of a vaccine (in process steps or in the finished product) should be used under the provision of the Ph. Eur. monograph 0062 Vaccines for Veterinary Use.

Only antibiotics with established MRLs and listed in table 1 of the annex to Regulation 37/2010 can be used if the vaccine is intended for food producing species. The number of antibiotics used has to be justified. The maximum amount of antibiotics used during the production should be defined and the remaining content at the level of the finished product should be indicated.

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 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 maximum residue limits which have been fixed for the preservative substance(s), if appropriate;
- possible effects on testing of the immunological veterinary medicinal product, for example tests on cell cultures or mammalian species.

The test procedures and microorganisms employed for demonstrating preservative efficacy should be as outlined in the Ph. Eur. monograph 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 should be described in appropriate detail by the applicant, who must in particular 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 preservative efficacy throughout the period of the immunological veterinary medicinal product shelf life should be demonstrated.

2.4. Diluents

2.4.1. Definition

Directive 2001/82/EC as amended by Directive 2009/9/EC, Annex I, Title II, Part 1.A states that:

"Information on diluents needed for making the final vaccine preparation shall be included in the dossier. An immunological veterinary medicinal product is regarded as one product even when more than one diluent 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."

2.4.2. Data requirements

The data for production and control should follow the principles for IVMPs (Annex I, Title 2) where applicable. The dossier should provide the relevant data especially for:

- Qualitative and quantitative particulars
- 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 ingredient by using the diluent to solve the active substance prior to titration
- Stability tests
- Starting materials used for the production should comply with the current MRL legislation

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

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

For viruses grown in eggs, each batch of clarified virus 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 studies and controlled in each harvest or bulk as an in process control.

2.6. Inactivation

Annex I of Directive 2001/82/EC as amended states under Title II, Part 2, D. 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."

Under E. Control tests on the finished product, it is mentioned that a test to verify inactivation shall be carried out on the product in the final container unless it has been conducted at a late stage in-process.

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 in most cases.

2.7. Samples

Samples of all seed materials, 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 I of Directive 2001/82/EC as amended under Title II, Part 2. E shall normally be performed on each batch or sub-batch of vaccine 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 bulk can be reproduced on the sub-batch(es) of the finished product. For example, it may be expected that tests of potency of liquid inactivated vaccines 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 vaccine, 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 vaccine 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. Safety tests

The Ph. Eur. monograph 0062 Vaccines for Veterinary Use and the Directive 2001/82/EC as amended request that an overdose safety test is performed on the finished product.

The pass criteria of this safety test for inactivated vaccines will be based on the results of the batch safety tests performed with the 3 consecutive batches produced to demonstrate batch-to-batch consistency.

Where no specific monograph exists for a live avian vaccine, if the vaccine is intended to be administered by spray or drinking water in the field, it shall be given by eye-drop in the batch safety test to ensure that a full dose is administered.

3.4. Batch protocols

The batch protocols should comply with the templates issued by the European Commission and the European Directorate for the Quality of Medicines (EDQM).

4. Stability tests

Stability testing shall be carried out as specified in the Directive 2001/82/EC as amended and in the European Pharmacopoeia monograph 0062 Vaccines for Veterinary Use on not fewer than 3 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 vaccine 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.

II Safety and efficacy tests

Animal welfare concerns should be taken into consideration 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 behavioural changes in the test animals.

The method used to identify vaccinated and controls animals (e.g. for studies involving fish) 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 questioned whenever possible; humane endpoints are preferable. Moribund animals should be humanely killed.

1. Safety tests

Safety testing shall be carried out as specified in the Ph. Eur. general chapter 5.2.6 Evaluation of safety of veterinary vaccines and immunosera and in Directive 2001/82/EC as amended[1]. The batch of vaccine to be tested shall be diluted in the batch of diluent with which it is to be marketed, if appropriate.

2. Field trials

Safety and efficacy must be studied in field trials performed on a sufficient number of target species distributed in more than one premises.

[1] The requirements of the Directive supersede those of the Ph. Eur. until they have been revised to be in compliance with VICH guidelines.

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 Directive 2001/82/EC as amended 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 European Pharmacopoiea monograph "Immunosera for Veterinary Use" (01/2008/0030) 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 European Pharmacopoeia monograph "Immunosera for Veterinary Use 01/2008/0030.

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 European Pharmacopoeia monograph "Immunosera for Veterinary Use 01/2008/0030.

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 Directive 2001/82/EC as amended.

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 Directive 2001/82/EC as amended 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

2.1 Sterility

The product shall be shown to meet the requirements of the European Pharmacopoeia for sterility and freedom from 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.