Technical Guide for the elaboration and use of monographs

FOR VACCINES AND IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

European Pharmacopoeia

EDQM
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European Directorate for the Quality of Medicines & HealthCare
# TABLE OF CONTENTS

1. PURPOSE OF THE GUIDE .............................................................................................................. 4
2. STATUS AND SCOPE OF THE GUIDE ............................................................................................ 4
3. GENERAL INFORMATION ................................................................................................................ 4
   3.1. PHARMACOPOEIAL REQUIREMENTS ....................................................................................... 4
   3.2. ALTERNATIVE METHODS............................................................................................................ 6
   3.3. GENERAL CHAPTERS AND GENERAL MONOGRAPHS ............................................................. 7
   3.4. INDIVIDUAL MONOGRAPHS ...................................................................................................... 8
   3.5. HOW MONOGRAPHS AND CHAPTERS FOR IMMUNOSERA AND VACCINES FOR VETERINARY USE ARE ELABORATED AND UPDATED .................................................................................. 8
   3.5.1. INCLUSION OF NEW MONOGRAPHS OR NEW GENERAL CHAPTERS FOR IMMUNOSERA AND VACCINES FOR VETERINARY USE IN THE EUROPEAN PHARMACOPOEIA .......................................................... 8
   3.5.2. REVISION OF MONOGRAPHS AND GENERAL CHAPTERS FOR IMMUNOSERA AND VACCINES FOR VETERINARY USE ............................................................................................................................ 10
4. CONTENT OF THE MONOGRAPHS .................................................................................................. 11
   4.1 CONTENT OF THE MONOGRAPHS FOR VACCINES FOR VETERINARY USE .............................. 11
      4.1.1. GENERAL POINTS .................................................................................................................. 11
      4.1.2. SECTIONS OF THE MONOGRAPHS ....................................................................................... 11
   4.2. SUMMARY OF THE CONTENT OF THE GENERAL MONOGRAPH .................................................. 19
      IMMUNOSERA FOR VETERINARY USE ......................................................................................... 19
5. RELATIONSHIP BETWEEN GENERAL MONOGRAPHS AND CHAPTERS AND INDIVIDUAL MONOGRAPHS .......................................................................................................................... 19
6. SUMMARY TABLE OF STATUS OF VARIOUS SECTIONS OF MONOGRAPHS .................................. 21
Technical guide for the elaboration and use of monographs for vaccines and immunological veterinary medicinal products

1. PURPOSE OF THE GUIDE

This document is intended to provide guidance to authors (and contributors) and users of European Pharmacopoeia monographs on veterinary vaccines and other immunological veterinary medicinal products (IVMPs). This applies in particular to:

1. Group of Experts no. 15V (Vaccines and sera for veterinary use),
2. authorities responsible for granting marketing authorisations for vaccines and immunosera for veterinary use,
3. Official Medicines Control Laboratories (OMCLs),
4. manufacturers of vaccines and immunosera for veterinary use,
5. public and private analytical laboratories working for one of the above,
6. the Secretariat of the European Pharmacopoeia and any other departments of the European Directorate for the Quality of Medicines & HealthCare (EDQM).

2. STATUS AND SCOPE OF THE GUIDE

The monographs and general chapters of the European Pharmacopoeia set out the official standards for medicinal products. This guide provides information on the elaboration and use of these standards but has no official status. In the event of doubt or dispute, the text of the European Pharmacopoeia alone is authoritative.

3. GENERAL INFORMATION

3.1. PHARMACOPOEIAL REQUIREMENTS

Monographs and general chapters of the European Pharmacopoeia must be interpreted with reference to the General Notices. All users of the European Pharmacopoeia must be familiar with this text. The main items relevant for IVMPs are given below:

• Statements in monographs are mandatory requirements unless otherwise stated – the General Notices state that: “Unless otherwise indicated in the General Notices or in the monographs, statements in monographs constitute mandatory requirements. General chapters become mandatory when referred to in a monograph, unless such reference is made in a way that indicates that it is not the intention to make the text referred to mandatory but rather to cite it for information.” (Ph. Eur. 6th Edition)

• As regards compliance with monographs, the General Notices state that: “(1) An article [that is the subject of a monograph] is not of Pharmacopoeia quality unless it complies with...
all the requirements stated in the monograph. This does not imply that performance of all the
tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance
with the Pharmacopoeia before release of a product. The manufacturer may obtain
assurance that a product is of Pharmacopoeia quality on the basis of its design, together
with its control strategy and data derived, for example, from validation studies of the
manufacturing process.

(2) An enhanced approach to quality control could utilise process analytical technology (PAT)
and/or real-time release testing (including parametric release) strategies as alternatives to
end-product testing alone. Real-time release testing in circumstances deemed appropriate by
the competent authority is thus not precluded by the need to comply with the Pharmacopoeia.

(3) Reduction of animal testing: the European Pharmacopoeia is dedicated to phasing out the
use of animals for test purposes, in accordance with the 3Rs (Replacement, Reduction,
Refinement) set out in the European Convention for the Protection of Vertebrate Animals used
for Experimental and Other Scientific Purposes. In demonstrating compliance with the
Pharmacopoeia as indicated above (1), manufacturers may consider establishing additional
systems to monitor consistency of production. With the agreement of the competent authority,
the choice of tests performed to assess compliance with the Pharmacopoeia when animal tests
are prescribed is established in such a way that animal usage is minimised as much as
possible.” (Ph. Eur. Supplement 8.2)

• **Quality systems.** Regarding quality systems in place for the production of IVMPs the Ph. Eur.
  General Notices state: “The quality standards represented by monographs are valid only where
  the articles in question are produced within the framework of a suitable quality system. The
  quality system must assure that the articles consistently meet the requirements of the
  Pharmacopoeia.” (Ph. Eur. 6th Edition)

• **Validation.** Regarding validation of Ph. Eur. methods, the General Notices state: “The test
  methods given in monographs and general chapters have been validated in accordance with
  accepted scientific practice and current recommendations on analytical validation. Unless
  otherwise stated in the monograph or general chapter, validation of the test methods by the
  analyst is not required.” In the context of vaccines for veterinary use, it is the practice that
  the test methods and their acceptance criteria constitute a compromise between the methods
  and specifications that have been approved at the time of elaboration of the monograph and
  the minimum requirements that are needed for a product to meet European Pharmacopoeia
  standards. Extensive validation according to current recommendations on analytical validation
  of these methods would require too many animals and would therefore not be in line with the
  3R’s approach. The current approach taken by Group 15V is to rationalise and update the
  methods currently in use (taking into account of the availability of more recent techniques,
  compliance with the 3Rs and GMP and performing risk analysis to avoid carrying out costly
  tests that are not strictly necessary) and to propose either validated methods or requirements
  for the validation of key parameters.

• **Alternative methods.** As regards to the use of alternative methods, the General Notices
  state: “The tests and assays described are the official methods upon which the standards of
  the Pharmacopoeia are based. With the agreement of the competent authority, alternative
  methods of analysis may be used for control purposes, provided that the methods used
  enable an unequivocal decision to be made as to whether compliance with the standards of the
  monographs would be achieved if the official methods were used. In the event of doubt or
  dispute, the methods of analysis of the Pharmacopoeia are alone authoritative.” (Ph. Eur. 6th
  Edition)
• Regarding the section **Choice of vaccine strain, Choice of vaccine composition**, the General Notices state in section 1.4: “The Production section of a monograph may define the characteristics of a vaccine strain or vaccine composition. Unless otherwise stated, test methods given for verification of these characteristics are provided for information as examples of suitable methods. Subject to approval by the competent authority, other test methods may be used without validation against the method shown in the monograph.”

(Ph. Eur. 6th Edition)

• **Particular circumstances which may require additional testing.** In case of necessity, the general monograph *Vaccines for veterinary use (0062)* foresee the possibility for additional testing with the agreement of the competent authority: “On a case-by-case basis, with the agreement of the competent authority, the choice and necessity of certain final product tests may be reconsidered, where in-process tests give at least an equal guarantee that the batch would comply if tested, or where alternative tests validated with respect to the Pharmacopoeia method have been carried out.”

The term “particular circumstances” could be viewed in two ways:

- exceptional circumstances as an extraordinary situation, which had to be justified (e.g. a significant change in production);
- exceptional circumstances as something that may accidentally happen in the lifecycle of a medicinal product and has negative consequences in the field (for example safety issues).

A justification for performing additional tests (*in vitro* or *in vivo*) in the context of veterinary vaccines could be:

- significant changes in the production process (e.g. change of seed material, changes in essential production media, change of blending [adjuvant], change of inactivation, etc.);
- issues raised, for example, by pharmacovigilance reports or any problem seen in the field. These would justify that investigations be carried out in order to identify and solve the problem.

Establishment of robust limits/specifications for a new test may require an existing back up test to be conducted alongside a new test for a period of time.

**3.2. ALTERNATIVE METHODS**

The test methods prescribed in monographs are the reference methods on which the quality standards are based. As indicated above under 3.1. PHARMACOPOEIAL REQUIREMENTS, other methods of analysis may be used for a variety of reasons.

First, pharmacopoeial methods have been chosen for application to all the relevant products that were available at the time of the elaboration of the monographs. Other available methods can be used if it is demonstrated by validation that the alternative method is equivalent to the official method or more suitable, in accordance with the General Notices. For example, an *in vitro* method would be “more suitable” regarding animal welfare.

Second, the methods have been developed for application in a variety of laboratories with standard equipment but this does not rule out the use of alternative, validated methods.

Monographs are periodically revised to keep pace with progress in techniques but pending these revisions new methods can be used as alternatives, if validated and authorized by the competent authorities.
Use of Animals: In accordance with the provisions of the *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes* (1986) and the European Directive on the same principles, European Pharmacopoeia tests must be carried out in such a way as to use the minimum number of animals for a significant result and to cause the least pain, suffering, distress or lasting harm. Humane endpoints must be used wherever possible for all tests, even if not referred to in an individual monograph since references to humane endpoints are included as examples only where practical advice can be given (see general monographs *Vaccines for veterinary use* and *Immunosera for veterinary use*).

In accordance with Directive 2010/63/EU, manufacturers must develop suitable *in vitro* methods as alternatives to tests using animals, and in particular for batch release use appropriate tools such as the monitoring of production consistency and appropriate antigen quantification. Therefore this is the first option of choice in the monographs.

In case a single universal alternative method cannot be developed due to various reasons but there is at least an alternative method developed for the product class/type, an alternative method is the 1st option of choice in the monograph and a reference to the type of alternative method may then be given as an example of suitable method (Ph. Eur. 9th Edition). This does not preclude manufacturers developing other types of alternative methods if more appropriate (for example new technique available).

### 3.3. GENERAL CHAPTERS AND GENERAL MONOGRAPHS

Certain general terms commonly used in monographs on vaccines for veterinary use are defined in the general chapter *Terminology used in monographs on biological products* (5.2.1).

The following general monographs apply to products for veterinary use:

- *Vaccines for veterinary use* (0062) applies to all vaccines for veterinary use, whether there is an individual monograph for the vaccine or not,
- *Immunosera for veterinary use* (0030) applies to all immunosera for veterinary use, whether there is an individual monograph for the immunoserum or not.

These monographs are published under the heading GENERAL MONOGRAPHS of the European Pharmacopoeia.

The following general chapters published under the heading 2.6. BIOLOGICAL TESTS and 5.2. GENERAL TEXTS ON BIOLOGICAL PRODUCTS apply whenever they are given as reference in a monograph on a vaccine or immunoserum for veterinary use:

**Biological tests specific to veterinary products**

- *Avian viral vaccines: tests for extraneous agents in seed lots* (2.6.24)
- *Avian live virus vaccines: tests for extraneous agents in batches of finished products* (2.6.25)

**General texts specific to veterinary products**

- *Chicken flocks free from specified pathogens for the production and quality control of vaccines* (5.2.2)
- *Healthy chicken flocks for the production of inactivated vaccines for veterinary use*
(5.2.13): sets quality requirements that will provide guarantees with regard to contamination by extraneous agents, making the test for specified extraneous agents performed on each final product obsolete.

- Cell cultures for the production of veterinary vaccines (5.2.4)
- Substances of animal origin for the production of veterinary vaccines (5.2.5)
- Evaluation of safety of veterinary vaccines and immunosera (5.2.6)
- Evaluation of efficacy of veterinary vaccines and immunosera (5.2.7)
- Evaluation of safety of each batch of immunosera for veterinary use (5.2.9)

Additional tests, not restricted to veterinary products:

- Sterility (2.6.1),
- Mycoplasmas (2.6.7)
- Pyrogens (2.6.8)
- Bacterial Endotoxins (2.6.14)

Sterility (2.6.1) and Mycoplasmas (2.6.7) are requirements for veterinary vaccines and immunosera, in compliance with the general monographs.

The general chapter Viral Safety (5.1.7) is an exception and does not apply to immunological veterinary medicinal products since the subject is addressed in more detail in monographs or the general chapters referred to above.

3.4. INDIVIDUAL MONOGRAPHS

Individual monographs on vaccines for veterinary use and on immunosera for veterinary use are published in the European Pharmacopoeia in alphabetical order of the title in two separate sections called “Vaccines for veterinary use” and “Immunosera for veterinary use”.

3.5. HOW MONOGRAPHS AND CHAPTERS FOR IMMUNOSERA AND VACCINES FOR VETERINARY USE ARE ELABORATED AND UPDATED

3.5.1. INCLUSION OF NEW MONOGRAPHS OR NEW GENERAL CHAPTERS FOR IMMUNOSERA AND VACCINES FOR VETERINARY USE IN THE EUROPEAN PHARMACOPOEIA

Proposals to add a new text on the work programme can be made by:

- the Chair of the European Pharmacopoeia Commission,
- a delegation,
- a National Pharmacopoeia Authority,
- a Group of Experts or Working Party through the intermediary of its Chair,
- EDQM’s Secretariat for example on the basis of information and data provided via the HelpDesk by a manufacturer or by a user of the European Pharmacopoeia.
- manufacturers and other interested parties from Member States through the intermediary of their National Pharmacopoeia Authority,
- manufacturers and other interested parties from Observer States through the intermediary of a National Pharmacopoeia Authority or the Secretariat,
- manufacturers and other interested parties from non-Member or non-Observer States through the intermediary of the Secretariat.
It is the European Pharmacopoeia Commission which accepts the proposal or not, and if accepted, it adds the item to the work programme of the Group of experts no. 15V (see the Rules of procedure of the European Pharmacopoeia Commission).

A proposal for addition of a monograph on a vaccine or an immunoserum for veterinary use to the work programme of Group of Experts no. 15V is agreed upon only when the vaccine or the immunoserum is produced by more than one manufacturer and licensed in one or more Member States. Monographs on vaccines for veterinary use are usually elaborated for one valence only. Monographs on combined vaccines are usually not elaborated and combined vaccines must comply with the individual monographs for each valence in the vaccine.

In general, the standards (i.e. of safety and efficacy) that are attained by vaccines that are already on the market are taken into consideration during the elaboration of a new monograph. Consequently, where there is sufficient information demonstrating that the product is of Pharmacopoeial quality, it will not be necessary to retest these vaccines to show compliance with the requirements of sections such as Safety and Immunogenicity when the monograph is finalised and published.

Once the new monograph is drafted, it is submitted to interested parties for written consultation before public enquiry. If necessary, a hearing is organised by EDQM, to which all manufacturers of the vaccine concerned may attend, give their comments and express directly their views to Group 15V members. After this consultation, the monograph is revised and published in Pharmeuropa for public enquiry. All the interested parties have 3 months to send their comments to their National Pharmacopoeial Authority (NPA), which centralises all the comments from that country. Then, NPAs have two months to send the compiled comments to EDQM’s Secretariat. Manufacturers outside Europe, industry associations and Pan-European organisations also have 3 months to send their comments to EDQM’s Secretariat via the EDQM HelpDesk. EDQM’s Secretariat makes a consolidated document from all the comments received.

The time between provision of a first draft to manufacturers and the end of the public enquiry is about one year. The consolidated comments are studied by Group 15V at the meeting following the end of the public enquiry.

After the study of these comments, if there is no major change in the text that had been published and if no restrictions are added to the text published for comment, the final text is proposed for adoption at the next Commission session. If there is a major change in the text or if restrictions are added, then the text is published again for public enquiry in Pharmeuropa.

If the text is adopted, it is published in the European Pharmacopoeia 6 months after the Commission session, and implemented 6 months later.

As a result of the time required for each stage, interested parties have at least two years from the provision of the first draft until the implementation of the monograph. During this time, any studies being undertaken or validation studies required can be planned and executed, taking account of the available draft text.

Should the text not be adopted, it will either go back to Group 15V and may be re-published in Pharmeuropa, or no individual monograph on this particular product will be published in the European Pharmacopoeia.
3.5.2. REVISION OF MONOGRAPHS AND GENERAL CHAPTERS FOR IMMUNOSERA AND VACCINES FOR VETERINARY USE

Proposals to revise a text can be made by:

- the Chair of the European Pharmacopoeia Commission,
- a delegation,
- a National Pharmacopoeia Authority,
- a Group of Experts or Working Party through the intermediary of its Chair,
- EDQM’s Secretariat for example on the basis of information and data provided via the HelpDesk by a manufacturer or by a user of the European Pharmacopoeia.
- manufacturers and other interested parties from Member States through the intermediary of their National Pharmacopoeia Authority,
- manufacturers and other interested parties from Observer States through the intermediary of a National Pharmacopoeia Authority or the Secretariat,
- manufacturers and other interested parties from non-Member or non-Observer States through the intermediary of the Secretariat.

It is the European Pharmacopoeia Commission which refers requests for revision to the Group of Experts no.15V (see the Rules of procedure of the European Pharmacopoeia Commission).

A request for revision must be submitted with a justification for this revision, supported by data and documents.

During the revision of a monograph, the standards attained by products that are already on the market will be taken into consideration.

Once the monograph is revised, it is published in Pharmeuropa for public enquiry. Hearings or pre-publication written consultation with interested parties are usually not organised for revised texts unless the revision is significant and requires an extra consultation step. All the interested parties have 3 months to send their comments to their NPA, which centralises all the comments of one country. Then, NPAs have 2 months to send the compiled comments to EDQM’s Secretariat. Manufacturers outside Europe, industry associations and Pan European organisations also have 3 months to send their comments to EDQM’s Secretariat via the EDQM HelpDesk. EDQM’s Secretariat makes consolidated comments from all the comments received.

The consolidated comments are studied by Group 15V at the meeting following the end of the public enquiry.

After the study of these comments, if there is no major change in the text and if no restrictions are added to the text published for comments, the text is proposed for adoption at the next Commission session. If there is a major change in the text or if restrictions are added, then the text is published again for public enquiry in Pharmeuropa.

If the revised text is adopted, it is published in the European Pharmacopoeia 6 months after the Commission session, and implemented 6 months later.

As a result of the time required for each stage, interested parties have at least 2 years from the provision of the first draft of the revised monograph until the implementation of the revised monograph. During this time, any studies being undertaken or validation studies required can be
planned and executed, taking account of the available draft text.

Should the text not be adopted, it will either go back to Group 15V for further study/revision and may be re-published in Pharmeuropa, or stay as it is and not be revised.

4. CONTENT OF THE MONOGRAPHS

4.1 CONTENT OF THE MONOGRAPHS FOR VACCINES FOR VETERINARY USE

4.1.1. GENERAL POINTS

The General Notices state: “Substances and preparations that are the subject of an individual monograph are also required to comply with relevant, applicable general monographs. Cross-references to applicable general monographs are not normally given in individual monographs. (...) General monographs and individual monographs are complementary. If the provisions of a general monograph do not apply to a particular product, this is expressly stated in the individual monograph.”

Therefore the pharmacopoeial requirements for vaccines and the tests to be carried out are those described in the general monograph Vaccines for veterinary use and those described in the relevant individual monograph where one exists.

Products not covered by an individual monograph are of pharmacopoeial quality if they comply with the relevant general monograph(s). It is up to the users to determine which general monograph(s) apply(ies).

The individual monographs have to be used and applied, taking account of the explanations, guidance and requirements given in all the documents mentioned in section 3.3 of this guide. Although in some cases, the individual monographs duplicate requirements specified elsewhere, often this is not the case. Users of monographs should be aware, therefore, that if a general point from Vaccines for veterinary use is included in one individual monograph but not in another, this does not mean that the point is not applicable to products covered by the latter monograph. When a requirement is deleted from an individual monograph because it is stated in the general monograph, this is not a lowering of requirements but a standardisation in order to avoid duplication; indeed, the test has still to be carried out.

It is expected that the batch tests and assay methods used routinely will be validated by the user, in accordance with accepted procedures e.g. those in the Technical Guides of the Pharmacopoeia.

The following notes are provided as background and to aid interpretation of the general and individual monographs on veterinary vaccines.

4.1.2. SECTIONS OF THE MONOGRAPHS

DEFINITION

It defines the scope of the monograph and its applicability to products on the market. The monograph sets the official standard for all products covered by this definition. In addition, in the individual monographs, the composition of the product is stated briefly.
In the individual monographs, the scope is linked to what is presented in the Safety and Immunogenicity sections of the monograph i.e. if passive protection is mentioned in the Definition, the test for Immunogenicity should contain a test to demonstrate that the vaccine can provide this. If vaccines are authorised with an active ingredient covered by an individual monograph but of a new type, which falls outside the scope of the existing monograph, this may lead to revision of the monograph or elaboration of a new one. If a product is not covered by the scope of an individual monograph, the monograph is not applicable to this product. Only the general monograph *Vaccines for veterinary use* (0062) applies in this case.

**PRODUCTION**

This section is primarily addressed to manufacturers. It contains principles and information on points to be addressed for the production of the vaccine, the type of tests expected to be conducted during development of the product, tests that may be conducted, routinely, in-process and tests that can be conducted on each batch by manufacturers, as part of the tests conducted to provide assurance that the product is of pharmacopoeial quality. The developmental tests provide guidance for manufacturers on how to demonstrate the clinical value and the efficacy of their products. Advice may also be included on how to demonstrate the safety of the products.

Information on how to address particular aspects such as the possible excretion of live vaccinal organisms may also be included.

To address these points, the Production section in the general and individual monographs contains a mixture of requirements and information on particular aspects of the manufacturing process, which may relate for example to source materials, to the manufacturing process itself and its validation and control and to in-process testing which notably enables the consistency of the manufacturing process to be demonstrated. Some of the topics are straightforward points that need to be addressed for the preparation or testing of each batch (e.g. points on the method of production; some details on the conduct of the test for inactivation). Others are points that need to be addressed during the development of the immunological product.

The section contains different sub-sections and the points raised in each sub-section must be addressed by the manufacturer but, because of the advisory nature of this section, the manufacturer may address the point through use of a method that is different from that described in the monograph. That having been said, the developmental tests and tests done on the batch must be conducted in such a way that assurances are obtained that the product and every batch marketed is of pharmacopoeial quality. (See also comments below, on Batch tests and the Potency test.)

“Routinely used in vivo tests can ultimately be replaced in accordance with the principles of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes, if the product profile is well defined by a set of parameters, including antigen content and antigen quality, established to verify that the manufacturing process consistently produces final batches equivalent to a final batch that fulfills the criteria of the European Pharmacopoeia.” The general chapter 5.2.13. Healthy chicken flocks for the production of inactivated vaccines for veterinary use, sets upstream quality requirements for the production of inactivated vaccines that provide guarantees with regard to contamination by extraneous agents, making the test for specified extraneous agents performed on each batch of final product obsolete. Consequently, the test for specified extraneous agents has been deleted in the related individual monographs, also published in the 9th Edition [Newcastle disease vaccine (inactivated) (0870); Avian infectious bronchitis vaccine (inactivated) (0959); Avian infectious bursal disease vaccine (inactivated) (0960); Egg drop syndrome ‘76 vaccine (inactivated) (1202); Avian paramyxovirus 3 vaccine (inactivated) for turkeys (1392); Equine influenza vaccine (inactivated) (0249); Porcine influenza vaccine (inactivated) (0963); Feline chlamydiosis vaccine (inactivated) (2324)]. For
media “Standard formulation’ is referred to in connection with consistency of production. Furthermore, in addition to the qualitative composition, the quantitative composition of media used must also be recorded.

Further to the introduction of the consistency of production concept in the context of the 3Rs in the General Notices (Supplement 8.2), this concept has been included in the general monograph Vaccines for veterinary use: a paragraph on general provisions has been added referring to the manufacturing process consistently producing final batches equivalent to a final batch that fulfilled the criteria (Ph. Eur. 9th Edition).

In the general and individual monograph points are included as follows:

2-1. STARTING MATERIAL

This is focused on the quality of starting materials and the production process. This subsection in the general monograph includes specific requirements for:

- the starting material;
- the substrate for production;
- the media used for the preparation of the seed lots and for production;
- the seed lots including propagation and controls (origin, identification, purity or extraneous agent tests);
- the inactivation process (inactivation kinetics, inactivating agents, testing for residual live virus or bacteria, detoxification).

Regarding the control of the inactivation, a first test must be performed on the bulk antigen immediately after the inactivation step (see section 2.3.2 of the general monograph).

The conditions under which the second test for residual live virus/bacteria may be omitted for batch release are stated in the general monograph Vaccines for veterinary use (under section 3.10).

The individual monographs may provide further details such as:

- the production process: separate culture of the different vaccine strains, possibility to use fractions of the antigen, to add an adjuvant, etc.;
- the quality of the substrate by reference to chapters Cell cultures for the production of veterinary vaccines (5.2.4), SPF chicken flocks for vaccines (5.2.2) and Healthy chicken flocks for the production of inactivated vaccines for veterinary use (5.2.13);
- the controls to be performed on the seed lots [i.e. for avian vaccines: reference to tests for extraneous agents in seed lots (2.6.24)];
- the method for testing of residual live virus/bacteria and/or detoxification of the antigen harvest.

2-2. CHOICE OF VACCINE COMPOSITION AND CHOICE OF VACCINE STRAIN

This sub-section refers to safety and efficacy tests to be conducted during development of a vaccine, as described in chapters 5.2.6. and 5.2.7.

To facilitate the reading of the general monograph, two sub-sections have been included: 2-2-1. Development studies on safety and efficacy and 2-2-1-2. Information for performing the safety and efficacy studies. These tests are usually carried out once in the lifetime of the vaccine. Unless otherwise stated, test methods given for verification of these characteristics, and acceptance limits where appropriate, are provided for information as examples of suitable methods and
associated suitable limits. Nevertheless, the developmental tests have to be conducted in such a way that assurances are obtained that the product is of pharmacopeial quality.

Further explanations on the interactions between the different texts published in the European Pharmacopoeia to establish the efficacy of vaccines are provided below (see section 5. RELATIONSHIP BETWEEN GENERAL MONOGRAPHS AND CHAPTERS AND INDIVIDUAL MONOGRAPHS of this guide).

*Note:* For a test conducted during development of a vaccine, the wording “to be recommended” is used (instead of “recommended”). This is because at this stage, routes and method of administration, age of animals, vaccination schedules are not fixed yet. Indeed it is the purpose of these tests to determine these parameters.

In this sub-section of the **general monograph** guidance is given on a number of other areas including:

- routes and methods of administration and categories of animals which are relevant to conducting the developmental tests,
- use of antimicrobial preservatives,
- stability requirements – it is mentioned that results are expected from tests for virus titrations, bacterial counts or potency, conducted on 3 batches at regular intervals until 3 months beyond the end of shelf-life. Results are also expected from tests for moisture content, tests for the adjuvant and chemical tests, as appropriate (but not necessarily with the same level of frequency of testing). It should be noted that although batches of products are expected to be in conformity with all the requirements of the section Batch tests throughout their shelf-life, for some requirements, such as inactivation, extraneous agents or sterility this does not mean that the stability studies need to include repeat testing for these throughout the proposed shelf-life. Details on how to use stability studies, what is expected for stability with regard to intermediates and the definition of appropriate formulation and release parameters are included.

- **Formulation** (section 2-2-4). For live vaccines, information on what is expected for the virus titre or bacterial count at release has been added. Furthermore, requirements for inactivated vaccines have been added.

In the **individual monographs**, information is provided on the conduct of developmental safety and efficacy tests:

- **Safety.** The detailed requirements in chapter 5.2.6 have to be addressed. The individual monograph may give technical details on some of the tests, in order to provide advice on what is considered an appropriate protocol for the work. For live vaccines, for example, details are usually provided for the conduct of the test for Increase in virulence.
- **Efficacy.** The detailed requirements in chapter 5.2.7 have to be addressed. Further explanation is given in section 5. RELATIONSHIP BETWEEN GENERAL MONOGRAPHS AND CHAPTERS AND INDIVIDUAL MONOGRAPHS of this guide.

These tests are conducted during development of the product and such tests are not usually described in European Pharmacopoeia monographs. They are included in veterinary vaccine monographs because there is a greater variability of antigens for veterinary vaccines compared to human vaccines, which are much more standardised. There is also a bigger diversity of vaccines and a greater number of manufacturers for veterinary vaccines compared to human vaccines.

As indicated in the monographs, attention must be given to the titre or potency of batches used
in the safety and efficacy/immunogenicity studies. When combined vaccines are being tested the
manufacturer may need to take particular steps to address the point including, for example,
choosing different batches for the tests to ensure that the component being tested meets the
requirements.

2-3. PREPARATION OF THE VACCINE
This sub-section refers to the various methods of preparation of vaccines (propagation and harvest
of bacterial and viral antigens, inactivation, preparation of the final bulk and the final batch).

2-4. MANUFACTURER’S TESTS
This is a section on tests that may be conducted by the manufacturer (or others) as part of the
testing conducted to show that each batch is of pharmacopoeial quality. These tests are
designed to provide part of the assurance that the batch would comply with the pharmacopoeial
requirements as defined by the tests given in the section BATCH TESTS.
This section contains a variety of types of tests, depending on the nature of the product. For
example, individual monographs for bacterial vaccines may have a test for bacterial endotoxin.

Some of the tests described are in-process tests that can only be done before final formulation (e.g.
checking the content of bulk antigens for key antigens) and are additional to tests that can be
carried out by an independent analyst. Other tests are given in this section because the
manufacturer can do a test that is more suitable for one reason or another, than the test that can
be carried out by an independent analyst; the batch potency test (instead of the test for Potency –
see below) is an example. Where it is more suitable for a manufacturer to perform a test
upstream this can be done instead of a test on the final product, even if it is prescribed in the
section on batch tests. This is on the condition that the test upstream will provide the same or a
better reassurance that the batch of the final product is of pharmacopoeial quality. It is also
explained in this section of the general monograph that it is expected that a batch potency test or
titration is conducted on each batch rather than the test described under Potency.

The Manufacturer’s tests section of the individual monographs brings together the tests which
are product specific. There are generally no limits expressed as figures, because the manufacturer
has to establish these limits based on the values observed from batches of vaccine
demonstrated as safe and/or efficacious. The tests the most commonly listed in the individual
monographs.

- Antigen content: determined to be within limits shown to allow preparation of satisfactory
  vaccines. The formulation of the vaccine is based, whenever possible, on the antigen content
determined on the harvest before or after inactivation and/or downstream processing, if
  applicable;
- Bacterial endotoxins: the maximum acceptable amount is that found for a batch of vaccine
  shown satisfactory in safety tests;
- Batch potency test: alternative test to the Potency test that may be performed by the
  manufacturer for routine testing for batch release (see below for details).

As with other points in the Production section, the manufacturer does not need to test batches
of antigen and/or final product with the tests described in this section. However, the tests
proposed in the Manufacturer’s test sub-section are provided as examples of tests which can
contribute to a suitably sensitive testing regime to show that each batch of the product is of
pharmacopoeial quality. Whatever system of testing is adopted by the manufacturer on each batch
of antigen and/or final product, these must be such as to provide the required level of
reassurance on the suitability of each batch.
**Batch potency test:** It is explained in this sub-section of the general monograph that the test described under Potency is not usually suitable for the routine testing of batches. Therefore an alternative test may be performed by the manufacturer for routine testing for batch release. This test must provide assurance that the batch would comply with the Potency test requirements. The model proposed is given as an example of a satisfactory method. A validation by the manufacturer for the particular product is necessary. The test used must be able to detect sub-potent vaccines.

The first model described may be *in vitro* even if it is not available for all products. This is to encourage manufacturers to develop *in vitro* methods.

It has to be noted that the *in vivo* method will remain in the monograph as long as all the products cannot be assessed using *in vitro* methods only and as long as it is considered as the golden standard by the scientific community.

For live vaccines, a test for virus titre or bacterial count is required by the relevant individual monographs and the general monograph and it is expected that the point will be addressed through setting a suitable acceptance criterion for this test. To this end:

- during the development studies the minimum acceptable viral titre or bacterial count must be established, based on that in the batch(es) of vaccine used in the Potency test or other efficacy studies,
- the loss observed during the stability studies should be added to this value to ensure that the content will be not less than the minimum acceptable titre or count at the end of the shelf-life,
- each batch must then be shown to contain, at release, not less than this calculated titre or count.

For inactivated vaccines, it is expected that a suitable batch potency test will be developed for routine use, instead of the Potency test. The acceptance criteria must be established from correlation with the results obtained for a batch shown satisfactory in the Potency test. In most individual monographs for inactivated vaccines, an example of a batch potency test is provided. It is usually described in some detail and may suggest alternative approaches. For inactivated vaccines, development of in-vitro methods is recommended, provided that:

- key in-process parameters are defined and monitored;
- in-process control tests (including antigen quantification after inactivation and/or concentration, if applicable) and target formulation of the final product are performed.

In all cases, the tests provided are given as examples of the type of test that may be carried out; as explained under 3.1 PHARMACOPOEIAL REQUIREMENTS of this guide, these examples are *per se* not validated. The manufacturer has to develop a suitable test for use for batch release. The method must be tightly specified. If a test in laboratory animals is necessary then specific details such as a fixed dosage regimen and a fixed interval between vaccination and sampling must be included in the description. An independent validation study is performed linked to an efficacy study to show that the proposed method and acceptance criteria are suitable. It has to provide assurance that each batch that passes the batch potency test would pass the Potency test specified in the monograph or, when no individual monograph exists, is of acceptable efficacy. The test must be able to detect sub-potent batches of vaccine.

### 3. BATCH TESTS

This is a section on tests that may be conducted by the manufacturer (or others) as part of the testing conducted to show that each batch is of pharmacopoeial quality. These tests are
designed to provide part of the assurance that the batch would comply with the pharmacopoeial requirements.

Taking into account the quality systems in place, advances in scientific knowledge and understanding of the products, manufacturing processes and their controls, the choice of tests to be performed may be reconsidered when assessing compliance with Pharmacopoeia monographs, in accordance with the General Notices. On a case-by-case basis, with the agreement of the competent authority, the choice and necessity of certain final product tests may be reconsidered, where in-process tests give at least an equal guarantee that the batch would comply if tested, or where alternative tests validated with respect to the Pharmacopoeia method have been carried out.

This section contains a variety of types of tests, depending on the nature of the product. It includes information on tests that should be conducted routinely and are applicable to a wide range of vaccines (i.e. physical tests, chemical tests, pH and water).

**Identification** (section 3-1). In the interest of animal welfare, the vaccine identification test by antibody induction in animals is not required for any inactivated vaccines, which allows the user to identify the antigen(s) by any suitable methods, for example nucleic acid amplification techniques (2.6.21). This allows manufacturers to replace animal tests with in vitro tests when appropriate, and reinforces the idea that it may be combined with the batch potency test.

**Bacteria and fungi** (section 3–8). This title, also used in the related individual monographs, replaces ‘Sterility’.

**Extraneous agents** (section 3–9). The requirement for mammalian live vaccines is stated in the general monograph and is therefore applicable to any mammalian live vaccines.

The tests are usually product specific. There are generally no limits expressed as figures, because the manufacturer has to establish these limits based on the values observed from batches of vaccine demonstrated as safe and/or efficacious.

The section in the **general monograph** includes points of guidance or qualification for the test for free formaldehyde, for phenol, identification tests, test for sterility, tests for mycoplasmas extraneous agents, and potency tests.

In the **individual monographs**, this section contains the tests and requirements that all batches of products must comply with throughout their shelf-life. This means that any batch on the market, if tested by an independent analyst, must comply with these requirements.

For the purpose of batch release by the manufacturer, the tests described do not need to be carried out on each batch where in-process or other final product tests give an equal or better guarantee that the batch would comply or where alternative tests validated with respect to the Pharmacopoeia method have been carried out. In addition, the manufacturer’s release specification or final product specification for a particular product may be more stringent than specified in the monograph. This could happen for example, to accommodate losses occurring during the shelf-life or to reflect the minimum that has been shown efficacious or to ensure batch consistency.

With few exceptions, the individual monographs have a section entitled Potency. This usually refers to conducting the test described under Immunogenicity. The Potency test is included in the monograph as a test that may be conducted on any batch, and therefore, only one recommended route of administration is used for this purpose.
4. STORAGE

General requirements are given in the general monograph Vaccines for veterinary use (0062). A Storage section is included in an individual monograph only if it is specific for the vaccine. Unless otherwise indicated in an individual monograph, the storage of vaccines is expected to conform to that described in the general monograph. If other storage conditions than those described in the general monograph apply, they are indicated in the individual monograph.

5. LABELLING

The appropriate requirements of the labelling described in the general monograph apply to all vaccines for veterinary use. In some cases, additional information may be necessary for a particular vaccine for example where additional information is needed to allow the application of a specific test. This information is then included in the individual monograph, in the Labelling section, and this is supplementary to the requirements of the general monograph.

Status of labelling is defined in the General notices: “In general, labelling of medicines is subject to supranational and national regulation and to international agreements. The statements under the heading Labelling are not therefore comprehensive and, moreover, for the purposes of the Pharmacopoeia only those statements that are necessary to demonstrate compliance or non-compliance with the monograph are mandatory. Any other labelling statements are included as recommendations. When the term “label” is used in the Pharmacopoeia, the labelling statements may appear on the container, the package, a leaflet accompanying the package, or a certificate of analysis accompanying the article, as decided by the competent authority.”
4.2. SUMMARY OF THE CONTENT OF THE GENERAL MONOGRAPH
IMMUNOSERA FOR VETERINARY USE

The general monograph *Immunosera for veterinary use (0030)* contains, in a general but
detailed way, the requirements and points that have to be addressed by manufacturers for the
preparation and testing of batches of all immunosera. Unlike veterinary vaccines, the bulk of the
requirements including the tests to be conducted on batches of products are contained in the
general monograph and there are only a small number of individual monographs with
limited additional information. Although the contents are different, the information provided for
sections such as Definition, Storage and Labelling can be interpreted in a similar manner to the
equivalent texts for the general monograph *Vaccines for veterinary use (0062)*.

The pharmacopoeial requirements for immunosera and the tests to be carried out are those
described in the General monograph *Immunosera for veterinary use (0030)* and those
described in the relevant individual monographs where one exists.

The Production section describes both requirements and specific information on the points to
be addressed for the manufacture of immunosera. This includes information on the source animal
selection and their testing and monitoring for freedom from extraneous agents, immunising the
source animals and preparation of the final product.

General information on the developmental safety and efficacy tests that should be conducted to
show the suitability of the product composition are contained in the general chapters
*Evaluation of safety of veterinary vaccines and immunosera (5.2.6)* and *Evaluation of efficacy of
veterinary vaccines and immunosera (5.2.7)* and some limited further information is included in
the individual monographs, including minimum potency test requirements.

5. RELATIONSHIP BETWEEN GENERAL MONOGRAPHS AND CHAPTERS
AND INDIVIDUAL MONOGRAPHS

The general monograph *Vaccines for veterinary use (0062)* is applicable to all vaccines for
veterinary use, and the general monograph *Immunosera for veterinary use (0030)* is
applicable to all immunosera for veterinary use. The mention of “vaccine” or “immunosera” in
the title of an individual monograph makes the relevant general monograph applicable, but the
provisions of the general monographs also apply to veterinary vaccines/immunoser having no
individual monograph in the European Pharmacopoeia.

The general monographs prescribe essential requirements, which supplement and expand on
requirements contained in the monographs on specific products (vaccines/immunoser). The
general monographs contain information on how to interpret references to requirements in the
individual monographs. The authors and users of individual monographs must be familiar with the
contents of the relevant general monographs in order to be able to use the individual monographs
correctly.

The requirements given in the general monographs are not usually repeated in the individual
monographs, i.e., no reference is made to the general monograph in the individual monographs
on vaccines/immunoser, unless this is necessary to avoid ambiguity.

As indicated above, requirements contained in other general chapters such as requirements for cell
cultures may be invoked through inclusion of a reference to it in a monograph. General
information on the developmental Safety and Efficacy tests that should be conducted to show the suitability of the product composition is contained in the general chapters Evaluation of safety of veterinary vaccines and immunosera (5.2.6) and Evaluation of efficacy of veterinary vaccines and immunosera (5.2.7). In certain cases, the provisions in other general monographs also apply, such as those in the monograph on Products with risk of transmitting agents of animal spongiform encephalopathies (1483).

The relationship between the various texts is complex but the general texts are an essential part of the European Pharmacopoeial requirements.

Examination of the texts referring to requirements for studying and establishing the efficacy of the vaccine provides an example of what is the most complex inter-relationship of texts.

The section of the general monograph entitled “Choice of vaccine composition and choice of vaccine strain” is related to the section headed ‘Choice of vaccine composition’ in individual monographs for inactivated vaccines and the similar section headed ‘Choice of vaccine strain’ in monographs for live vaccines.

In the general monograph, this section contains a range of topics including:

- explanatory notes on the general requirements for conducting the developmental studies,
- the terms used and the relationship between Immunogenicity and Potency tests described in individual monographs,
- a reference to the general requirements for efficacy included in chapter 5.2.7.

In most of the individual monographs this section contains a general reference to the need to address the requirements of Evaluation of efficacy of veterinary vaccines and immunosera (5.2.7). In addition, in many monographs, details are provided of the Immunogenicity test(s) that should be conducted as part of the work undertaken to test the product and to demonstrate its efficacy, during development, in accordance with the requirements of 5.2.7. These Immunogenicity tests have specific requirements reflecting what is considered as the important parameters to be evaluated and results expected in studies on the efficacy of products of the particular type.

Taking into consideration the information given in the general and individual monographs, in the general chapter 5.2.7 and in the General Notices, it becomes clear that:

- the efficacy of the vaccine has to be studied in accordance with the requirements of chapter 5.2.7;
- a test for Immunogenicity is required as part of the studies to establish the efficacy of the vaccine;
- the test method given for studying the immunogenicity of the vaccine and showing it is in conformity with the specified acceptance limits, where appropriate, are provided for information as examples of suitable methods and associated suitable limits. Subject to approval by the Competent Authority, other test methods may be used without validation against the method shown in the monograph (see General Notices 1.4). The acceptance criteria of the example tests mentioned in the monographs are indicative of the minimum Pharmacopoeial standards expected of the results of alternative tests for the products within the scope of that individual monograph;
- to be in conformity with the legal requirements, any batch of product on the market must be in compliance with the requirements of the Potency test in the Batch test section of the individual monograph, if tested.
### 6. SUMMARY TABLE OF STATUS OF VARIOUS SECTIONS OF MONOGRAPHS

<table>
<thead>
<tr>
<th>Section</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. DEFINITION</td>
<td>Defines the scope of the monograph.</td>
</tr>
<tr>
<td>2. PRODUCTION</td>
<td></td>
</tr>
<tr>
<td>2.1. Preparation of the vaccine</td>
<td>Mandatory</td>
</tr>
<tr>
<td>2.2. Choice of vaccine composition</td>
<td>The vaccine is shown to be satisfactory with respect to safety (5.2.6) and efficacy (5.2.7) The performance of the tests to establish the safety and efficacy according to chapters 5.2.6 and 5.2.7 is mandatory, but the test described in the individual monographs are given as examples of suitable methods.</td>
</tr>
<tr>
<td>2.2.1. Safety</td>
<td>Mandatory</td>
</tr>
<tr>
<td>A test is carried out for each route and method of administration</td>
<td>Advisory: the description of the test is given as an example of suitable method. If the test is carried out as described, it will be acceptable to Competent Authorities in Ph. Eur. Member States.</td>
</tr>
<tr>
<td>Detailed safety test.</td>
<td></td>
</tr>
<tr>
<td>2.2.2. Reversion to virulence</td>
<td>Advisory. If the test is carried out as described, it will be acceptable to Competent Authorities in Ph. Eur. Member States.</td>
</tr>
<tr>
<td>2.2.3. Immunogenicity</td>
<td>Mandatory</td>
</tr>
<tr>
<td>A test is carried out for each route and method of administration/for each species, category…</td>
<td>Advisory: the description of the test is given as an example of suitable method. If the test is carried out as described, it will be acceptable to Competent Authorities in Ph. Eur. Member States. Where immunogenicity has to be demonstrated for different routes/species/categories, an alternative method (for example, serology) may be applied after the initial demonstration of compliance with the test given, subject to agreement by the Competent Authority.</td>
</tr>
<tr>
<td>Detailed immunogenicity test</td>
<td></td>
</tr>
<tr>
<td>Antimicrobial preservatives</td>
<td>Mandatory</td>
</tr>
<tr>
<td>Stability</td>
<td>Mandatory</td>
</tr>
<tr>
<td>2.4. Manufacturer’s tests (inactivated vaccines)</td>
<td>The verification of the parameters listed is mandatory. The methods are given as examples of suitable methods.</td>
</tr>
<tr>
<td>Residual live virus/bacteria and/or detoxification</td>
<td>The verification of the inactivation is mandatory.</td>
</tr>
<tr>
<td>Batch potency test</td>
<td>The verification of the potency is mandatory. The model proposed is given as an example of satisfactory method. A validation by the manufacturer for the particular product is necessary. The test used must be able to detect sub-potent vaccines.</td>
</tr>
<tr>
<td>Bacterial endotoxins (bacterial vaccines)</td>
<td>Mandatory</td>
</tr>
<tr>
<td>3. BATCH TESTS</td>
<td>Mandatory. Apply throughout shelf-life. The tests are not necessarily carried out on each batch for batch release.</td>
</tr>
<tr>
<td>3.1. Identification</td>
<td>Must comply if tested; alternative test may be used.</td>
</tr>
<tr>
<td>3.2. Formaldehyde/Phenol</td>
<td>Must comply if tested.</td>
</tr>
<tr>
<td>3.3. Sterility/Bacteria and fungi</td>
<td>Must comply if tested, e.g. parametric release may be applied.</td>
</tr>
<tr>
<td>3.4. Extraneous agents (viral vaccines)</td>
<td>Must comply if tested.</td>
</tr>
<tr>
<td>3.5. Mycoplasmas</td>
<td>Must comply if tested.</td>
</tr>
<tr>
<td>3.7. Inactivation – Residual live virus/bacteria (inactivated vaccines)</td>
<td>Must comply if tested – can be tested upstream. This test may be omitted for batch release, as stated in the monograph <em>Vaccines for veterinary use</em> (0062).</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Virus titre/Live bacteria (live vaccines)</td>
<td></td>
</tr>
<tr>
<td>3.8. Potency</td>
<td>Must comply if tested. The detailed test is given as an example of a suitable method. The method used may be the method developed by the manufacturer during the development of the vaccine subject to agreement by the Competent Authority (see 2.4.3).</td>
</tr>
<tr>
<td>4. STORAGE</td>
<td>Advisory; storage conditions for each product are decided during licensing.</td>
</tr>
<tr>
<td>5. LABELLING</td>
<td>Items necessary for use of the monograph are mandatory, others are advisory. Labelling requirements are decided during licensing.</td>
</tr>
</tbody>
</table>

The table summarises the status but for full details, the different sections of the present guide must be consulted.
The Council of Europe is the continent’s leading human rights organisation. It comprises 47 member states, 28 of which are members of the European Union. The European Directorate for the Quality of Medicines & HealthCare (EDQM) is a directorate of the Council of Europe. Its mission is to contribute to the basic human right of access to good quality medicines and healthcare and to promote and protect public health.