

# Technical Guide

for the elaboration and use of  
monographs for

# Immunological veterinary medicinal products

## European Pharmacopoeia

**European Directorate for the Quality of Medicines & HealthCare**



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## TABLE OF CONTENTS

1		
2		
3		
4	<b>1. PURPOSE OF THE GUIDE</b> .....	2
5	<b>2. STATUS AND SCOPE OF THE GUIDE</b> .....	2
6	<b>3. GENERAL INFORMATION</b> .....	2
7	3.1. PHARMACOPOEIAL REQUIREMENTS .....	2
8	3.2. ALTERNATIVE METHODS .....	3
9	3.3. GENERAL CHAPTERS AND GENERAL MONOGRAPHS .....	4
10	3.4. SPECIFIC MONOGRAPHS.....	5
11	3.5. HOW MONOGRAPH AND CHAPTER FOR IMMUNOSERA AND VACCINES FOR VETERINARY	
12	USE ARE ELABORATED AND UPDATED .....	5
13	3.5.1. Inclusion of new monographs or new general chapters for immunosera and	
14	vaccines for veterinary use in the European Pharmacopoeia .....	5
15	3.5.2. Revision of monographs or general chapters for immunosera and vaccines for	
16	veterinary use .....	6
17	<b>4. CONTENT OF THE MONOGRAPHS</b> .....	8
18	4.1. CONTENT OF THE MONOGRAPHS FOR VACCINES FOR VETERINARY USE .....	8
19	4.1.1. General points.....	8
20	4.1.2. Sections of the monographs.....	8
21	4.2. SUMMARY OF THE CONTENT OF THE GENERAL MONOGRAPH ON IMMUNOSERA FOR	
22	VETERINARY USE.....	14
23	<b>5. RELATIONSHIP BETWEEN GENERAL MONOGRAPHS AND CHAPTERS</b>	
24	<b>AND SPECIFIC MONOGRAPHS</b> .....	14
25	<b>6. SUMMARY TABLE OF STATUS OF VARIOUS SECTIONS</b>	
26	<b>OF MONOGRAPHS</b> .....	17
27		

# 1           **Technical guide for the elaboration and use of monographs for** 2           **immunological veterinary medicinal products**

## 3   **1.    PURPOSE OF THE GUIDE**

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

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

## 15   **2.    STATUS AND SCOPE OF THE GUIDE**

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

## 20   **3.    GENERAL INFORMATION**

### 21   3.1.   PHARMACOPOEIAL REQUIREMENTS

22   Monographs and general chapters of the European Pharmacopoeia must be interpreted with  
23   reference to the *General Notices*. All users of the European Pharmacopoeia must be familiar  
24   with this text. The main items relevant for immunological veterinary medicinal products are  
25   given below:

- 26   •   Statements in monographs are mandatory requirements unless otherwise stated, the  
27   General Notices state that: “*Unless otherwise indicated in the General Notices or in the*  
28   *monographs, statements in monographs constitute mandatory requirements. General*  
29   *chapters become mandatory when referred to in a monograph, unless such reference is*  
30   *made in a way that indicates that it is not the intention to make the text referred to*  
31   *mandatory but rather to cite it for information.*” (Ph.Eur. 6<sup>th</sup> Edition)
- 32   •   As regards compliance with monographs, the General Notices state that: “*An article [that*  
33   *is the subject of a monograph] is not of Pharmacopoeia quality unless it complies with all*  
34   *the requirements stated in the monograph. This does not imply that performance of all the*  
35   *tests in a monograph is necessarily a prerequisite for a manufacturer in assessing*

1 *compliance with the Pharmacopoeia before release of a product. The manufacturer may*  
2 *obtain assurance that a product is of Pharmacopoeia quality from data derived, for*  
3 *example, from validation studies of the manufacturing process and from in-process*  
4 *controls. Parametric release in circumstances deemed appropriate by the competent*  
5 *authority is thus not precluded by the need to comply with the Pharmacopoeia. (Ph.Eur. 6<sup>th</sup>*  
6 *Edition)*

- 7 • Validation. As regard to validation of Ph. Eur. methods, the General Notices state: “*The*  
8 *test methods given in monographs and general chapters have been validated in accordance*  
9 *with accepted scientific practice and current recommendations on analytical validation.*  
10 *Unless otherwise stated in the monograph or general chapter, validation of the test*  
11 *methods by the analyst is not required.”* In the context of vaccines for veterinary use, it is  
12 the practice that the tests methods and their acceptance criteria constitute a compromise  
13 between the methods and specifications that have been approved at the time of elaboration  
14 of the monograph and the minimum requirements that are needed for a product to meet  
15 European Pharmacopoeia standards. Extensive validation according to current  
16 recommendations on analytical validation of these methods would require too many  
17 animals and would therefore not be in line with the 3R’s approach.

- 18 • Alternative methods. As regard to the use of alternative methods, the General Notices  
19 state:  
20 “*The tests and assays described are the official methods upon which the standards of the*  
21 *Pharmacopoeia are based. With the agreement of the competent authority, alternative*  
22 *methods of analysis may be used for control purposes, provided that the methods used*  
23 *enable an unequivocal decision to be made as to whether compliance with the standards of*  
24 *the monographs would be achieved if the official methods were used. In the event of doubt*  
25 *or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative.”*  
26 (Ph.Eur. 6<sup>th</sup> Edition)

- 27 • In section 1.4 of the General Notices, special provisions apply to the section **Choice of**  
28 **Vaccine Strain and Choice of Vaccine composition**: “*The production section of a*  
29 *monograph may define the characteristics of a vaccine strain or vaccine composition.*  
30 *Unless otherwise stated, test methods given for verification of these characteristics are*  
31 *provided for information as examples of suitable methods. Subject to approval by the*  
32 *competent authority, other test methods may be used without validation against the method*  
33 *shown in the monograph.”* (Ph.Eur. 6<sup>th</sup> Edition)

### 34 3.2. ALTERNATIVE METHODS

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

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

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

1 Monographs are revised periodically to keep pace with progress in techniques but pending  
2 these revisions new methods can be used as alternatives, if validated and authorized by the  
3 competent authorities.

4 Use of Animals: In accordance with the provisions of the *European Convention for the*  
5 *Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes*  
6 *(1986)* and the European Directive on the same principles, European Pharmacopoeia tests  
7 must be carried out in such a way as to use the minimum number of animals for a significant  
8 result and to cause the least pain, suffering, distress or lasting harm. Humane endpoints must  
9 be used wherever possible for all tests, even if not referred to in a specific monograph since  
10 references to humane endpoints are included as examples only where practical advice can be  
11 given (see General monograph on *Vaccines for veterinary use* and *Immunosera for veterinary*  
12 *use*).

### 13 3.3. GENERAL CHAPTERS AND GENERAL MONOGRAPHS

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

16 The following general monographs apply to products for veterinary use:

- 17 • *Vaccines for veterinary use (0062)* applies to all vaccines for veterinary use, whether there  
18 is a specific monograph for the vaccine or not,
- 19 • *Immunosera for veterinary use (0030)* applies to all immunosera for veterinary use,  
20 whether there is a specific monograph for the immunoserum or not.

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

23 The following general chapters published under the heading 2.6. BIOLOGICAL TESTS and  
24 5.2. GENERAL TEXTS ON VACCINES apply whenever they are given as reference in a  
25 monograph on a vaccine or immunoserum for veterinary use:

#### 26 **Biological tests specific to veterinary products**

- 27 • *Avian viral vaccines: tests for extraneous agents in seed lots (2.6.24)*
- 28 • *Avian live virus vaccines: tests for extraneous agents in batches of finished product*  
29 *(2.6.25)*

#### 30 **General texts specific to veterinary products**

- 31 • *Chicken flocks free from specified pathogens for the production and quality control of*  
32 *vaccines (5.2.2)*
- 33 • *Cell cultures for the production of veterinary vaccines (5.2.4)*
- 34 • *Substances of animal origin for the production of veterinary vaccines (5.2.5)*
- 35 • *Evaluation of safety of veterinary vaccines and immunosera (5.2.6)*
- 36 • *Evaluation of efficacy of veterinary vaccines and immunosera (5.2.7)*
- 37 • *Evaluation of safety of each batch of veterinary vaccines and immunosera (5.2.9)*

1 Additional tests, not restricted to veterinary products:

- 2 • *Sterility (2.6.1)*,
- 3 • *Mycoplasmas (2.6.7)*
- 4 • *Pyrogens (2.6.8)*
- 5 • *Bacterial Endotoxins (2.6.14)*

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

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

### 11 3.4. SPECIFIC MONOGRAPHS

12 Specific monographs on vaccines for veterinary use and on immunosera for veterinary use are  
13 published in the European Pharmacopoeia in alphabetical order of the title in 2 separate  
14 sections called “Vaccines for veterinary use” and “Immunosera for veterinary use”.

### 15 3.5. HOW MONOGRAPH AND CHAPTER FOR IMMUNOSERA AND 16 VACCINES FOR VETERINARY USE ARE ELABORATED AND 17 UPDATED

#### 18 3.5.1. INCLUSION OF NEW MONOGRAPHS OR NEW GENERAL CHAPTERS FOR 19 IMMUNOSERA AND VACCINES FOR VETERINARY USE IN THE EUROPEAN 20 PHARMACOPOEIA

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

- 22 • the chair of the European Pharmacopoeia Commission,
- 23 • a delegation,
- 24 • the chair on behalf of Group of experts No.15V,
- 25 • EDQM’s secretariat for example on the basis of information and data provided via the  
26 helpdesk by a manufacturer or by a user of the European Pharmacopoeia.

27 It is the European Pharmacopoeia Commission which accepts the proposal or not, and if  
28 accepted, it adds the item to the work programme of the Group of experts No. 15V (see the  
29 RULES OF PROCEDURE OF THE EUROPEAN PHARMACOPOEIA COMMISSION).

30 A proposal for addition of a monograph on a vaccine or an immunosera for veterinary use to  
31 the work programme of Group of experts No.15V is agreed upon only when the vaccine or  
32 the immunosera is produced by more than one manufacturer and licensed in one or more  
33 member states.

1 Monographs on vaccines for veterinary use are usually elaborated for one valence only.  
2 Monographs on combined vaccines are usually not elaborated and combined vaccines must  
3 comply with the specific monographs for each valence in the vaccine.

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

10 Once the new monograph is drafted, it is submitted to interested parties for written  
11 consultation before public enquiry. If necessary, a hearing is organised by EDQM, to which  
12 all manufacturers of the vaccine concerned may attend, give their comments and express  
13 directly their views to Group 15V members. After this consultation period, the monograph is  
14 revised and published in *Pharmeuropa* for public enquiry. All the interested parties have 3  
15 months to send their comments to their National Pharmacopoeial Authority (NPA), which  
16 centralises all the comments from that country. Then, NPAs have 2 months to send the  
17 compiled comments to EDQM's Secretariat. Manufacturers outside Europe, Industry  
18 associations and Paneuropean organisations have 3 months to send their comments to  
19 EDQM's Secretariat via the EDQM Helpdesk. EDQM's Secretariat makes a consolidated  
20 document from all the comments received.

21 The time between provision of a first draft to manufacturers and the end of the public enquiry  
22 is about 1 year.

23 The consolidated comments are studied by Group 15V at the meeting following the end of the  
24 consultation period.

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

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

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

35 Should the text not be adopted, it will either go back to the Group or no specific monograph  
36 on this particular product will be published in the European Pharmacopoeia.

### 37 **3.5.2. REVISION OF MONOGRAPHS AND GENERAL CHAPTERS FOR IMMUNOSERA** 38 **AND VACCINES FOR VETERINARY USE**

39 Proposals to revise a text can be made by:

- 40 • the chair of the European Pharmacopoeia Commission,

- 1 • a delegation,
- 2 • the chair on behalf of Group 15V,
- 3 • EDQM's secretariat for example on the basis of information and data provided via the  
4 helpdesk by a manufacturer or by a user of the European Pharmacopoeia.
- 5 It is the European Pharmacopoeia Commission, which refers requests for revision to Group of  
6 experts No. 15V (see the RULES OF PROCEDURE OF THE EUROPEAN  
7 PHARMACOPOEIA COMMISSION).
- 8 A request for revision must be submitted with a justification for this revision, supported by  
9 data and documents.
- 10 During the revision of a monograph, the standards attained by products that are already on the  
11 market will be taken into consideration.
- 12 Once the monograph is revised, it is published in *Pharmeuropa* for public enquiry. Hearings  
13 or pre-publication written consultation with interested parties are usually not organised for  
14 revised texts unless the revision is significant and requires an extra consultation step. All the  
15 interested parties have 3 months to send their comments to their NPA, which centralises all  
16 the comments of one country. Then, NPAs have 2 months to send the compiled comments to  
17 EDQM's Secretariat. Manufacturers outside Europe, industry associations and Paneuropean  
18 organisations have 3 months to send their comments to EDQM's Secretariat via the EDQM  
19 Helpdesk. EDQM's Secretariat makes consolidated comments from all the comments  
20 received.
- 21 The consolidated comments are studied by Group 15V at the meeting following the end of the  
22 consultation period.
- 23 After the study of these comments, if there is no major change in the text and if no restrictions  
24 are added to the text published for comments, the text is proposed for adoption at the next  
25 Commission session. If there is a major change in the text or if restrictions are added, then the  
26 text is published again for public enquiry in *Pharmeuropa*.
- 27 If the revised text is adopted, it is published in the European Pharmacopoeia 6 months after  
28 the Commission session, and implemented 6 months later.
- 29 As a result of the time required for each stage, interested parties have at least 2 years from the  
30 provision of the first draft of the revised monograph until implementation of the revised  
31 monograph. During this time, any studies being undertaken or validation studies required can  
32 be planned and executed, taking account of the available draft text.
- 33 Should the text not be adopted, it will either go back to the Group for further study/revision or  
34 stay as it is and not be revised.
- 35

## 1 **4. CONTENT OF THE MONOGRAPHS**

### 2 **4.1 CONTENT OF THE MONOGRAPHS FOR VACCINES FOR** 3 **VETERINARY USE**

#### 4 **4.1.1. GENERAL POINTS**

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

11 Therefore the pharmacopoeial requirements for vaccines and the tests to be carried out are  
12 those described in the General monograph on *Vaccines for Veterinary Use* and those  
13 described in the relevant specific monograph where one exists.

14 The specific monographs have to be used and applied, taking account of the explanations,  
15 guidance and requirements given in all the documents mentioned in section 3.3 of this guide,  
16 including the general monographs. Although in some cases the specific monographs duplicate  
17 requirements specified elsewhere, often this is not the case. Users of monographs should be  
18 aware, therefore, that if a general point from *Vaccines for Veterinary Use* is included in one  
19 specific monograph but not in another, this does not mean that the point is not applicable to  
20 products covered by the latter monograph.

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

24 When the term “development” or “developmental test” is used in the guide, the following is  
25 meant: test conducted to demonstrate the suitability of the proposed final composition.

26  
27 The following notes are provided as background and to aid interpretation of the general and  
28 specific monographs on veterinary vaccines.

#### 29 **4.1.2. SECTIONS OF THE MONOGRAPHS**

##### 30 **1. DEFINITION**

31 It defines the scope of the monograph and its applicability to products on the market. The  
32 monograph sets the official standard for all products covered by this definition. In addition, in  
33 the specific monographs, the composition of the product is stated briefly.

34 In the specific monographs, the scope is linked to what is presented in the Safety and  
35 Immunogenicity sections of the monograph i.e. if passive protection is mentioned in the  
36 Definition, the test for Immunogenicity should contain a test to demonstrate that the vaccine  
37 can provide this. If vaccines are authorised with an active ingredient covered by a specific  
38 monograph but of a new type, which falls outside the scope of the existing monograph, this  
39 may lead to revision of the monograph or elaboration of a new one. If a product is not covered  
40 by the scope of a specific monograph, the monograph is not applicable to this product. Only  
41 the general monograph on vaccines for veterinary use applies in this case.

## 1 2. PRODUCTION

2 The section is primarily addressed to manufacturers. It contains principles and information on  
3 points to be addressed for the production of the vaccine, the type of tests that it is expected  
4 will be conducted during development of the product, tests that may be conducted, routinely,  
5 in-process and tests that can be conducted on each batch by manufacturers, as part of the tests  
6 conducted to provide assurance that the product is of pharmacopoeial quality. The  
7 developmental tests provide guidance for manufacturers on how to demonstrate the clinical  
8 value and the efficacy of their products. Advice may also be included on how to demonstrate  
9 the safety of the products and may include information on how to address particular aspects  
10 such as the possible excretion of live vaccinal organisms.

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

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

26 In the general and specific monographs points are included as follows:

### 27 *2.1. PREPARATION OF THE VACCINE*

28 This is focused on the quality of starting materials and the production process. This sub-  
29 section in the **general monograph** includes specific requirements for:

- 30 • the substrate for production
- 31 • the media used for the preparation of the seed lots and for production
- 32 • the seed lots including propagation and controls (origin, identification, purity or extraneous  
33 agents tests)
- 34 • the inactivation process (inactivation kinetics, inactivating agents, testing for residual live  
35 virus or bacteria, detoxification)

36 Regarding the control of the inactivation, a first test must be performed on the bulk antigen  
37 immediately after the inactivation step (see section 2-1-4-5 of the general monograph). A  
38 second test must be performed by the manufacturer at a latest step of the manufacturing  
39 process where the test has a suitable sensitivity (on the final product or earlier, as indicated in  
40 section 2-3-1 of the general monograph).

41 The **specific monographs** may provide further details such as:

- 42 • the production process: separate culture of the different vaccine strains, possibility to use  
43 fractions of the antigen, to add an adjuvant...

- 1 • the quality of the substrate by reference to chapters *cell cultures for the production of*  
2 *veterinary vaccines (5.2.4.), SPF chicken flocks for vaccines (5.2.2.) ...*
- 3 • the controls to be performed on the seed lots (i.e. *for avian vaccines: reference to tests for*  
4 *extraneous agents in seed lots (2.6.24)*)
- 5 • the method for testing of residual live virus/bacteria and/or detoxification of the antigen  
6 harvest.

## 7 2.2. CHOICE OF VACCINE COMPOSITION AND CHOICE OF VACCINE STRAIN

8 This sub-section refers to the safety and efficacy tests to be conducted during the development  
9 of a vaccine, as described in chapters 5.2.6. and 5.2.7. These tests are usually carried out once  
10 in the lifetime of the vaccine. Unless otherwise stated, test methods given for verification of  
11 these characteristics, and acceptance limits where appropriate, are provided for information as  
12 examples of suitable methods and associated suitable limits. Nevertheless, the developmental  
13 tests have to be conducted in such a way that assurances are obtained that the product is of  
14 pharmacopeial quality. Further explanations on the interactions between the different texts  
15 published in the European Pharmacopoeia to establish the efficacy of vaccines are provided  
16 below (see section 5. RELATIONSHIP BETWEEN GENERAL MONOGRAPHS AND  
17 CHAPTERS AND SPECIFIC MONOGRAPHS of this guide).

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

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

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

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

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

1 diversity of vaccines and a greater number of manufacturers for veterinary vaccines compared  
2 to human vaccines.

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

8

### 9 2.3. MANUFACTURER'S TESTS

10 This is a section on tests that may be conducted by the manufacturer (or others) as part of the  
11 testing conducted to show that each batch is of pharmacopoeial quality. These tests are  
12 designed to provide part of the assurance that the batch would comply with the  
13 pharmacopoeial requirements as defined by the tests given in the section BATCH TESTS.  
14 This section contains a variety of types of tests, depending on the nature of the product. For  
15 example, in specific monographs for inactivated vaccines there is likely to be a reference to  
16 conducting a test for inactivation in addition to the inactivation test done under production.  
17 Monographs for bacterial vaccines may have a test for endotoxin content.

18 Some of the tests described are in-process tests that can only be done before final formulation  
19 (e.g. checking the content of bulk antigens for key antigens) and are additional to tests that  
20 can be carried out by an independent analyst. Other tests are given in this section because the  
21 manufacturer can do a test that is more suitable for one reason or another, than the test that  
22 can be carried out by an independent analyst; the test conducted for residual live organisms in  
23 the bulk blend of antigens before addition of the adjuvant (instead of a final product test) and  
24 the batch potency test (instead of the test for Potency – see below) are two examples. Where it  
25 is more suitable for a manufacturer to perform a test upstream this can be done instead of a  
26 test on the final product, even if it is prescribed in the section on BATCH TESTS. This is on  
27 the condition that the test upstream will provide the same or a better reassurance that the batch  
28 of final product is of pharmacopoeial quality. It is also explained in this section of the general  
29 monograph that it is expected that a batch potency test or titration is conducted on each batch  
30 rather than the test described under Potency.

31 In the **general monograph**, the Manufacturer's test section contains information on topics  
32 such as the expectation that the manufacturer will not conduct the batch safety test on each  
33 batch and the need to comply with the provisions of the European Convention for the  
34 Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes.  
35 Finally, this section contains information on tests that should be conducted routinely and are  
36 applicable to a wide range of vaccines (i.e. physical tests, chemical tests, pH and water).

37 The Manufacturer's tests section of the **specific monographs** brings together the tests which  
38 are product specific. There are generally no limits expressed as figures, because the  
39 manufacturer has to establish these limits based on the values observed from batches of  
40 vaccine demonstrated as safe and/or efficacious. The tests the most commonly listed in the  
41 **specific monographs** are, for example, the:

- 42 • Antigen content: determined to be within limits shown to allow preparation of satisfactory  
43 vaccines
- 44 • Bacterial endotoxins: the maximum acceptable amount is that found for a batch of vaccine  
45 shown satisfactory in safety tests

- 1 • Batch potency test: alternative test to the Potency test that may be performed by the  
2 manufacturer for routine testing for batch release (see below for details).

3 As with other points in the Production section, the manufacturer need not test batches of  
4 antigen and/or final product with the tests described in this section. However, the tests  
5 proposed in the Manufacturer's tests sub-section are provided as examples of tests which can  
6 contribute to a suitably sensitive testing regime to show that each batch of product is of  
7 pharmacopoeial quality. Whatever system of testing is adopted by the manufacturer on each  
8 batch of antigen and/or final product, these must be such as to provide the required level of  
9 reassurance on the suitability of each batch.

10 **Batch potency test:** It is explained in this sub-section of the general monograph that the test  
11 described under Potency is not usually suitable for the routine testing of batches. Therefore an  
12 alternative test may be performed by the manufacturer for routine testing for batch release.  
13 This test must provide assurance that the batch would comply with the Potency test  
14 requirements.

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

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

26 For inactivated vaccines, it is expected that a suitable batch potency test will be developed for  
27 routine use, instead of the Potency test. The acceptance criteria must be established from  
28 correlation with the results obtained for a batch shown satisfactory in the Potency test. In  
29 most specific monographs for inactivated vaccines, an example of a batch potency test is  
30 provided. This is usually a test in laboratory animals and is described in some detail. In some  
31 cases, it contains suggestions for alternative approaches e.g. different types of animals,  
32 number and size of doses administered and a range of days from vaccination to time of  
33 collecting blood samples or use of an *in vitro* test method. In all cases, the tests provided are  
34 given as examples of the type of test that may be carried out; as explained under 3.1  
35 PHARMACOPOEIAL REQUIREMENTS of this guide, these examples are *per se* not  
36 validated. The manufacturer has to develop a suitable test for use for batch release. The  
37 method must be tightly specified including, for example, a fixed dosage regimen and a fixed  
38 interval between vaccination and sampling. An independent validation study is performed  
39 linked to an efficacy study to show that the proposed method and acceptance criteria are  
40 suitable. It has to provide assurance that each batch that passes the batch potency test would  
41 pass the Potency test specified in the monograph or, when no specific monograph exists, is of  
42 acceptable efficacy. The test must be able to detect sub-potent batches of vaccines.

43

1 3. BATCH TESTS

2 The section in the **general monograph** includes points of guidance or qualification for the  
3 test for free formaldehyde, for phenol, identification tests, test for sterility, tests for  
4 mycoplasmas, extraneous agents, safety tests and potency tests. Important general information  
5 that should be taken into account for the conduct of the batch safety test and the type of  
6 animals to be used is also included in this section. Note should also be taken of the guidance  
7 and requirements specified in general chapter 5.2.9.

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

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

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

23 4. STORAGE

24 General requirements are given in the general monograph on *Vaccines for veterinary use*  
25 (0062). A storage section is included in an individual monograph only if it is specific for the  
26 vaccines. Unless otherwise indicated in a specific monograph, the storage of vaccines is  
27 expected to conform to that described in the general monograph. If other storage conditions  
28 than those described in the general monograph apply, they are indicated in the specific  
29 monograph.

30 5. LABELLING

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

36 Status of Labelling is defined in the General notices: *In general, labelling of medicines is*  
37 *subject to supranational and national regulation and to international agreements. The*  
38 *statements under the heading Labelling are not therefore comprehensive and, moreover, for*  
39 *the purposes of the Pharmacopoeia only those statements that are necessary to demonstrate*  
40 *compliance or non-compliance with the monograph are mandatory. Any other labelling*  
41 *statements are included as recommendations. When the term "label" is used in the*  
42 *Pharmacopoeia, the labelling statements may appear on the container, the package, a leaflet*

1 *accompanying the package, or a certificate of analysis accompanying the article, as decided*  
2 *by the competent authority.*

#### 3 4.2. SUMMARY OF THE CONTENT OF THE GENERAL MONOGRAPH 4 ON IMMUNOSERA FOR VETERINARY USE

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

13  
14 The pharmacopoeial requirements for immunosera and the tests to be carried out are those  
15 described in the General monograph on *Immunosera for veterinary use (0030)* and those  
16 described in the relevant specific monographs where one exists.

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

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

#### 26 **5. RELATIONSHIP BETWEEN GENERAL MONOGRAPHS AND** 27 **CHAPTERS AND SPECIFIC MONOGRAPHS**

28 The general monograph on *Vaccines for veterinary use (0062)* is applicable to all vaccines for  
29 veterinary use, and the general monograph on *Immunosera for veterinary use (0030)* is  
30 applicable to all immunosera for veterinary use. The mention of “vaccine” or “immunosera”  
31 in the title of a specific monograph makes the relevant general monograph applicable, but the  
32 provisions of the general monographs also apply to veterinary vaccines/immunosera having  
33 no specific monograph in the European Pharmacopoeia.

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

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

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

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

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

13 The section of the general monograph entitled Choice of vaccine composition and choice of  
14 vaccine strain is related to the section headed 'Choice of vaccine composition' in specific  
15 monographs for inactivated vaccines and the similar section headed 'Choice of vaccine strain'  
16 in monographs for live vaccines.

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

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

22 In most of the **specific monographs** this section contains a general reference to the need to  
23 address the requirements of *Evaluation of efficacy of veterinary vaccines and immunosera*  
24 *(5.2.7)*. In addition, in many monographs, details are provided of the Immunogenicity test(s)  
25 that should be conducted as part of the work undertaken to test the product and to demonstrate  
26 its efficacy, during development, in accordance with the requirements of 5.2.7. These  
27 Immunogenicity tests have specific requirements reflecting what is considered as the  
28 important parameters to be evaluated and results expected in studies on the efficacy of  
29 products of the particular type.

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

- 32 • the efficacy of the vaccine has to be studied in accordance with the requirements of chapter  
33 5.2.7.
- 34 • a test for Immunogenicity is required as part of the studies to establish the efficacy of the  
35 vaccine.
- 36 • the test method given for studying the Immunogenicity of the vaccine and showing it is in  
37 conformity with the specified acceptance limits where appropriate, are provided for  
38 information as examples of suitable methods and associated suitable limits. Subject to  
39 approval by the competent authority, other test methods may be used without validation

1 against the method shown in the monograph (see *General Notices 1.4*). The acceptance  
2 criteria of the example tests mentioned in the monographs are indicative of the minimum  
3 Pharmacopoeial standards expected of the results of alternative tests for the products  
4 within the scope of that specific monograph.

- 5 • to be in conformity with the legal requirements, any batch of product on the market must  
6 be in compliance with the requirements of the Potency test in the Batch test section of the  
7 specific monograph, if tested.

8

1 SUMMARY TABLE OF STATUS OF VARIOUS SECTIONS OF MONOGRAPHS

Section	Status
1. DEFINITION	Defines the scope of the monograph.
2. PRODUCTION	
2.1. Preparation of the vaccine	Mandatory
2.2. Choice of vaccine composition	
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.
2.2.1. Safety A test is carried out for each route and method of administration	Mandatory
Detailed safety test.	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.
2.2.2. Reversion to virulence	Advisory. If the test is carried out as described, it will be acceptable to Competent Authorities in Ph. Eur. Member States.
2.2.3. Immunogenicity A test is carried out for each route and method of administration/for each species, category ...	Mandatory
Detailed immunogenicity test	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.
Antimicrobial preservatives	Mandatory
Stability	Mandatory
2.3. Manufacturer's tests (inactivated vaccines)	The verification of the parameters listed is mandatory. The methods are given as examples of suitable methods.
Residual live virus/bacteria and/or detoxification	The verification of the inactivation is mandatory.
Batch potency test	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.
Bacterial endotoxins (bacterial vaccines)	Mandatory
3. BATCH TESTS	Mandatory. Apply throughout shelf-life. The tests are not necessary carried out on each batch for batch release.
3.1. Identification	Must comply if tested; alternative test may be used.
3.2. Formaldehyde/Phenol	Must comply if tested.
3.3. Sterility/Bacteria and fungi	Must comply if tested, e.g. parametric release may be applied.
3.4. Extraneous agents (viral vaccines)	Must comply if tested.
3.5. Mycoplasmas	Must comply if tested.
3.6. Safety	Must comply if tested; routine application of this test can be waived for batch release (see general monograph).

3.7. Inactivation - Residual live virus/bacteria (inactivated vaccines) Virus titre/Live bacteria (live vaccines)	Must comply if tested – can be tested upstream.
3.8. Potency	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).
4. STORAGE	Advisory; storage conditions for each product are decided during licensing.
5. LABELLING	Items necessary for use of the monograph are mandatory, others are advisory. Labelling requirements are decided during licensing.

- 1 The table summarises the status but for full details, the different sections of the present Guide
- 2 must be consulted.