



Technical Guide for the
elaboration and use
of monographs
**FOR VACCINES AND
IMMUNOLOGICAL
VETERINARY
MEDICINAL PRODUCTS**



European Pharmacopoeia

EDQM
2nd Revision
Edition 2020

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English version

2020

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Cover image: © Budimir Jevtic – Fotolia
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1 NOTE ON THE TECHNICAL GUIDE

2 *The guide has undergone a general update to take into account the latest revisions of Ph. Eur. texts, and in*
3 *particular the revised approach for extraneous agents testing.*

4 **Pharmacopoeia requirements (3.1).** *Updated to reflect the latest version of the General Notices [§ on*
5 *compliance with monographs] and of the general monograph Vaccines for veterinary use (0062) [§ on particular*
6 *circumstances which may require additional testing].*

7 **Alternative methods (3.2).** *General information has been added to explain the link between the European*
8 *Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes and*
9 *Directive 2010/63/EU. It is also stated that, in accordance with Directive 2010/63/EU, manufacturers must*
10 *develop suitable in vitro methods as alternatives to animal tests, in particular for routine tests. A reference to*
11 *general chapter 5.2.14 on “Substitution of in vivo method(s) by in vitro method(s) for the quality control of*
12 *vaccines”, providing guidance when a one to one replacement is not possible, is also added. In case several*
13 *alternative methods have been developed, none of the method can be required in the Ph. Eur., but one of these*
14 *methods can nevertheless be mentioned as an example of a suitable method.*

15 **General chapters and general monographs (3.3).** *Updated to reflect the latest version of the Ph. Eur. texts. [e.g.*
16 *deletion of chapters 2.6.24 and 2.6.25 -and how to consult them once deleted- replaced by a new chapter 2.6.37,*
17 *addition of chapter 5.2.13 on healthy flocks, new scope of chapter 5.2.5]*

18 **Individual monographs (3.4).** *“Individual” instead of “specific”, with the same meaning (editorial).*

19 **Update of Ph. Eur. texts (3.5).** *Updated to reflect the latest version of the Rules of procedures of the European*
20 *Pharmacopoeia Commission [[PA/PH/SG \(16\) 85 COM from Nov 2016](#)]*

21 **Content of the monographs for vaccines for veterinary use (4.1).** *General information has been added to*
22 *explain that:*

- 23 - *products not covered by an individual monograph are of pharmacopoeial quality if they comply*
24 *with the relevant general monograph(s) ;*
- 25 - *when a requirement is deleted from an individual monograph because it is already stated in the*
26 *general monograph, the test has still to be carried out,*
- 27 - *what is meant by “development” in Ph. Eur. texts.*

28 **Sections of the monographs (4.1.2).** *Updated to reflect the latest version of the general monograph Vaccines*
29 *for veterinary use (0062), including explanations on how the concept of consistency of production in the context*
30 *of the 3Rs is built in the Ph. Eur., with a focus on the risk management approach developed in chapter 5.2.5.*
31 *and an example of how a risk assessment and the consistency concept can be employed to provide guarantees*
32 *making other tests unnecessary. In addition, the use of antibiotics during vaccine production is still allowed,*
33 *provided it has been evaluated.*

34 **Choice of vaccine composition and choice of vaccine strain (2-2.).** *General information has been added*
35 *to explain:*

- 36 - *how the minimum number of animals to be used in such tests is fixed (balance between the 3Rs*
37 *and obtaining valid results),*
- 38 - *the editorial style due to the purpose of these tests (i.e. use of “to be”),*
- 39 - *the changes made in the general monograph Vaccines for veterinary use (0062) regarding*
40 *stability studies and formulation and release parameters.*

41 **Manufacturer’s tests (2-4.).** *The example of inactivated vaccines requiring two tests for inactivation*
42 *has been deleted as the second test may now be omitted under certain conditions. More details are*
43 *included regarding the batch potency test, in particular a hierarchy of the tests to be used between in*
44 *vitro and in vivo, explaining why an animal test must be replaced by an alternative method (giving the*
45 *same pass/fail results) for routine tests, even when the animal test is still described in the Ph. Eur.*
46 *monograph.*

1 **TABLE OF CONTENTS**

2	1. PURPOSE OF THE GUIDE.....	5
3	2. STATUS AND SCOPE OF THE GUIDE.....	5
4	3. GENERAL INFORMATION.....	5
5	3.1. PHARMACOPOEIAL REQUIREMENTS.....	5
6	3.2. ALTERNATIVE METHODS.....	7
7	3.3. GENERAL CHAPTERS AND GENERAL MONOGRAPHS.....	8
8	3.4. INDIVIDUAL MONOGRAPHS.....	9
9	3.5. HOW MONOGRAPHS AND CHAPTERS FOR IMMUNOSERA AND VACCINES FOR VETERINARY USE	
10	ARE ELABORATED AND UPDATED.....	9
11	3.5.1. INCLUSION OF NEW MONOGRAPHS OR NEW GENERAL CHAPTERS FOR IMMUNOSERA AND	
12	VACCINES FOR VETERINARY USE IN THE EUROPEAN PHARMACOPOEIA.....	9
13	3.5.2. REVISION OF MONOGRAPHS AND GENERAL CHAPTERS FOR IMMUNOSERA AND VACCINES FOR	
14	VETERINARY USE.....	11
15	4. CONTENT OF THE MONOGRAPHS.....	12
16	4.1 CONTENT OF THE MONOGRAPHS FOR VACCINES FOR VETERINARY USE.....	12
17	4.1.1. GENERAL POINTS.....	12
18	4.1.2. SECTIONS OF THE MONOGRAPHS.....	12
19	4.2. SUMMARY OF THE CONTENT OF THE GENERAL MONOGRAPH.....	20
20	<i>IMMUNOSERA FOR VETERINARY USE</i>	20
21	5. RELATIONSHIP BETWEEN GENERAL MONOGRAPHS AND.....	21
22	CHAPTERS AND INDIVIDUAL MONOGRAPHS.....	21
23	6. SUMMARY TABLE OF STATUS OF VARIOUS SECTIONS OF MONOGRAPHS.....	22
24		
25		

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*

1 monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the
 2 Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product
 3 is of Pharmacopoeia quality on the basis of its design, together with its control strategy and data
 4 derived, for example, from validation studies of the manufacturing process.

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

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

17
 18 • **Quality systems.** Regarding quality systems in place for the production of IVMPs the Ph. Eur. General
 19 Notices state: “*The quality standards represented by monographs are valid only where the articles in*
 20 *question are produced within the framework of a suitable quality system. The quality system must*
 21 *assure that the articles consistently meet the requirements of the Pharmacopoeia.*” (Ph. Eur. 6th
 22 Edition)

23
 24 • **Validation.** Regarding validation of Ph. Eur. methods, the General Notices state: “*The test methods*
 25 *given in monographs and general chapters have been validated in accordance with accepted*
 26 *scientific practice and current recommendations on analytical validation. Unless otherwise stated*
 27 *in the monograph or general chapter, validation of the test methods by the analyst is not required.*”
 28 In the context of vaccines for veterinary use, it is the practice that the test methods and their
 29 acceptance criteria constitute a compromise between the methods and specifications that have been
 30 approved at the time of elaboration of the monograph and the minimum requirements that are
 31 needed for a product to meet European Pharmacopoeia standards. Extensive validation according to
 32 current recommendations on analytical validation of these methods would require too many animals
 33 and would therefore not be in line with the 3R’s approach. The current approach taken by Group 15V
 34 is to rationalise and update the methods currently in use (taking into account of the availability of
 35 more recent techniques, compliance with the 3Rs, GMP and performing risk analysis to avoid
 36 carrying out costly tests that are not strictly necessary) and to propose either validated methods or
 37 requirements for the validation of key parameters.

38
 39 • **Alternative methods.** As regards to the use of alternative methods, the General Notices state:
 40 “*The tests and assays described are the official methods upon which the standards of the*
 41 *Pharmacopoeia are based. With the agreement of the competent authority, alternative methods*
 42 *of analysis may be used for control purposes, provided that the methods used enable an*
 43 *unequivocal decision to be made as to whether compliance with the standards of the monographs*
 44 *would be achieved if the official methods were used. In the event of doubt or dispute, the methods of*
 45 *analysis of the Pharmacopoeia are alone authoritative.*” (Ph. Eur. 6th Edition)

46
 47 • Regarding the section **Choice of vaccine strain, Choice of vaccine composition**, the General
 48 Notices state in section 1.4: “*The Production section of a monograph may define the characteristics*
 49 *of a vaccine strain or vaccine composition. Unless otherwise stated, test methods given for*
 50 *verification of these characteristics are provided for information as examples of suitable methods.*”

1 *Subject to approval by the competent authority, other test methods may be used without validation*
2 *against the method shown in the monograph.” (Ph. Eur. 6th Edition)*
3

- 4 • **Particular circumstances which may require additional testing.** In case of necessity, the general
5 monograph *Vaccines for veterinary use (0062)* foresee the possibility for additional testing with the
6 agreement of the competent authority: “*On a case-by-case basis, with the agreement of the competent*
7 *authority, the choice of and need for certain final product tests may be reconsidered, where in-process*
8 *tests are able to demonstrate that the finished product meets the requirements of the monograph, or*
9 *where alternative tests validated with respect to the Pharmacopoeia method have been carried out.”*
10

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

- 12 ➤ exceptional circumstances as an extraordinary situation, which had to be justified (e.g. a
13 significant change in production);
14 ➤ exceptional circumstances as something that may accidentally happen in the lifecycle of a
15 medicinal product and has negative consequences in the field (for example safety issues).
16

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

- 19 ➤ significant changes in the production process (e.g. change of seed material, changes in essential
20 production media, change of blending [adjuvant], change of inactivation, etc.);
21 ➤ issues raised, for example, by pharmacovigilance reports or any problem seen in the field. These
22 would justify that investigations be carried out in order to identify and solve the problem.
23

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

26 **3.2. ALTERNATIVE METHODS**

27

28 The test methods prescribed in monographs are the reference methods on which the quality standards
29 are based. As indicated above under 3.1. PHARMACOPOEIAL REQUIREMENTS, other
30 methods of analysis may be used for a variety of reasons.
31

32 First, pharmacopoeial methods have been chosen for application to all the relevant products that were
33 available at the time of the elaboration of the monographs. Other available methods can be used if it is
34 demonstrated by validation that the alternative method is equivalent to the official method or more
35 suitable, in accordance with the General Notices. For example, an *in vitro* method would be “more
36 suitable” regarding animal welfare and in line with the *European Convention for the Protection of*
37 *Vertebrate Animals used for Experimental and Other Scientific Purposes* (which paved the way for the
38 EU’s Directive 86/609/EEC, adopted in 1986, as the provisions in it are based on the Convention. In
39 September 2010, the EU adopted a new Directive 2010/63/EU on the same subject replacing Directive
40 86/609/EEC, which came into effect in 2013).
41

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

45 Monographs are periodically revised to keep pace with progress in techniques but pending these
46 revisions new methods can be used as alternatives, if validated and authorized by the competent
47 authorities.
48

49 Use of Animals: In accordance with the provisions of the *European Convention for the Protection*
50 *of Vertebrate Animals Used for Experimental and Other Scientific Purposes (1986)* and the European
51 Directive (2010/63/EU) on the same principles, European Pharmacopoeia tests must be carried out

1 in such a way as to use the minimum number of animals for a significant result and to cause the least
2 pain, suffering, distress or lasting harm.

3 Humane endpoints must be used wherever possible for all tests, even if not referred to in an individual
4 monograph since references to humane endpoints are included as examples only where practical advice
5 can be given (see general monographs *Vaccines for veterinary use* and *Immunosera for veterinary use*).
6

7 In accordance with Directive 2010/63/EU, manufacturers must develop suitable *in vitro* methods as
8 alternatives to tests using animals, and in particular for batch release use appropriate tools such as the
9 monitoring of production consistency and appropriate antigen quantification. Therefore this is the first
10 option of choice in the monographs. General chapter *Substitution of in vivo method(s) by in vitro*
11 *method(s) for the quality control of vaccines (5.2.14)* provides guidance for substituting *in vivo*
12 method(s) with one or several *in vitro* methods.
13

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

19 **3.3. GENERAL CHAPTERS AND GENERAL MONOGRAPHS**

20
21 Certain general terms commonly used in monographs on vaccines for veterinary use are defined
22 in the general chapter *Terminology used in monographs on biological products (5.2.1)*.
23

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

- 25
- 26 ■ *Vaccines for veterinary use (0062)* applies to all vaccines for veterinary use, whether there is an
27 individual monograph for the vaccine or not,
- 28 ■ *Immunosera for veterinary use (0030)* applies to all immunosera for veterinary use, whether
29 there is an individual monograph for the immunoserum or not.
30

31 These monographs are published under the heading GENERAL MONOGRAPHS of the European
32 Pharmacopoeia.
33

34 The following general chapters published under the heading 2.6. BIOLOGICAL TESTS and 5.2.
35 GENERAL TEXTS ON BIOLOGICAL PRODUCTS apply whenever they are given as reference
36 in a monograph on a vaccine or immunoserum for veterinary use:
37

38 **Biological tests specific to veterinary products**

- 39
- 40 • *Principles for the detection of extraneous viruses in IVMPs by using culture methods (2.6.37)*.
41

42 **General texts specific to veterinary products**

- 43
- 44 • *Chicken flocks free from specified pathogens for the production and quality control of*
45 *vaccines (5.2.2)*
- 46 • *Healthy chicken flocks for the production of inactivated vaccines for veterinary use (5.2.13):*
47 *sets quality requirements that will provide guarantees with regard to contamination by*
48 *extraneous agents, making the test for specified extraneous agents performed on each final*
49 *product obsolete*
- 50 • *Cell cultures for the production of veterinary vaccines (5.2.4)*
- 51 • *Management of extraneous agents in immunological veterinary medicinal products (IVMPs)*

1 (5.2.5): This outlines a risk identification, risk assessment and risk management approach to the
2 presence of live extraneous agents in all starting materials and across the process of production
3 and the finished product. This allows the manufacturer to develop a coherent risk management
4 strategy across the whole process of production and the employment of fit for purpose testing at
5 justified points in the production of the product batches.

- 6 • *Evaluation of safety of veterinary vaccines and immunosera (5.2.6)*
- 7 • *Evaluation of efficacy of veterinary vaccines and immunosera (5.2.7)*
- 8 • *Evaluation of safety of each batch of immunosera for veterinary use (5.2.9)*

9
10 Additional tests, not restricted to veterinary products:

- 11 • *Sterility (2.6.1),*
- 12 • *Mycoplasmas (2.6.7)*
- 13 • *Pyrogens (2.6.8)*
- 14 • *Bacterial Endotoxins (2.6.14)*

15
16
17 *Sterility (2.6.1)* and *Mycoplasmas (2.6.7)* are requirements for veterinary vaccines and immunosera, in
18 compliance with the general monographs.

19
20 The general chapter *Viral Safety (5.1.7)* is an exception and does not apply to immunological veterinary
21 medicinal products since the subject is addressed in more detail in monographs or the general chapters
22 referred to above.

23
24 Note: The protocols described for example in deleted Chapters 2.6.24 “*Avian viral vaccines: tests for*
25 *extraneous agents in seed lots*”, and 2.6.25 “*Avian live virus vaccines: tests for extraneous agents in*
26 *batches of finished product*”, were fit for purpose for testing of extraneous agents when these chapters
27 were extant (i.e. until 1st July 2020). After this date, they can still be consulted in the Ph. Eur. online
28 archives.

29 **3.4. INDIVIDUAL MONOGRAPHS**

30
31 Individual monographs on vaccines for veterinary use and on immunosera for veterinary use are
32 published in the European Pharmacopoeia in alphabetical order of the title in two separate sections
33 called “Vaccines for veterinary use” and “Immunosera for veterinary use”.

34 **3.5. HOW MONOGRAPHS AND CHAPTERS FOR IMMUNOSERA AND VACCINES FOR** 35 **VETERINARY USE ARE ELABORATED AND UPDATED**

36 **3.5.1. INCLUSION OF NEW MONOGRAPHS OR NEW GENERAL CHAPTERS FOR IMMUNOSERA** 37 **AND VACCINES FOR VETERINARY USE IN THE EUROPEAN PHARMACOPOEIA**

38
39 Proposals to add a new text on the work programme can be made by:

- 40
- 41 • the Chair of the Commission,
- 42 • a delegation,
- 43 • a National Pharmacopoeia Authority,
- 44 • a Group of Experts or Working Party through the intermediary of its Chair,
- 45 • the Secretariat [for example on the basis of information and data provided via the HelpDesk
- 46 by a manufacturer or by a user of the European Pharmacopoeia],
- 47 • manufacturers and other interested parties from Member States through the intermediary of their
- 48 National Pharmacopoeia Authority,

- 1 • manufacturers and other interested parties from Observer States through the intermediary of a
2 National Pharmacopoeia Authority or the Secretariat,
- 3 • manufacturers and other interested parties from non-Member or non-Observer States through
4 the intermediary of the Secretariat.

5
6 It is the European Pharmacopoeia Commission which accepts the proposal or not, and if accepted,
7 it adds the item to the work programme of the Group of experts no. 15V (see the *Rules of procedure*
8 *of the European Pharmacopoeia Commission*).

9
10 A proposal for addition of a monograph on a vaccine or an immunoserum for veterinary use to the
11 work programme of Group of Experts no.15V is agreed upon only when the vaccine or the
12 immunoserum is produced by more than one manufacturer and licensed in one or more Member
13 States.

14 Monographs on vaccines for veterinary use are usually elaborated for one valence only.
15 Monographs on combined vaccines are usually not elaborated and combined vaccines must comply
16 with the individual monographs for each valence in the vaccine.

17
18 In general, the standards (i.e. of safety and efficacy) that are attained by vaccines that are already
19 on the market are taken into consideration during the elaboration of a new monograph. Consequently,
20 where there is sufficient information demonstrating that the product is of Pharmacopoeial quality, it
21 will not be necessary to retest these vaccines to show compliance with the requirements of sections
22 such as Safety and Immunogenicity when the monograph is finalised and published.

23
24 Once the new monograph is drafted, it is submitted to interested parties for written consultation before
25 public enquiry. If necessary, a hearing is organised by EDQM, to which all manufacturers of the
26 vaccine concerned may attend, give their comments and express directly their views to Group 15V
27 members. After this consultation, the monograph is revised and published in *Pharmeuropa* for public
28 enquiry. All the interested parties have 3 months to send their comments to their National
29 Pharmacopoeial Authority (NPA), which centralises all the comments from that country. Then,
30 NPAs have two months to send the compiled comments to EDQM's Secretariat. Manufacturers
31 outside Europe, industry associations and Pan-European organisations also have 3 months to send their
32 comments to EDQM's Secretariat via the EDQM HelpDesk. EDQM's Secretariat makes a
33 consolidated document from all the comments received.

34
35 The time between provision of a first draft to manufacturers and the end of the public enquiry is about
36 one year.

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

39
40 After the study of these comments, if there is no major change in the text that had been published
41 and if no restrictions are added to the text published for comment, the final text is proposed for
42 adoption at the next Commission session. If there is a major change in the text or if restrictions are added,
43 then the text is published again for public enquiry in *Pharmeuropa*.

44
45 If the text is adopted, it is published in the European Pharmacopoeia 6 months after the
46 Commission session, and implemented 6 months later.

47
48 As a result of the time required for each stage, interested parties have at least two years from the
49 provision of the first draft until the implementation of the monograph. During this time, any studies
50 being undertaken or validation studies required can be planned and executed, taking account of the
51 available draft text.

1
2 Should the text not be adopted, it will either go back to Group 15V and may be re-published in
3 *Pharmeuropa*, or no individual monograph on this particular product will be published in the European
4 *Pharmacopoeia*.

5 **3.5.2. REVISION OF MONOGRAPHS AND GENERAL CHAPTERS FOR IMMUNOSERA AND** 6 **VACCINES FOR VETERINARY USE**

7
8 Proposals to revise a text can be made by:

- 9
- 10 • the Chair of the Commission,
- 11 • a delegation,
- 12 • a National Pharmacopoeia Authority,
- 13 • a Group of Experts or Working Party through the intermediary of its Chair,
- 14 • the Secretariat [for example on the basis of information and data provided via the HelpDesk
- 15 by a manufacturer or by a user of the European Pharmacopoeia],
- 16 • manufacturers and other interested parties from Member States through the intermediary of their
- 17 National Pharmacopoeia Authority,
- 18 • manufacturers and other interested parties from Observer States through the intermediary of a
- 19 National Pharmacopoeia Authority or the Secretariat,
- 20 • manufacturers and other interested parties from non-Member or non-Observer States through
- 21 the intermediary of the Secretariat.
- 22

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

25
26 A request for revision must be submitted with a justification for this revision, supported by data and
27 documents.

28
29 During the revision of a monograph, the standards attained by products that are already on the market
30 will be taken into consideration.

31
32 Once the monograph is revised, it is published in *Pharmeuropa* for public enquiry. Hearings or pre-
33 publication written consultation with interested parties are usually not organised for revised texts
34 unless the revision is significant and requires an extra consultation step. All the interested parties have
35 3 months to send their comments to their NPA, which centralises all the comments of one country.
36 Then, NPAs have 2 months to send the compiled comments to EDQM's Secretariat. Manufacturers
37 outside Europe, industry associations and Pan European organisations also have 3 months to send
38 their comments to EDQM's Secretariat via the EDQM HelpDesk. EDQM's Secretariat makes
39 consolidated comments from all the comments received.

40
41 The consolidated comments are studied by Group 15V at the meeting following the end of the public
42 enquiry.

43
44 After the study of these comments, if there is no major change in the text and if no restrictions are added
45 to the text published for comments, the text is proposed for adoption at the next Commission session.
46 If there is a major change in the text or if restrictions are added, then the text is published again for
47 public enquiry in *Pharmeuropa*.

48
49 If the revised text is adopted, it is published in the European Pharmacopoeia 6 months after the
50 Commission session, and implemented 6 months later.

1
2 As a result of the time required for each stage, interested parties have at least 2 years from the provision
3 of the first draft of the revised monograph until the implementation of the revised monograph.
4 During this time, any studies being undertaken or validation studies required can be planned and
5 executed, taking account of the available draft text.
6

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

9 **4. CONTENT OF THE MONOGRAPHS**

10 **4.1 CONTENT OF THE MONOGRAPHS FOR VACCINES FOR VETERINARY USE**

11 **4.1.1. GENERAL POINTS**

12
13 The General Notices state: “*Substances and preparations that are the subject of an individual*
14 *monograph are also required to comply with relevant, applicable general monographs. Cross-*
15 *references to applicable general monographs are not normally given in individual monographs.*
16 *(...) General monographs and individual monographs are complementary. If the provisions of a*
17 *general monograph do not apply to a particular product, this is expressly stated in the individual*
18 *monograph.”*

19
20 Therefore the pharmacopoeial requirements for vaccines and the tests to be carried out are those
21 described in the general monograph *Vaccines for veterinary use* and those described in the relevant
22 individual monograph where one exists.

23
24 Products not covered by an individual monograph are of pharmacopoeial quality if they comply with
25 the relevant general monograph(s). It is up to the users to determine which general monograph(s)
26 apply(ies).
27

28 The individual monographs have to be used and applied, taking account of the explanations,
29 guidance and requirements given in all the documents mentioned in section 3.3 of this guide. Although
30 in some cases, the individual monographs duplicate requirements specified elsewhere, often this is not
31 the case. Users of monographs should be aware, therefore, that if a general point from *Vaccines for*
32 *veterinary use* is included in one individual monograph but not in another, this does not mean that
33 the point is not applicable to products covered by the latter monograph. When a requirement is deleted
34 from an individual monograph because it is stated in the general monograph, this is not a lowering of
35 requirements but a standardisation in order to avoid duplication; indeed, the test has still to be carried
36 out.
37

38 It is expected that the batch tests and assay methods used routinely will be validated by the user, in
39 accordance with accepted procedures e.g. those in the Technical Guides of the Pharmacopoeia.
40

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

43 **4.1.2. SECTIONS OF THE MONOGRAPHS**

44 45 DEFINITION

1 It defines the scope of the monograph and its applicability to products on the market. The monograph
2 sets the official standard for all products covered by this definition. In addition, in the individual
3 monographs, the composition of the product is stated briefly.
4

5 In the individual monographs, the scope is linked to what is presented in the Safety and
6 Immunogenicity sections of the monograph i.e. if passive protection is mentioned in the Definition,
7 the test for Immunogenicity should contain a test to demonstrate that the vaccine can provide this. If
8 vaccines are authorised with an active ingredient covered by an individual monograph but of a new
9 type, which falls outside the scope of the existing monograph, this may lead to revision of the
10 monograph or elaboration of a new one. If a product is not covered by the scope of an individual
11 monograph, the monograph is not applicable to this product. Only the general monograph *Vaccines*
12 *for veterinary use* (0062) applies in this case.
13

14 PRODUCTION

15

16 This section is primarily addressed to manufacturers. It contains principles and information on points
17 to be addressed for the production of the vaccine, the type of tests expected to be conducted during
18 development of the product, tests that may be conducted, routinely, in-process and tests that can be
19 conducted on each batch by manufacturers, as part of the tests conducted to provide assurance that the
20 product is of pharmacopoeial quality. The developmental tests provide guidance for manufacturers on
21 how to demonstrate the clinical value and the efficacy of their products. Advice may also be included
22 on how to demonstrate the safety of the products. Information on how to address particular aspects
23 such as the possible excretion of live vaccinal organisms may also be included.
24

25 To address these points, the Production section in the general and individual monographs contains
26 a mixture of requirements and information on particular aspects of the manufacturing process, which
27 may relate for example to source materials, to the manufacturing process itself and its validation and
28 control and to in-process testing which notably enables the consistency of the manufacturing process
29 to be demonstrated. Some of the topics are straightforward points that need to be addressed for the
30 preparation or testing of each batch (e.g. points on the method of production; some details on the
31 conduct of the test for inactivation). Others are points that need to be addressed during the development
32 of the immunological product.
33

34 The section contains different sub-sections and the points raised in each sub-section must be
35 addressed by the manufacturer but, because of the advisory nature of this section, the manufacturer
36 may address the point through use of a method that is different from that described in the
37 monograph. That having been said, the developmental tests and tests done on the batch must be
38 conducted in such a way that assurances are obtained that the product and every batch marketed is of
39 pharmacopoeial quality. (See also comments below, on Batch tests and the Potency test).
40

41 The concept of consistency of production is acknowledged in the context of the 3Rs in the General
42 Notices and is built upon in the general monograph *Vaccines for veterinary use* where reference is
43 specifically made to a manufacturing process consistently producing final batches equivalent to a final
44 batch which fulfills the criteria of the European Pharmacopoeia. For media ‘Standard formulation’ is
45 referred to in connection with consistency of production. Furthermore, in addition to the qualitative
46 composition, the quantitative composition of media used must also be recorded.
47

48 The consistency of production concept allows a risk management approach to extraneous agents
49 testing both during the production process and on the final product. As such the general monograph
50 supports the use of fit for purpose methods for extraneous agent detection such as molecular or cell
51 culture methods. The risk management rationale also forms the basis of chapter 5.2.5 *Management of*
52 *extraneous agents in IVMPs*. In this chapter, the factors to be taken into account when assessing risks

1 of biological starting materials as well as control and management strategies are outlined. By
 2 employing these strategies it may be possible to justify that routine testing final batches for the
 3 presence of extraneous agents is unnecessary. Annex 1 of Chapter 5.2.5. lists the species specific
 4 agents to be taken into account in a risk assessment and Annex II gives an example of a testing strategy
 5 decision tree for substrates which is irrespective of the target and sources species.

6
 7 An example of how risk assessment and the consistency concept can be employed can be seen from
 8 the introduction of general chapter 5.2.13 *Healthy flocks for the production of inactivated vaccines for*
 9 *veterinary use* which sets upstream quality requirements for the production of inactivated vaccines that
 10 provide guarantees with regard to contamination by extraneous agents making the test for specified
 11 extraneous agents in each final batch obsolete. In terms of live viral vaccines produced on SPF eggs,
 12 providing the SPF status is re-confirmed appropriately, the final product batch does not need to be
 13 tested. For live viral vaccines produced from cell lines demonstrated to be free of extraneous agents
 14 by risk assessment or testing the final product test for extraneous agents is unnecessary (refer to Annex
 15 II chapter 5.2.5).

16
 17 In the general and individual monograph points are included as follows:

18 19 *2-1. STARTING MATERIAL*

20
 21 This is focused on the quality of starting materials and the production process. This sub-section
 22 in the **general monograph** includes specific requirements for:

- 23 • the starting material;
- 24 • the substrate for production;
- 25 • the media used for the preparation of the seed lots and for production [the use of antibiotics
 26 during vaccine production is still allowed, provided it has been evaluated];
- 27 • the seed lots including propagation and controls (origin, identification, purity or extraneous agent
 28 tests);
- 29 • the inactivation process (inactivation kinetics, inactivating agents, testing for residual live virus
 30 or bacteria, detoxification).

31
 32 Regarding extraneous testing requirements reference is made to chapter 5.2.5, management of
 33 extraneous agents in IVMPs.

34
 35 Regarding the control of the inactivation, a first test must be performed on the bulk antigen
 36 immediately after the inactivation step (see section 2.3.2 of the general monograph).

37
 38 The conditions under which the second test for residual live virus/bacteria may be omitted for batch
 39 release are stated in the general monograph Vaccines for veterinary use (under section 3.10).

1 The **individual monographs** may provide further details such as:

- 2 • the production process: separate culture of the different vaccine strains, possibility to use
- 3 fractions of the antigen, to add an adjuvant, etc.;
- 4 • the quality of the substrate by reference to chapters *Cell cultures for the production of veterinary*
- 5 *vaccines (5.2.4)*, *SPF chicken flocks for vaccines (5.2.2)* and *Healthy chicken flocks for the*
- 6 *production of inactivated vaccines for veterinary use (5.2.13)*;
- 7 • the controls to be performed on the seed lots [i.e. *detection of extraneous viruses in IVMPs*
- 8 *(2.6.37)*];
- 9 • the method for testing of residual live virus/bacteria and/or detoxification of the antigen
- 10 harvest.

11 2-2. CHOICE OF VACCINE COMPOSITION AND CHOICE OF VACCINE STRAIN

12 This sub-section refers to safety and efficacy tests to be conducted during development of a vaccine,

13 as described in chapters 5.2.6. and 5.2.7.

14 To facilitate the reading of the general monograph, two sub-sections have been included: 2-2-1.

15 *Development studies on safety and efficacy* and 2-2-1-2. *Information for performing the safety and*

16 *efficacy studies*. These tests are usually carried out once in the lifetime of the vaccine. Therefore the

17 number of animals stated in the example protocols balance using minimum numbers of

18 animals against obtaining valid tests. When appropriate, they are based on VICH Guidelines,

19 unless otherwise justified. For example when fewer animals had been required before the

20 VICH guidelines came into force, this number was maintained.

21 Unless otherwise stated, test methods given for verification of these characteristics, and acceptance

22 limits where appropriate, are provided for information as examples of suitable methods and associated

23 suitable limits. Nevertheless, the developmental tests have to be conducted in such a way that

24 assurances are obtained that the product is of pharmacopeial quality.

25 Further explanations on the interactions between the different texts published in the European

26 Pharmacopoeia to establish the efficacy of vaccines are provided below (see section 5.

27 RELATIONSHIP BETWEEN GENERAL MONOGRAPHS AND CHAPTERS AND INDIVIDUAL

28 MONOGRAPHS of this guide).

29 *Note:* For a test conducted during development of a vaccine, the wording “to be recommended” is used

30 (instead of “recommended”). This is because at this stage, routes and method of administration, age of

31 animals, vaccination schedules are not fixed yet. Indeed it is the purpose of these tests to determine

32 these parameters.

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

- 34 • routes and methods of administration and categories of animals which are relevant to
- 35 conducting the developmental tests,
- 36 • use of antimicrobial preservatives,
- 37 • stability requirements – it is mentioned that results are expected from tests for virus
- 38 titrations, bacterial counts or potency, conducted on 3 batches at regular intervals until 3
- 39 months beyond the end of shelf-life. Results are also expected from tests for moisture
- 40 content, tests for the adjuvant and chemical tests, as appropriate (but not necessarily with the
- 41 same level of frequency of testing). It should be noted that although batches of products are
- 42 expected to be in conformity with all the requirements of the section Batch tests throughout
- 43 their shelf-life, for some requirements, such as inactivation, extraneous agents or sterility this
- 44 does not mean that the stability studies need to include repeat testing for these throughout the
- 45 proposed shelf-life. Details on how to use stability studies, what is expected for stability with
- 46
- 47
- 48
- 49
- 50
- 51
- 52

1 regard to intermediates and the definition of appropriate formulation and release parameters are
2 included.

- 3 • **Formulation** (section 2-2-4). For live vaccines, information on what is expected for the virus
4 titer or bacterial count at release has been added. Furthermore, requirements for inactivated
5 vaccines have been added.
6

7 In the **individual monographs**, information is provided on the conduct of developmental safety and
8 efficacy tests:
9

- 10 • **Safety.** The detailed requirements in chapter 5.2.6 have to be addressed. The individual
11 monograph may give technical details on some of the tests, in order to provide advice on what
12 is considered an appropriate protocol for the work. For live vaccines, for example, details are
13 usually provided for the conduct of the test for Increase in virulence.
14
- 15 • **Efficacy.** The detailed requirements in chapter 5.2.7 have to be addressed. Further explanation
16 is given in section 5. RELATIONSHIP BETWEEN GENERAL MONOGRAPHS AND
17 CHAPTERS AND INDIVIDUAL MONOGRAPHS of this guide.
18

19 These tests are conducted during development of the product and such tests are not usually described
20 in European Pharmacopoeia monographs. They are included in veterinary vaccine monographs
21 because there is a greater variability of antigens for veterinary vaccines compared to human vaccines,
22 which are much more standardised. There is also a bigger diversity of vaccines and a greater number
23 of manufacturers for veterinary vaccines compared to human vaccines.
24

25 As indicated in the monographs, attention must be given to the titre or potency of batches used in
26 the safety and efficacy/immunogenicity studies. When combined vaccines are being tested the
27 manufacturer may need to take particular steps to address the point including, for example, choosing
28 different batches for the tests to ensure that the component being tested meets the requirements.
29

30 2-3. PREPARATION OF THE VACCINE

31 This sub-section refers to the various methods of preparation of vaccines (propagation and harvest of
32 bacterial and viral antigens, inactivation, preparation of the final bulk and the final batch).
33

34 2-4. MANUFACTURER'S TESTS

35

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

40 This section contains a variety of types of tests, depending on the nature of the product. For example,
41 individual monographs for bacterial vaccines may have a test for bacterial endotoxin.
42

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

1
2 The Manufacturer's tests section of the **individual monographs** brings together the tests which are
3 product specific. There are generally no limits expressed as figures, because the manufacturer has to
4 establish these limits based on the values observed from batches of vaccine demonstrated as safe
5 and/or efficacious. The tests the most commonly listed in the **individual monographs**.
6

- 7 • Antigen content: determined to be within limits shown to allow preparation of satisfactory
8 vaccines. The formulation of the vaccine is based, whenever possible, on the antigen content
9 determined on the harvest before or after inactivation and/or downstream processing, if
10 applicable;
- 11 • Bacterial endotoxins: the maximum acceptable amount is that found for a batch of vaccine
12 shown satisfactory in safety tests;
- 13 • Batch potency test: alternative test to the Potency test that may be performed by the
14 manufacturer for routine testing for batch release (see below for details).
15

16 As with other points in the Production section, the manufacturer does not need to test batches of
17 antigen and/or final product with the tests described in this section. However, the tests proposed in the
18 Manufacturer's test sub-section are provided as examples of tests which can contribute to a suitably
19 sensitive testing regime to show that each batch of the product is of pharmacopoeial quality.
20 Whatever system of testing is adopted by the manufacturer on each batch of antigen and/or final
21 product, these must be such as to provide the required level of reassurance on the suitability of each
22 batch.
23

24 **Batch potency test:** It is explained in this sub-section of the general monograph that the test described
25 under Potency is not usually suitable for the routine testing of batches. Therefore an alternative test may
26 be performed by the manufacturer for routine testing for batch release. This test must provide
27 assurance that the batch would comply with the Potency test requirements. The model proposed is given
28 as an example of a satisfactory method. A validation by the manufacturer for the particular product is
29 necessary. The test used must be able to detect sub-potent vaccines.

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

32 It has to be noted that the *in vivo* method will remain in the monograph as long as all the products cannot
33 be assessed using *in vitro* methods only and as long as it is considered as the golden standard by the
34 scientific community.
35

36 For live vaccines, a test for virus titre or bacterial count is required by the relevant individual
37 monographs and the general monograph and it is expected that the point will be addressed through
38 setting a suitable acceptance criterion for this test. To this end:
39

- 40 • during the development studies the minimum acceptable viral titre or bacterial count must be
41 established, based on that in the batch(es) of vaccine used in the Potency test or other efficacy
42 studies,
- 43 • the loss observed during the stability studies should be added to this value to ensure that the
44 content will be not less than the minimum acceptable titre or count at the end of the shelf-
45 life,
- 46 • each batch must then be shown to contain, at release, not less than this calculated titre or count.
47

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

1 methods is recommended, provided that:

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

5
6 The potency depends on the immunogenicity of the vaccine antigen as well as the co-stimulatory,
7 inflammatory response induced by the adjuvant. In an *in vivo* test model both the immunogenicity and
8 the inflammatory induction will be measured simultaneously and therefore it is possible that any *in vitro*
9 replacement may involve more than one test to cover potency measurement such as a test for antigen
10 quantification and a test for adjuvant quantification and/or functionality.

11
12 In all cases, the tests provided are given as examples of the type of test that may be carried out; as
13 explained under 3.1 PHARMACOPOEIAL REQUIREMENTS of this guide, these examples are *per*
14 *se* not validated. The manufacturer has to develop a suitable test for use for batch release. The
15 method must be tightly specified. If a test in laboratory animals is necessary then specific details such
16 as a fixed dosage regimen and a fixed interval between vaccination and sampling must be included in
17 the description. An independent validation study is performed linked to an efficacy study to show
18 that the proposed method and acceptance criteria are suitable. It has to provide assurance that each
19 batch that passes the batch potency test would pass the Potency test specified in the monograph or,
20 when no individual monograph exists, is of acceptable efficacy. The test must be able to detect sub-
21 potent batches of vaccine.

22 23 3. BATCH TESTS

24
25 This is a section on tests that may be conducted by the manufacturer (or others) as part of the testing
26 conducted to show that each batch is of pharmacopoeial quality. These tests are designed to provide
27 part of the assurance that the batch would comply with the pharmacopoeial requirements.

28
29 Taking into account the quality systems in place, advances in scientific knowledge and understanding
30 of the products, manufacturing processes and their controls, the choice of tests to be performed may be
31 reconsidered when assessing compliance with Pharmacopoeia monographs, in accordance with the
32 General Notices. On a case-by-case basis, with the agreement of the competent authority, the choice
33 and necessity of certain final product tests may be reconsidered, where in-process tests give at least an
34 equal guarantee that the batch would comply if tested, or where alternative tests validated with respect
35 to the Pharmacopoeia method have been carried out. Chapter 5.2.5 Management of Extraneous Agents
36 in IVMPs, allows a coherent risk management strategy to the presence of extraneous agents across the
37 production process. This can reduce the overall number of tests performed during production and on
38 the final product by a process of risk reduction (e.g. sourcing of raw materials, manufacturing standards)
39 and risk identification thereby targeting testing to risk areas using fit for purpose tests.

40
41 This section contains a variety of types of tests, depending on the nature of the product.

42 It includes information on tests that should be conducted routinely and are applicable to a wide range
43 of vaccines (i.e. physical tests, chemical tests, pH and water).

44
45 **Identification** (section 3-1). In the interest of animal welfare, the vaccine identification test by
46 antibody induction in animals is not required for any inactivated vaccines, which allows the user to
47 identify the antigen(s) by any suitable methods, for example nucleic acid amplification techniques
48 (2.6.21). This allows manufacturers to replace animal tests with *in vitro* tests when appropriate, and
49 reinforces the idea that it may be combined with the batch potency test.

50
51 **Bacteria and fungi** (section 3–8). This title, also used in the related individual monographs, replaces

1 'Sterility'.
2

3 **Extraneous agents** (section 3–9). The requirement that the vaccine is free from extraneous agents
4 is stated in the general monograph. The risk management strategy described in Chapter 5.2.5 allows
5 this to be established by a combination of risk management and fit for purpose testing throughout
6 the production process and final product.
7

8 The tests are usually product specific. There are generally no limits expressed as figures, because
9 the manufacturer has to establish these limits based on the values observed from batches of vaccine
10 demonstrated as safe and/or efficacious.
11

12 The section in the **general monograph** includes points of guidance or qualification for the test for
13 free formaldehyde, for phenol, identification tests, test for sterility, tests for mycoplasmas extraneous
14 agents, and potency tests.
15

16 In the **individual monographs**, this section contains the tests and requirements that all batches of
17 products must comply with throughout their shelf-life. This means that any batch on the market, if
18 tested by an independent analyst, must comply with these requirements.
19

20 For the purpose of batch release by the manufacturer, the tests described do not need to be carried
21 out on each batch where in-process or other final product tests give an equal or better guarantee that
22 the batch would comply or where alternative tests validated with respect to the Pharmacopoeia method
23 have been carried out. In addition, the manufacturer's release specification or final product specification
24 for a particular product may be more stringent than specified in the monograph. This could happen for
25 example, to accommodate losses occurring during the shelf-life or to reflect the minimum that has
26 been shown efficacious or to ensure batch consistency.
27

28 With few exceptions, the individual monographs have a section entitled Potency. This usually refers
29 to conducting the test described under Immunogenicity. The Potency test is included in the monograph
30 as a test that may be conducted on any batch, and therefore, only one recommended route of
31 administration is used for this purpose.
32

33 4. STORAGE 34

35 General requirements are given in the general monograph *Vaccines for veterinary use (0062)*. A
36 Storage section is included in an individual monograph only if it is specific for the vaccine. Unless
37 otherwise indicated in an individual monograph, the storage of vaccines is expected to conform
38 to that described in the general monograph. If other storage conditions than those described in the
39 general monograph apply, they are indicated in the individual monograph.
40

41 5. LABELLING

42 The appropriate requirements of the labelling described in the general monograph apply to all vaccines
43 for veterinary use. In some cases, additional information may be necessary for a particular vaccine
44 for example where additional information is needed to allow the application of a specific test. This
45 information is then included in the individual monograph, in the Labelling section, and this is
46 supplementary to the requirements of the general monograph.
47

48 Status of labelling is defined in the General notices: "*In general, labelling of medicines is subject*
49 *to supranational and national regulation and to international agreements. The statements under the*
50 *heading Labelling are not therefore comprehensive and, moreover, for the purposes of the*
51 *Pharmacopoeia only those statements that are necessary to demonstrate compliance or non-*

1 *compliance with the monograph are mandatory. Any other labelling statements are included as*
2 *recommendations. When the term “label” is used in the Pharmacopoeia, the labelling statements may*
3 *appear on the container, the package, a leaflet accompanying the package, or a certificate of analysis*
4 *accompanying the article, as decided by the competent authority.”*
5

6 **4.2. SUMMARY OF THE CONTENT OF THE GENERAL MONOGRAPH *IMMUNOSERA*** 7 ***FOR VETERINARY USE*** 8

9 The general monograph *Immunosera for veterinary use (0030)* contains, in a general but detailed
10 way, the requirements and points that have to be addressed by manufacturers for the preparation and
11 testing of batches of all immunosera. Unlike veterinary vaccines, the bulk of the requirements
12 including the tests to be conducted on batches of products are contained in the general monograph
13 and there are only a small number of individual monographs with limited additional information.
14 Although the contents are different, the information provided for sections such as Definition, Storage
15 and Labelling can be interpreted in a similar manner to the equivalent texts for the general monograph
16 *Vaccines for veterinary use (0062)*.
17

18 The pharmacopoeial requirements for immunosera and the tests to be carried out are those described
19 in the General monograph *Immunosera for veterinary use (0030)* and those described in the
20 relevant individual monographs where one exists.
21

22 The Production section describes both requirements and specific information on the points to be
23 addressed for the manufacture of immunosera. This includes information on the source animal selection
24 and their testing and monitoring for freedom from extraneous agents, immunising the source animals
25 and preparation of the final product.
26

27 General information on the developmental safety and efficacy tests that should be conducted to show
28 the suitability of the product composition are contained in the general chapters *Evaluation of safety*
29 *of veterinary vaccines and immunosera (5.2.6)* and *Evaluation of efficacy of veterinary vaccines and*
30 *immunosera (5.2.7)* and some limited further information is included in the individual monographs,
31 including minimum potency test requirements.
32

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/immunosera 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/immunosera). 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/immunosera, 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

1 expected in studies on the efficacy of products of the particular type.

2
3 Taking into consideration the information given in the general and individual monographs, in the
4 general chapter 5.2.7 and in the General Notices, it becomes clear that:

- 5
- 6 • the efficacy of the vaccine has to be studied in accordance with the requirements of chapter
- 7 5.2.7;
- 8 • a test for Immunogenicity is required as part of the studies to establish the efficacy of the
- 9 vaccine;
- 10 • the test method given for studying the immunogenicity of the vaccine and showing it is in
- 11 conformity with the specified acceptance limits, where appropriate, are provided for information
- 12 as examples of suitable methods and associated suitable limits. Subject to approval by the
- 13 Competent Authority, other test methods may be used without validation against the method
- 14 shown in the monograph (see General Notices 1.4). The acceptance criteria of the example
- 15 tests mentioned in the monographs are indicative of the minimum Pharmacopoeial standards
- 16 expected of the results of alternative tests for the products within the scope of that individual
- 17 monograph;
- 18 • to be in conformity with the legal requirements, any batch of product on the market must be
- 19 in compliance with the requirements of the Potency test in the Batch test section of the
- 20 individual monograph, if tested.

21 6. 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	
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
2.2.1. Safety A test is carried out for each route and method of	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
2.2.3. Immunogenicity A test is carried out for each route and method of	Mandatory

Section	Status
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
2.4. 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 necessarily 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.
3.7. Inactivation – Residual live virus/bacteria (inactivated vaccines) Virus titre/Live bacteria (live vaccines)	Must comply if tested – can be tested upstream. This test may be omitted for batch release, as stated in the monograph <i>Vaccines for veterinary use (0062)</i> .
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.

The table summarises the status but for full details, the different sections of the present guide must be consulted.

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The Council of Europe is the continent's leading human rights organisation. It comprises 47 member states, including all 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.