

[^{F1}ANNEX I

CHEMICAL, PHARMACEUTICAL AND ANALYTICAL STANDARDS, SAFETY AND RESIDUE TESTS, PRE-CLINICAL AND CLINICAL TRIALS IN RESPECT OF TESTING OF VETERINARY MEDICINAL PRODUCTS

Textual Amendments

- F1** Substituted by [Commission Directive 2009/9/EC of 10 February 2009 amending Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to medicinal products for veterinary use \(Text with EEA relevance\)](#).

TITLE II

REQUIREMENTS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Without prejudice to specific requirements laid down by Community legislation for the control and eradication of specific infectious animal diseases, the following requirements shall apply to immunological veterinary medicinal products, except when the products are intended for use in some species or with specific indications as defined in Title III and in relevant guidelines.

PART 1:

SUMMARY OF THE DOSSIER

A. ADMINISTRATIVE INFORMATION

The immunological veterinary medicinal product, which is the subject of the application, shall be identified by name and by name of the active substance(s), together with the biological activity, potency or titre, the pharmaceutical form, the route and method if appropriate of administration and a description of the final presentation of the product, including packaging, labelling and leaflet. Diluents may be packed together with the vaccine vials or separately.

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.

The name and address of the applicant shall be given, together with the name and address of the manufacturer and the sites involved in the different stages of manufacture and control (including the manufacturer of the finished product and the manufacturer(s) of the active substance(s)) and where relevant the name and address of the importer.

The applicant shall identify the number and titles of volumes of documentation submitted in support of the application and indicate what samples, if any, are also provided.

Annexed to the administrative information shall be copies of a document showing that the manufacturer is authorised to produce immunological veterinary medicinal products, as defined in Article 44. Moreover, the list of organisms handled at the production site shall be given.

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The applicant shall submit a list of countries in which authorisation has been granted, and a list of countries in which an application has been submitted or refused.

B. SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The applicant shall propose a summary of the product characteristics, in accordance with Article 14.

A proposed labelling text for the immediate and outer packaging shall be provided in accordance with Title V of this Directive, together with a package leaflet where one is required pursuant to Article 61. In addition the applicant shall provide one or more specimens or mock-ups of the final presentation(s) of the veterinary medicinal product in at least one of the official languages of the European Union; the mock-up may be provided in black and white and electronically where prior agreement from the competent authority has been obtained.

C. DETAILED AND CRITICAL SUMMARIES

Each detailed and critical summary referred to in the second subparagraph of Article 12(3) shall be prepared in the light of the state of scientific knowledge at the time of submission of the application. It shall contain an evaluation of the various tests and trials, which constitute the marketing authorisation dossier and shall address all points relevant to the assessment of the quality, safety and efficacy of the immunological veterinary medicinal product. It shall give the detailed results of the tests and trials submitted and precise bibliographic references.

All important data shall be summarised in an appendix to the detailed and critical summaries, whenever possible in tabular or graphic form. The detailed and critical summaries shall contain precise cross references to the information contained in the main documentation.

The detailed and critical summaries shall be signed and dated, and information about the author's educational background, training and occupational experience shall be attached. The professional relationship of the author with the applicant shall be declared.

PART 2:

**CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL/
MICROBIOLOGICAL INFORMATION (QUALITY)**

All test procedures shall fulfil the necessary criteria for analysis and control of the quality of the starting materials and the finished product and shall be validated procedures. The results of the validation studies shall be provided. Any special apparatus and equipment which may be used shall be described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be supplemented, if necessary, by the manufacturing method.

In the case of test procedures included in the *European Pharmacopoeia* or the pharmacopoeia of a Member State, this description may be replaced by a detailed reference to the pharmacopoeia in question.

Where available, chemical and biological reference material of the *European Pharmacopoeia* shall be used. If other reference preparations and standards are used, they shall be identified and described in detail.

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

1. Qualitative particulars

‘Qualitative particulars’ of all the constituents of the immunological veterinary medicinal product shall mean the designation or description of:

- the active substance(s),
- the constituents of the adjuvants,
- the constituent(s) of the excipients, whatever their nature or the quantity used, including preservatives, stabilisers, emulsifiers, colouring matter, flavouring, aromatic substances, markers, etc.,
- the constituents of the pharmaceutical form administered to animals.

These particulars shall be supplemented by any relevant data concerning the container and, where appropriate, its manner of closure, together with details of devices with which the immunological veterinary medicinal product will be used or administered and which will be delivered with the medicinal product. If the device is not delivered together with the immunological veterinary medicinal product, relevant information about the device shall be provided, where necessary for the assessment of the product.

2. ‘Usual terminology’

The ‘usual terminology’, to be used in describing the constituents of immunological veterinary medicinal products, shall mean, notwithstanding the application of the other provisions of Article 12(3)(c):

- in respect of substances which appear in the *European Pharmacopoeia* or, failing this, in the pharmacopoeia of one of the Member States, the main title of the monograph in question, which will be obligatory for all such substances, with reference to the pharmacopoeia concerned,
- in respect of other substances, the international non-proprietary name recommended by the World Health Organisation, which may be accompanied by another non-proprietary name or, failing these, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,
- in respect of colouring matter, designation by the ‘E’ code assigned to them in Directive 78/25/EEC.

3. Quantitative particulars

In order to give the ‘quantitative particulars’ of the active substances of an immunological veterinary medicinal product, it is necessary to specify whenever possible the number of organisms, the specific protein content, the mass, the number of International Units (IU) or units of biological activity, either per dosage-unit or volume, and with regard to the adjuvant and to the constituents of the excipients, the mass or the volume of each of them, with due allowance for the details provided in Section B.

Where an international unit of biological activity has been defined, this shall be used.

The units of biological activity for which no published data exist shall be expressed in such a way as to provide unambiguous information on the activity of the ingredients, e.g. by stating the immunological effect on which the method of determining the dose is based.

4. Product development

An explanation shall be provided with regard to the composition, components and containers, supported by scientific data on product development. The overage, with justification thereof, shall be stated.

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B. DESCRIPTION OF MANUFACTURING METHOD

The description of the manufacturing method accompanying the application for marketing authorisation pursuant to Article 12(3)(d), shall be drafted in such a way as to give an adequate description of the nature of the operations employed.

For this purpose the description shall include at least:

- the various stages of manufacture (including production of the antigen and purification procedures) so that an assessment can be made of the reproducibility of the manufacturing procedure and of the risks of adverse effects on the finished products, such as microbiological contamination; the validation of key stages in the production process shall be demonstrated and the validation of the production process as a whole shall be demonstrated with provision of results of three consecutive batches produced using the method described,
- in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity and consistency of each batch of the finished product,
- listing of all the substances at the appropriate steps where they are used, including those which cannot be recovered in the course of manufacturing,
- the details of the blending, with the quantitative particulars of all the substances used,
- a statement of the stages of manufacture at which sampling is carried out for control tests during production.

C. PRODUCTION AND CONTROL OF STARTING MATERIALS

For the purposes of this paragraph ‘starting materials’ means all components used in the production of the immunological veterinary medicinal product. Culture media consisting of several components used for production of the active substance shall be regarded as one starting material. Nevertheless, the qualitative and quantitative composition of the any culture media shall be presented in so far as the authorities consider that this information is relevant to the quality of the finished product and any risks that might be posed. If materials of animal origin are used for preparation of these culture media, the animal species and the tissue used have to be included.

The dossier shall include the specifications, information on the tests to be conducted for the quality control of all batches of starting materials and results for a batch for all components used and shall be submitted in accordance with the following provisions.

1. Starting materials listed in pharmacopoeias

The monographs of the *European Pharmacopoeia* shall be applicable to all starting materials appearing in it.

In respect of other substances, each Member State may require observance of its own national pharmacopoeia with regard to products manufactured in its territory.

Constituents fulfilling the requirements of the *European Pharmacopoeia* or the pharmacopoeia of one of the Member States shall be deemed to comply sufficiently with Article 12(3)(i). In this case the description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

Colouring matter shall, in all cases, satisfy the requirements of Directive 78/25/EEC.

The routine tests carried out on each batch of starting materials must be as stated in the application for marketing authorisation. If tests other than those mentioned in the

pharmacopoeia are used, proof must be supplied that the starting materials meet the quality requirements of that pharmacopoeia.

In cases where a specification or other provisions contained in a monograph of the *European Pharmacopoeia* or in the pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the applicant for marketing authorisation. The alleged insufficiency shall be reported to the authorities responsible for the pharmacopoeia in question.

In cases where a starting material is described neither in the *European Pharmacopoeia* nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted; in such cases, the applicant shall submit a copy of the monograph accompanied where necessary by the validation of the test procedures contained in the monograph and by a translation where appropriate.

When starting materials of animal origin are used, they shall comply with the relevant monographs including general monographs and general chapters of the *European Pharmacopoeia*. The tests and controls conducted shall be appropriate to the starting material.

The applicant shall supply documentation to demonstrate that the starting materials and the manufacturing of the veterinary medical product is in comply with the requirements of the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, as well as with the requirements of the corresponding monograph of the *European Pharmacopoeia*. Certificates of Suitability issued by the European Directorate for the Quality of Medicines and HealthCare, with reference to the relevant monograph of the *European Pharmacopoeia*, may be used to demonstrate compliance.

2. Starting materials not listed in a pharmacopoeia

2.1. Starting materials of biological origin

The description shall be given in the form of a monograph.

Whenever possible, vaccine production shall be based on a seed lot system and on established cell seeds. For the production of immunological veterinary medicinal products consisting of serums, the origin, general health and immunological status of the producing animals shall be indicated and defined pools of source materials shall be used.

The origin, including geographical region, and history of starting materials shall be described and documented. For genetically engineered starting materials this information shall include details such as the description of the starting cells or strains, the construction of the expression vector (name, origin, function of the replicon, promoter enhancer and other regulator elements), control of the sequence of DNA or RNA effectively inserted, oligonucleotidic sequences of plasmid vector in cells, plasmid used for cotransfection, added or deleted genes, biological properties of the final construct and the genes expressed, copy number and genetic stability.

Seed materials, including cell seeds and raw serum for anti-serum production shall be tested for identity and extraneous agents.

Information shall be provided on all substances of biological origin used at any stage in the manufacturing procedure. The information shall include:

- details of the source of the materials,
- details of any processing, purification and inactivation applied, with data on the validation of these process and controls during production,
- details of any tests for contamination carried out on each batch of the substance.

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If the presence of extraneous agents is detected or suspected, the corresponding material shall be discarded or used in very exceptional circumstances only when further processing of the product ensures their elimination and/or inactivation; elimination and/or inactivation of such extraneous agents shall be demonstrated.

When cell seeds are used, the cell characteristics shall be shown to have remained unchanged up to the highest passage level used for the production.

For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given.

Documentation shall be supplied to demonstrate that the seed materials, cell seeds, batches of serum and other material originating from animal species relevant for the transmission of TSE comply with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, as well as with the corresponding monograph of the *European Pharmacopoeia*. Certificates of Suitability issued by the European Directorate for the Quality of Medicines and HealthCare, with reference to the relevant monograph of the *European Pharmacopoeia*, can be used to demonstrate compliance.

When required, samples of the biological starting material or reagents used in the testing procedures shall be provided to enable the competent authority to arrange for check tests to be carried out.

2.2. Starting materials of non-biological origin

The description shall be given in the form of a monograph under the following headings:

- the name of the starting material meeting the requirements of point 2 of Section A shall be supplemented by any trade or scientific synonyms,
- the description of the starting material, set down in a form similar to that used in a descriptive item in the *European Pharmacopoeia*,
- the function of the starting material,
- methods of identification,
- any special precautions which may be necessary during storage of the starting material and, if necessary, its storage life shall be given.

D. CONTROL TESTS DURING THE MANUFACTURING PROCESS

1. The dossier shall include particulars relating to the control tests, which are carried out on intermediate products with a view to verifying the consistency of the manufacturing process and the final product.
2. 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.

E. CONTROL TESTS ON THE FINISHED PRODUCT

For all tests, the description of the techniques for analysing the finished product shall be set out in sufficiently precise detail for quality assessment.

The dossier shall include particulars relating to control tests on the finished product. Where appropriate monographs exist, if test procedures and limits other than those mentioned in the monographs of the *European Pharmacopoeia*, or failing this, in the pharmacopoeia of a Member State, are used, proof must be supplied that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for

the pharmaceutical form concerned. The application for marketing authorisation shall list those tests, which are carried out on representative samples of each batch of finished product. The frequency of the tests, which are not carried out on each batch, shall be stated. Release limits shall be indicated.

Where available, chemical and biological reference material of the *European Pharmacopoeia* shall be used. If other reference preparations and standards are used, they shall be identified and described in detail.

1. General characteristics of the finished product

The tests of general characteristics shall, wherever applicable, relate to the control of average masses and maximum deviations, to mechanical, physical or chemical tests, physical characteristics such as density, pH, viscosity, etc. For each of these characteristics, specifications, with appropriate confidence limits, shall be established by the applicant in each particular case.

2. Identification of active substance(s)

Where necessary, a specific test for identification shall be carried out.

3. Batch titre or potency

A quantification of the active substance shall be carried out on each batch to show that each batch will contain the appropriate potency or titre to ensure its safety and efficacy.

4. Identification and assay of adjuvants

Insofar as testing procedures are available, the quantity and nature of the adjuvant and its components shall be verified on the finished product.

5. Identification and assay of excipient components

Insofar as is necessary, the excipient(s) shall be subject at least to identification tests.

An upper and lower limit test shall be obligatory in respect of preserving agents. An upper limit test for any other excipient components liable to give rise to an adverse reaction shall be obligatory.

6. Safety tests

Apart from the results of tests submitted in accordance with Part 3 of this Title (Safety Tests), particulars of the batch safety tests shall be submitted. These tests shall preferably be overdose studies carried out in at least one of the most sensitive target species and by at least the recommended route of administration posing the greatest risk. Routine application of the batch safety test may be waived in the interests of animal welfare when a sufficient number of consecutive production batches have been produced and been found to comply with the test.

7. Sterility and purity test

Appropriate tests to demonstrate the absence of contamination by extraneous agents or other substances shall be carried out according to the nature of the immunological veterinary medicinal product, the method and the conditions of manufacture. If fewer tests than required by the relevant *European Pharmacopoeia* are routinely employed for each batch, the tests carried out shall be critical to the compliance with the monograph. Proof must be supplied that the immunological veterinary medicinal product would meet the requirements, if fully tested according to the monograph.

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8. Residual humidity

Each batch of lyophilised product shall be tested for residual humidity.

9. Inactivation

For inactivated vaccines, 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.

F. BATCH-TO-BATCH CONSISTENCY

In order to ensure that quality of the product is consistent from batch to batch and to demonstrate conformity with specifications a full protocol of three consecutive batches giving the results for all tests performed during production and on the finished product shall be provided.

G. STABILITY TESTS

The particulars and documents accompanying the application for marketing authorisation pursuant to Article 12(3)(f) and (i) shall be submitted in accordance with the following requirements.

A description shall be given of the tests undertaken to support the shelf life proposed by the applicant. These tests shall always be real-time studies; they shall be carried out on a sufficient number of batches produced according to the described production process and on products stored in the final container(s); these tests include biological and physico-chemical stability tests.

The conclusions shall contain the results of analyses, justifying the proposed shelf life under all proposed storage conditions.

In the case of products administered in feed, information shall also be given as necessary on the shelf life of the product, at the different stages of mixing, when mixed in accordance with the recommended instructions.

Where a finished product requires reconstitution prior to administration or is administered in drinking water, details of the proposed shelf life are required for the product reconstituted as recommended. Data in support of the proposed shelf life for the reconstituted product shall be submitted.

Stability data obtained from combined products may be used as preliminary data for derivative products containing one or more of the same components.

The proposed in-use shelf life shall be justified.

The efficacy of any preservative system shall be demonstrated.

Information on the efficacy of preservatives in other similar immunological veterinary medicinal products from the same manufacturer may be sufficient.

H. OTHER INFORMATION

Information relating to the quality of the immunological veterinary medicinal product not covered by the previous sections may be included in the dossier.

PART 3:

SAFETY TESTS

A. INTRODUCTION AND GENERAL REQUIREMENTS

The safety tests shall show the potential risks from the immunological veterinary medicinal product, which may occur under the proposed conditions of use in animals: these shall be evaluated in relation to the potential benefits of the product.

Where immunological veterinary medicinal products consist of live organisms, especially those, which could be shed by vaccinated animals, the potential risk to unvaccinated animals of the same or of any other potentially exposed species shall be evaluated.

The safety studies shall be carried out in the target species. The dose to be used shall be the quantity of the product to be recommended for use and the batch used for safety testing shall be taken from a batch or batches produced according to the manufacturing process described in Part 2 of the application.

In the case of an immunological veterinary medicinal products containing a live organism, the dose to be used in the laboratory tests described in Sections B.1 and B.2 shall be the quantity of the product containing the maximum titre. If necessary the concentration of the antigen may be adjusted to achieve the required dose. For inactivated vaccines the dose to be used shall be that quantity recommended for use containing the maximum antigen content unless justified.

The safety documentation shall be used for assessment of the potential risks which may result from the exposure of human beings to the veterinary medicinal product, for example during its administration to the animal.

B. LABORATORY TESTS

1. Safety of the administration of one dose

The immunological veterinary medicinal product shall be administered at the recommended dose and by each recommended route of administration to animals of each species and category in which it is intended for use, including animals of the minimum age of administration. The animals shall be observed and examined for signs of systemic and local reactions. Where appropriate, these studies shall include detailed post-mortem macroscopic and microscopic examinations of the injection site. Other objective criteria shall be recorded, such as rectal temperature and performance measurements.

The animals shall be observed and examined until reactions may no longer be expected, but in all cases, the observation and examination period shall be at least 14 days after administration.

This study may be part of the repeated dose study required under point 3 or omitted if the results of the overdose study required under point 2 have revealed no signs of systemic or local reactions.

2. Safety of one administration of an overdose

Only live immunological veterinary medicinal products require overdose testing.

An overdose of the immunological veterinary medicinal product shall be administered by each recommended route(s) of administration to animals of the most sensitive categories of the target species, unless the selection of the most sensitive of several similar routes is justified. In the case of immunological veterinary medicinal products administered by injection, the doses and route(s) of administration shall be chosen to take account of the maximum volume, which can

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be administered at any one single injection site. The animals shall be observed and examined for at least 14 days after administration for signs of systemic and local reactions. Other criteria shall be recorded, such as rectal temperature and performance measurements.

Where appropriate, these studies shall include detailed post-mortem macroscopic and microscopic examinations of the injection site if this has not been done under point 1.

3. Safety of the repeated administration of one dose

In the case of immunological veterinary medicinal products to be administered more than once, as part of the basic vaccination scheme, a study of the repeated administration of one dose shall be required to reveal any adverse effects induced by such administration. These tests shall be carried out on the most sensitive categories of the target species (such as certain breeds, age groups), using each recommended route of administration.

The animals shall be observed and examined for at least 14 days after the last administration for signs of systemic and local reactions. Other objective criteria shall be recorded, such as rectal temperature and performance measurements.

4. Examination of reproductive performance

Examination of reproductive performance shall be considered when data suggest that the starting material from which the product is derived may be a potential risk factor. Reproductive performance of males and non-pregnant and pregnant females shall be investigated with the recommended dose and by the most sensitive route of administration. In addition, harmful effects on the progeny, as well as teratogenic and abortifacient effects, shall be investigated.

These studies may form part of the safety studies described in points 1, 2, 3 or of the field studies provided for in Section C.

5. Examination of immunological functions

Where the immunological veterinary medicinal product might adversely affect the immune response of the vaccinated animal or of its progeny, suitable tests on the immunological functions shall be carried out.

6. Special requirements for live vaccines

6.1. Spread of the vaccine strain

Spread of the vaccine strain from vaccinated to unvaccinated target animals shall be investigated, using the recommended route of administration most likely to result in the spread. Moreover, it may be necessary to investigate the spread to non-target animal species which could be highly susceptible to a live vaccine strain.

6.2. Dissemination in the vaccinated animal

Faeces, urine, milk, eggs, oral, nasal and other secretions shall be tested for the presence of the organism as appropriate. Moreover, studies may be required of the dissemination of the vaccine strain in the body, with particular attention being paid to the predilection sites for replication of the organism. In the case of live vaccines for zoonoses within the meaning of Directive 2003/99/EC of the European Parliament and of the Council⁽¹⁾ to be used for food producing animals, these studies must take particularly into account the persistence of the organism at the injection site.

6.3. Reversion to virulence of attenuated vaccines

Reversion to virulence shall be investigated with the master seed. If the master seed is not available in sufficient quantity the lowest passage seed used for the production shall be examined. Use of another passage option shall be justified. The initial vaccination shall be carried out using the route of administration most likely to lead to reversion to virulence. Serial passages shall be made in target animals through five groups of animals, unless there is justification to make more passages or the organism disappears from the test animals sooner. Where the organism fails to replicate adequately, as many passages as possible shall be carried out in the target species.

6.4. Biological properties of the vaccine strain

Other tests may be necessary to determine as precisely as possible the intrinsic biological properties of the vaccine strain (e.g. neurotropism).

6.5. Recombination or genomic reassortment of strains

The probability of recombination or genomic reassortment with field or other strains shall be discussed.

7. User safety

This section shall include a discussion of the effects found in the preceding sections, which shall relate those effects to the type and extent of human exposure to the product with a view to formulating appropriate user warnings and other risk management measures.

8. Study of residues

For immunological veterinary medicinal products, it will normally not be necessary to undertake a study of residues. However, where adjuvants and/or preservatives are used in the manufacture of immunological veterinary medicinal products, consideration shall be given to the possibility of any residue remaining in the foodstuffs. If necessary, the effects of such residues shall be investigated.

A proposal for a withdrawal period shall be made and its adequacy shall be discussed in relation to any residue studies which have been undertaken.

9. Interactions

If there is a compatibility statement with other veterinary immunological products in the summary of product characteristics the safety of the association shall be investigated. Any other known interactions with veterinary medicinal products shall be described.

C. FIELD STUDIES

Unless justified, results from laboratory studies shall be supplemented with data from field studies, using batches according to the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same field studies.

D. ENVIRONMENTAL RISK ASSESSMENT

The purpose of the environmental risk assessment is to assess the potential harmful effects, which the use of the product may cause to the environment and to identify any precautionary measures, which may be necessary to reduce such risks.

This assessment shall normally be conducted in two phases. The first phase of the assessment shall always be performed. The details of the assessment shall be provided in accordance with established guidance. It shall indicate the potential exposure of the environment to the product

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and the level of risk associated with any such exposure, taking into account in particular the following items:

- the target animal species and the proposed pattern of use,
- the method of administration, in particular the likely extent to which the product will enter directly into the environmental system,
- the possible excretion of the product, its active substances into the environment by treated animals, persistence in such excreta,
- the disposal of unused or waste product.

In the case of live vaccine strains which may be zoonotic, the risk to humans shall be assessed.

Where the conclusions of the first phase indicate potential exposure of the environment to the product, the applicant shall proceed to the second phase and evaluate the potential risk(s) that the veterinary medicinal product might pose to the environment. Where necessary, further investigations on the impact of the product (soil, water, air, aquatic systems, non-target organisms) shall be carried out.

E. ASSESSMENT REQUIRED FOR VETERINARY MEDICINAL PRODUCTS CONTAINING OR CONSISTING OF GENETICALLY MODIFIED ORGANISMS

In the case of veterinary medicinal products containing or consisting of genetically modified organisms the application shall also be accompanied by the documents required under Article 2 and Part C of Directive 2001/18/EC.

PART 4:

EFFICACY TESTS

CHAPTER General principles

I

The purpose of the trials described in this Part is to demonstrate or to confirm the efficacy of the immunological veterinary medicinal product. All claims made by the applicant with regard to the properties, effects and use of the product, shall be fully supported by results of specific trials contained in the application for marketing authorisation.

2. Performance of trials

All efficacy trials shall be conducted in accordance with a fully considered detailed protocol, which shall be recorded in writing prior to commencement of the trial. The welfare of the trial animals shall be subject to veterinary supervision and shall be taken fully into consideration during the elaboration of any trial protocol and throughout the conduct of the trial.

Pre-established systematic written procedures for the organisation, conduct, data collection, documentation and verification of efficacy trials shall be required.

Field trials shall be conducted in accordance with established principles of good clinical practice, unless otherwise justified.

Before the commencement of any field trial, the informed consent of the owner of the animals to be used in the trial shall be obtained and documented. In particular, the animal owner shall be informed in writing of the consequences of participation in the trial for the subsequent disposal of treated animals or for the taking of foodstuffs from treated animals. A copy of this notification, countersigned and dated by the animal owner, shall be included in the trial documentation.

Unless the field trial is conducted with a blind design, the provisions of Articles 55, 56 and 57 shall apply by analogy to the labelling of formulations intended for use in veterinary field trials. In all cases, the words ‘for veterinary field trial use only’ shall appear prominently and indelibly upon the labelling.

CHAPTER I. General requirements

II

The choice of antigens or vaccine strains shall be justified on the basis of epizootological data.

2. Efficacy trials carried out in the laboratory shall be controlled trials, including untreated control animals unless this is not justified for animal welfare reasons and efficacy can be otherwise demonstrated.

In general, these laboratory trials shall be supported by trials carried out in field conditions, including untreated control animals.

All trials shall be described in sufficiently precise details so as to be reproducible in controlled trials, carried out at the request of the competent authorities. The investigator shall demonstrate the validity of all the techniques involved.

All results obtained, whether favourable or unfavourable, shall be reported.

3.

The efficacy of an immunological veterinary medicinal product shall be demonstrated for each category of target animal species recommended for vaccination, by each recommended route of administration and using the proposed schedule of administration. The influence of passively acquired and maternally derived antibodies on the efficacy of a vaccine shall be adequately evaluated, if appropriate. Unless justified, the onset and duration of immunity shall be established and supported by data from trials.

4.

The efficacy of each of the components of multivalent and combined immunological veterinary medicinal products shall be demonstrated. If the product is recommended for administration in combination with or at the same time as another veterinary medicinal product, they shall be shown to be compatible.

5.

Whenever a product forms part of a vaccination scheme recommended by the applicant, the priming or booster effect or the contribution of the veterinary immunological product to the efficacy of the scheme as a whole shall be demonstrated.

6.

The dose to be used shall be the quantity of the product to be recommended for use and the batch used for efficacy testing shall be taken from a batch or batches produced according to the manufacturing process described in Part 2 of the application.

7.

If there is a compatibility statement with other immunological products in the summary of product characteristics, the efficacy of the association shall be investigated. Any other known interactions with any other veterinary medicinal products shall be described. Concurrent or simultaneous use may be allowed if supported by appropriate studies.

8.

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For diagnostic immunological veterinary medicinal products administered to animals, the applicant shall indicate how reactions to the product are to be interpreted.

9.

For vaccines intended to allow a distinction between vaccinated and infected animals (marker vaccines), where the efficacy claim is reliant on *in vitro* diagnostic tests, sufficient data on the diagnostic tests shall be provided to allow adequate assessment of the claims related to the marker properties.

B. Laboratory trials

1. In principle, demonstration of efficacy shall be undertaken under well-controlled laboratory conditions by challenge after administration of the immunological veterinary medicinal product to the target animal under the recommended conditions of use. Insofar as possible, the conditions under which the challenge is carried out shall mimic the natural conditions for infection. Details of the challenge strain and its relevance shall be provided.

For live vaccines, batches containing the minimum titre or potency shall be used unless justified. For other products, batches containing the minimum active content shall be used unless otherwise justified.

2. If possible, the immune mechanism (cell-mediated/humoral, local/general classes of immunoglobulin) which is initiated after the administration of the immunological veterinary medicinal product to target animals by the recommended route of administration shall be specified and documented.

C. Field trials

1. Unless justified, results from laboratory trials shall be supplemented with data from field trials, using batches representative of the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same field study.
2. Where laboratory trials cannot be supportive of efficacy, the performance of field trials alone may be acceptable.

PART 5:

PARTICULARS AND DOCUMENTS

A. INTRODUCTION

The dossier of the safety and efficacy studies shall include an introduction defining the subject and indicating the tests which have been carried out in compliance with Parts 3 and 4 as well as a summary, with detailed references to the published literature. This summary shall contain an objective discussion of all the results obtained and lead to a conclusion on the safety and efficacy of the immunological veterinary medicinal product. Omission of any tests or trials listed shall be indicated and discussed.

B. LABORATORY STUDIES

The following shall be provided for all studies:

1. a summary;

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2. the name of the body having carried out the studies;
3. a detailed experimental protocol giving a description of the methods, apparatus and materials used, details such as species or breed of animals, categories of animals, where they were obtained, their identification and number, the conditions under which they were housed and fed (stating, inter alia, whether they were free from any specified pathogens and/or specified antibodies, the nature and quantity of any additives contained in the feed), dose, route, schedule and dates of administration, a description and a justification of the statistical methods used;
4. in the case of control animals, whether they received a placebo or no treatment;
5. in the case of treated animals and where appropriate, whether they received the test product or another product authorised in the Community
6. all general and individual observations and results obtained (with averages and standard deviations), whether favourable or unfavourable. The data shall be described in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author. The raw data shall be presented in tabular form. By way of explanation and illustration, the results may be accompanied by reproductions of recordings, photomicrographs, etc;
7. the nature, frequency and duration of observed adverse reactions;
8. the number of animals withdrawn prematurely from the studies and reasons for such withdrawal;
9. a statistical analysis of the results, where such is called for by the test programme, and variance within the data;
10. occurrence and course of any intercurrent disease;
11. all details concerning veterinary medicinal products (other than the product under study), the administration of which was necessary during the course of the study;
12. an objective discussion of the results obtained, leading to conclusions on the safety and efficacy of the product.

C. FIELD STUDIES

Particulars concerning field studies shall be sufficiently detailed to enable an objective judgement to be made. They shall include the following:

1. a summary;
2. name, address, function and qualifications of the investigator in charge;
3. place and date of administration, identity code that can be linked to the name and address of the owner of the animal(s);
4. details of the trial protocol, giving a description of the methods, apparatus and materials used, details such as the route of administration, the schedule of administration, the dose, the categories of animals, the duration of observation, the serological response and other investigations carried out on the animals after administration;
5. in the case of control animals, whether they received a placebo or no treatment;

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6. identification of the treated and control animals (collective or individual, as appropriate), such as species, breeds or strains, age, weight, sex, physiological status;
7. a brief description of the method of rearing and feeding, stating the nature and quantity of any additives contained in the feed;
8. all the particulars on observations, performances and results (with averages and standard deviation); individual data shall be indicated when tests and measurements on individuals have been carried out;
9. all observations and results of the studies, whether favourable or unfavourable, with a full statement of the observations and the results of the objective tests of activity required to evaluate the product; the techniques used must be specified and the significance of any variations in the results explained;
10. effects on the animals' performance;
11. the number of animals withdrawn prematurely from the studies and reasons for such withdrawal;
12. the nature, frequency and duration of observed adverse reactions;
13. occurrence and course of any intercurrent disease;
14. all details concerning veterinary medicinal products (other than the product under study) which have been administered either prior to or concurrently with the test product or during the observation period; details of any interactions observed;
15. an objective discussion of the results obtained, leading to conclusions on the safety and efficacy of the product.

PART 6:

BIBLIOGRAPHICAL REFERENCES

The bibliographical references cited in the summary mentioned under Part 1 shall be listed in detail and copies shall be provided.]

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(1) [^{F1}OJ L 325, 12.12.2003, p. 31.]

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Textual Amendments

- F1** Substituted by [Commission Directive 2009/9/EC of 10 February 2009 amending Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to medicinal products for veterinary use \(Text with EEA relevance\)](#).