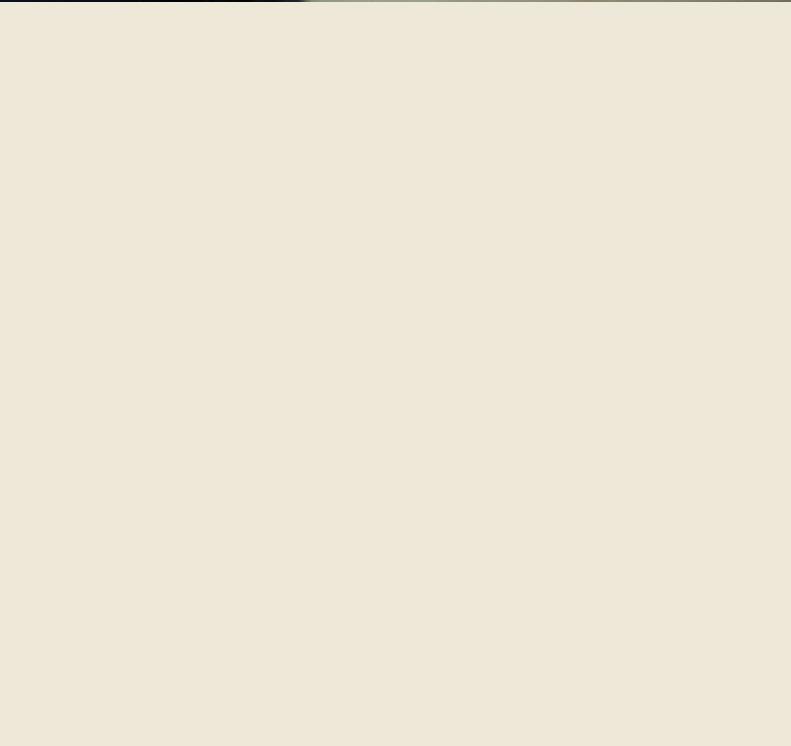




Guide for the elaboration
and use of monographs
**ON VACCINES AND
IMMUNOSERA FOR
HUMAN USE**



European Pharmacopoeia

EDQM

Edition 2019

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Guide for the elaboration and use of monographs on vaccines and immunosera for human use

1. Purpose of the guide

This document is intended to provide guidance to authors, contributors and users of European Pharmacopoeia (Ph. Eur.) on the elaboration of monographs for vaccines and other immunological human medicinal products (animal immunosera for human use). This applies in particular to:

- Group of Experts 15 (Vaccines and immunosera for human use);
- Authorities responsible for granting marketing authorisations for vaccines and immunosera for human use;
- Official Medicines Control Laboratories (OMCLs);
- Manufacturers of vaccines and immunosera for human use;
- Bodies that procure vaccines and immunosera for health services;
- Public and private analytical laboratories working for one of the above;
- The Ph. Eur. Secretariat and 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 Ph. Eur. 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 Ph. Eur. alone is authoritative.

Immunological products for human use prepared with human plasma (i.e. immunoglobulins) are not covered by the present guide.

3. General information

3.1. Pharmacopoeial requirements

Monographs and general chapters of the Ph. Eur. must be interpreted with reference to the *General Notices*. All users of the Ph. Eur. must be familiar with these notices.

Statements in monographs are mandatory requirements unless otherwise stated:

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. 9th Edition)

As regards demonstration of compliance with the Ph. Eur., the *General Notices* state that:

- (1) An article [that is the subject of a monograph] is not of Pharmacopoeia quality unless it complies with all the requirements stated in the monograph. This does not imply that performance of all the tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality on the basis of its design, together with its control strategy and data derived, for example, from validation studies of the manufacturing process.
- (2) An enhanced approach to quality control could utilise process analytical technology (PAT) and/or real-time release testing (including parametric release) strategies as alternatives to end-product testing alone.¹ Real-time release testing in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia. (Ph. Eur. 9th Edition)

As regards the use of alternative methods of analysis, the *General Notices* state that:

The tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. In the event of doubt or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative. (Ph. Eur. 9th Edition).

Special provisions apply to the section Choice of vaccine strain:

The production section of a monograph may define the characteristics of a vaccine strain or vaccine composition. Unless otherwise stated, test methods given for verification of these characteristics are provided for information as examples of suitable methods. Subject to approval by the competent authority, other test methods may be used without validation against the method shown in the monograph. (Ph. Eur. 9th Edition)

3.2. Alternative methods

The test methods prescribed in monographs and general chapters are the reference methods on which the quality standards are based. As indicated in 3.1. Pharmacopoeial requirements, in accordance with the *General Notices* and subject to approval by the competent authority, alternative validated methods of analysis may be used.

¹ Note: It should be noted that for vaccines, release testing is performed at several stages of the manufacturing process (i.e., on intermediates), and is not limited to the finished product. PAT and/or real time release testing would nevertheless remain alternatives to the testing strategies described in vaccine monographs.

In certain cases, a method description may be given as an 'example' of method that has been found suitable. The term 'example' means that the test method may be used as such, or, subject to approval by the competent authority, replaced by a suitable validated procedure without having to demonstrate its equivalence to the 'example' method.

3.2.1. Use of animals

In accordance with the *European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (1986)*,²

the Ph. Eur. Commission is committed to the reduction of animal usage wherever possible in pharmacopoeial testing, and encourages those associated with its work to seek alternative procedures.

An animal test is included in a monograph only if it has clearly been demonstrated that it is necessary to achieve satisfactory control for pharmaceutical purposes.

According to the provisions of the Convention, the tests described in the Ph. Eur. monographs must be carried out in such a way as to use the minimum number of animals to obtain a valid result and to cause the least pain, suffering, distress or lasting harm. Humane endpoints must be used wherever possible for all tests, even if this requirement is not referred to in a specific monograph, since references to humane endpoints are included as examples only where practical advice can be given (see general monograph *Vaccines for human use*).

Additionally, as stated in the *General Notices*, when demonstrating compliance with the Ph. Eur., manufacturers may consider establishing additional systems to monitor consistency of production. With the agreement of the competent authority, the choice of tests performed to assess compliance with the Ph. Eur. when animal tests are prescribed is established in such a way that animal usage is minimised as much as possible.

An alternative method may offer improvements in terms of animal welfare, in line with the principles of Replacement, Reduction and Refinement of animals used in testing. However, the introduction of alternative *in vitro* methods to replace *in vivo* methods has often been prevented due to the characteristics of the latter rather than the suitability of the former, and demonstration of equivalence may not only be problematic, but also of limited relevance. With these difficulties in mind, general chapter 5.2.14 *Substitution of in vivo method(s) by in vitro methods for the quality control of vaccines* was developed to facilitate the transition from *in vivo* to *in vitro* methods.

General chapter 5.2.14 provides guidance on how to validate alternative *in vitro* methods, where a typical head-to-head comparison to an existing *in vivo* method is not appropriate for reasons unrelated to the suitability of the *in vitro* method. The chapter envisages the possibility that the validity of an alternative *in vitro* method can be demonstrated without such head-to-head comparison (concept of 'substitution') and discusses alternative approaches for the *in vivo* method replacement. A key element of the chapter is its focus on the scientific rationale behind the *in vitro* methods, relative to what is provided with current *in vivo* methods. The chapter provides examples of methodological frameworks for the substitution of new *in vitro* methods for *in vivo* measures of vaccine potency and safety, which includes the detection of viral extraneous agents in vaccines.

² European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes. European Treaty series No. 123. Council of Europe (1986).

3.3. General chapters

Certain general terms commonly used in monographs on vaccines for human use are defined in the general chapter 5.2.1. *Terminology used in monographs on vaccines.*

General methods	Chapter number	Applicable to	
		vaccines for human use	immunosera for human use
Assays			
Aluminium in adsorbed vaccines	2.5.13	×	
Calcium in adsorbed vaccines	2.5.14	×	
Phenol in immunosera and vaccines	2.5.15	×	×
Protein in polysaccharide vaccines	2.5.16	×	
Nucleic acids in polysaccharide vaccines	2.5.17	×	
Phosphorus in polysaccharide vaccines	2.5.18	×	
O-acetyl in polysaccharide vaccines	2.5.19	×	
Hexosamines in polysaccharide vaccines	2.5.20	×	
Methylpentoses in polysaccharide vaccines	2.5.21	×	
Uronic acids in polysaccharide vaccines	2.5.22	×	
Sialic acid in polysaccharide vaccines	2.5.23	×	
Ribose in polysaccharide vaccines	2.5.31	×	
Biological tests			
Tests for extraneous agents in viral vaccines for human use	2.6.16	×	
Test for neurovirulence of live virus vaccines	2.6.18	×	
Residual pertussis toxin	2.6.33	×	
Biological assays			
Assay of diphtheria vaccine (adsorbed)	2.7.6	×	
Assay of pertussis vaccine (whole cell)	2.7.7	×	
Assay of tetanus vaccine (adsorbed)	2.7.8	×	
Assay of hepatitis A vaccine	2.7.14	×	
Assay of hepatitis B vaccine (rDNA)	2.7.15	×	
Assay of pertussis vaccine (acellular)	2.7.16	×	
In vivo assay of poliomyelitis vaccine (inactivated)	2.7.20	×	
Flocculation value (Lf) of diphtheria and tetanus toxins and toxoids (Ramon assay)	2.7.27	×	
Immunonephelometry for vaccine component assay	2.7.35	×	

General texts	Chapter number	Applicable to	
		vaccines for human use	immunosera for human use
Chicken flocks free from specified pathogens for the production and quality control of vaccines	5.2.2	×	
Cell substrates for the production of vaccines for human use	5.2.3	×	
Carrier proteins for the production of conjugated polysaccharide vaccines for human use	5.2.11	×	
Substitution of <i>in vivo</i> methods by <i>in vitro</i> methods for the quality control of vaccines	5.2.14	×	×

The general chapters in the above table are published under the heading 2.5. *Assays*, 2.6. *Biological tests*, 2.7. *Biological assays* and 5.2. *General texts on biological products* and apply whenever they are

given as a reference in a monograph for a vaccine/immunoserum for human use. The list refers to texts that are applicable exclusively to vaccines and/or immunosera for human use.

3.4. General monographs

The following general monographs apply to vaccines and immunosera for human use, respectively:

- *Vaccines for human use (0153)*;
- *Immunosera for human use, animal (0084)*.

These monographs are published under the heading General monographs in the Ph. Eur.

In certain cases, the provisions in other general monographs also apply, such as those in the monographs listed below, unless such reference is made in the monograph related to a specific vaccine/immunoserum:

- *Recombinant DNA technology, products of (0784)*
- *Products with risk of transmitting agents of animal spongiform encephalopathies (1483)*

3.5. Individual monographs

Individual monographs on vaccines for human use and on immunosera for human use are published, in alphabetical order by title, separately under *Vaccines for human use* or *Immunosera for human use* in the Ph. Eur.

3.6. Process for elaboration and update of monographs and general chapters

3.6.1. Inclusion of a new monograph or new general chapter in the Ph. Eur.

Proposals to add a new monograph or new general chapter to the work programme of the Ph. Eur. can be made by:

- the Chair of the Ph. Eur. Commission;
- a delegation to the Ph. Eur. Commission;
- the Chair of Group 15 on behalf of the Group of Experts;
- the Secretariat of the Ph. Eur., for example on the basis of information and data provided via the EDQM *Helpdesk*³ by a manufacturer or by a user of the Ph. Eur.

The Ph. Eur. Commission takes a decision to accept or refuse the proposal for a new monograph or new general chapter. If accepted, the elaboration of the new monograph or general chapter is added to the work programme of the Group of Experts (see the *Rules of procedure of the European Pharmacopoeia Commission*⁴).

For many classes of medicinal substances or products, monographs are usually (but not always) only included in the Ph. Eur. when the medicinal substance or product is produced by more than one manufacturer. This limitation has not been applied to vaccines since it has been found that there can be a need for an official Ph. Eur. standard even when there is only one producer. The system of control authority batch release for vaccines has increased this need, particularly with the advent of mutual recognition of this system within the EU. The existence of an official standard facilitates this mutual recognition by providing a mutually accepted public statement of the basis of control authority batch release.

³ www.edqm.eu/hd.

⁴ Rules of Procedure of the European Pharmacopoeia Commission (document reference: PA/PH/SG (16) 85 COM). Council of Europe, European Directorate for the Quality of Medicines & HealthCare (2016), www.edqm.eu/en/european-pharmacopoeia-commission.

Monographs on vaccines for human use are elaborated either for a single type of vaccine or for a combination. In the latter case, the combined vaccine must also comply with the specific monographs for each valence of the vaccine.

The quality standards attained by vaccines that are already on the market are taken into consideration during the elaboration of a new monograph or general chapter. Consequently, where there is sufficient information demonstrating that the product is of pharmacopoeial quality, it will not be necessary to retest these vaccines to show compliance with the pharmacopoeial requirements when the monograph or general chapter is finalised and published in the Ph. Eur.

Once the new monograph or general chapter is drafted, it is published in *Pharmeuropa*⁵ for public enquiry. Interested parties have 3 months to send their comments to their National Pharmacopoeial Authority (NPA) which collates all the comments from that country. NPAs then have 2 months to send the compiled comments to the Secretariat of the Ph. Eur. via the *EDQM Document Review Tool (DRT)*. Manufacturers outside Europe and pan-European organisations have 3 months to send their comments to the Secretariat via the *Helpdesk*.

The Secretariat consolidates the submitted comments which are then examined by Group 15 following the end of the consultation period.

After review of these comments, if there are no major changes made to the monograph or general chapter published for comment in *Pharmeuropa*, the monograph or general chapter is proposed for adoption at the next Ph. Eur. Commission session. If a major change is made to the monograph or general chapter, it is again published for public enquiry in *Pharmeuropa*.

When the monograph or general chapter is adopted, it is published in the Ph. Eur. 6 months after the Commission session at which it was adopted, and implemented 6 months later. If the monograph or general chapter is not adopted by the Ph. Eur. Commission, either it returns to the Group for further elaboration or no monograph or general chapter on this particular product or method is published in the Ph. Eur.

3.6.2. Revision of monographs and general chapters

Proposals to revise a text can be made by:

- the Chair of the Ph. Eur. Commission;
- a delegation to the Ph. Eur. Commission;
- the Chair of Group 15 on behalf of Group of Experts;
- the Secretariat of the Ph. Eur., for example on the basis of information and data provided via the EDQM Helpdesk by a manufacturer or by a user of the Ph. Eur.

The Ph. Eur. Commission refers requests for revision to the relevant Group of Experts (see the *Rules of procedure of the European Pharmacopoeia Commission*).

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

During the revision of a monograph or general chapter, the standards attained by vaccines that are already on the market are taken into consideration, and it is expected that in most situations these vaccines will not need to be retested to show compliance with any new requirement when the revised monograph or general chapter is published.

Once the monograph or general chapter is revised, it is published in *Pharmeuropa* for public enquiry. Interested parties have 3 months to submit their comments to their NPA, which

5 <http://pharmeuropa.edqm.eu/TextsForComment/>.

consolidates all the comments from that country. NPAs then have 2 months to send the compiled comments to the Secretariat of the Ph. Eur. via the *EDQM Document Review Tool (DRT)*. Manufacturers outside Europe and pan-European organisations have 3 months to send their comments to the Secretariat of the Ph. Eur. via the *Helpdesk*.

The Secretariat consolidates the submitted comments which are then examined by Group 15 following the end of the consultation period.

After review of these comments, if there are no major changes to be made to the monograph or general chapter published for comment in *Pharmeuropa*, it is proposed for adoption at the next Ph. Eur. Commission session. If a major change is made to the monograph or general chapter, it is again published for public enquiry in *Pharmeuropa*.

When the revised monograph or general chapter is adopted, it is published in the Ph. Eur. 6 months after the Commission session at which it was adopted, and implemented 6 months later. If the revised monograph or general chapter is not adopted by the Ph. Eur. Commission, it either returns to the Group for further elaboration or remains as previously published.

4. Structure and content of monographs on vaccines for human use

4.1. General principles

The pharmacopoeial requirements for vaccines and tests to be carried out are described in the general monograph *Vaccines for Human Use (0153)* and in the relevant individual monograph, where one exists.

The provisions of the general monograph apply to all vaccines for human use, including those for which there is no individual monograph. The general monograph prescribes essential requirements which supplement and expand on requirements contained in the monographs for specific vaccines. The authors and users of individual vaccine monographs must be familiar with the contents of the general monograph in order to be able to draft or use the individual monographs correctly. The requirements given in the general monograph are usually not repeated in the individual monographs, i.e., reference is not made to the general monograph in the individual vaccine monographs, unless this is necessary to avoid ambiguity (e.g. *BCG for immunotherapy (1929)* which is not a vaccine but where the general monograph on *Vaccines for human use (0153)* applies).

The individual monographs must be used and applied, taking account of the explanations, guidance and requirements given in the *General Notices* and general monograph mentioned above.

It is expected that the tests and assay methods used routinely are implemented appropriately (including suitability check) by the users, in accordance with accepted procedures, for example those in the *Technical Guide for the Elaboration of Monographs (2015)* of the Ph. Eur.

For animal tests, ethical considerations may require that validation is limited to what is necessary for the laboratory to have reasonable assurance that the assay performs in a statistically controlled and qualified manner.

4.2. Monograph sections

The following information is provided as background and to aid interpretation of general and individual monographs on human vaccines.

The various sections contained in the monographs are mandatory, with the exception of the Storage section and, for some products, the Labelling section. Statements provided for information are identified by their content and drafting style. See also the *General Notices*.

4.2.1. Definition

This section defines the scope of the monograph and its applicability to products on the market. In the individual monographs, the composition of the product is briefly stated. The monograph sets the official standard for all products covered by this definition.

If a vaccine of a new type is developed against the same disease as a vaccine already covered by an individual monograph, this may lead to revision of the monograph or elaboration of a new one. If a product is not covered by the scope of an individual monograph, the monograph is not applicable to this product. Only the general monograph *Vaccines for human use* applies in this case.

4.2.2. Production

This section describes essential features of the manufacturing process, prior to and including batch release. It generally follows the chronological order of the production of a vaccine.

This section is primarily addressed to manufacturers.

It contains information on points to be addressed for production of the vaccine, the type of tests expected to be conducted during development of the product, tests that may be conducted routinely on intermediates, and tests that can be conducted on each batch by manufacturers, as part of the tests conducted to provide assurance that the product is of pharmacopoeial quality.

4.2.2.1. General provisions

This section describes requirements and other aspects of the manufacturing process, which may relate, for example, to source materials, to the manufacturing process itself and to its validation and control, as well as in-process requirements which enable the consistency of the manufacturing process to be demonstrated.

Reference preparations. In individual monographs, this paragraph defines the reference preparation or preparations to be used for the control of the vaccine.

4.2.2.2. Substrate for propagation

Culture media for bacterial vaccines or substrates for virus propagation. The requirements are described in the general monograph. Any additional requirements are given in the individual monograph.

Cell substrates. General chapter 5.2.3 gives the requirements for cell lines. Requirements for primary cells (and other cells when a cell bank system is not used) are given in the individual monograph.

Eggs from specified-pathogen-free flocks (SPF). Chapter 5.2.2 gives the requirements for such eggs.

4.2.2.3. Seed lots

The requirements for a seed lot to be used for propagation are given in this section: identification, test for extraneous agents for viral vaccines, test for contaminants for bacterial vaccines, possibly test for virulence, etc.

4.2.2.4. *Propagation and harvest of the virus or Culture and harvest of bacteria*

The purity of the harvest is checked before purification. Testing for contaminants may also be required at this stage.

In the case of viral vaccines, a requirement for control cells from the production cell culture to comply with an identification test and with the requirements for extraneous agents (2.6.16) is included.

4.2.2.5. *Purification and inactivation (inactivated vaccines)*

The concentration of micro-organisms or the antigen content is checked and taken into account when there is inactivation.

If production involves continuous cell lines (this is the case for certain viral vaccines), this section includes a requirement that the purification process should be demonstrated to consistently reduce the host cell DNA content and its size, as appropriate. If a limit for residual DNA content is mentioned in an individual monograph, it applies to the vaccine concerned. In accordance with chapter 5.2.3, an acceptable upper limit for each vaccine produced in continuous cell lines should be established based on a risk-based approach.

For inactivated vaccines, the absence of residual infectious virus is verified through the evaluation of the consistency of the inactivation process, as well as testing during the course, and at the final stage, of inactivation.

4.2.2.6. *Final bulk vaccines*

If an antimicrobial preservative is added to a vaccine, a requirement to determine its content is included in this section.

A test for sterility/bacterial and fungal contamination (2.6.7) is described in this section. The term 'bacterial and fungal contamination' is used for live vaccines (these cannot be sterile) and for vaccines containing micro-organisms at a given stage of their production (e.g. before inactivation) whereas the term 'sterility' is used for inactivated vaccines (therefore free from live micro-organisms). In addition, the test for bacterial and fungal contamination is also used in certain cases to verify the absence of contamination during production.

Only a final bulk that complies with the requirements of this section may be used in the preparation of the final lot. A statement to this effect is included under *Final bulk (vaccine)*.

4.2.2.7. *Final lot*

The term 'final lot' applies to the final bulk vaccine aseptically distributed into sterile tamper-proof containers.

Only a final lot that complies with each of the tests described under Identification, Tests and Assay may be released. Certain tests in the individual monograph may be omitted on the final lot if they have been carried out with satisfactory results upstream (e.g., the tests for specific toxicity, residual live virus, antimicrobial preservatives, free formaldehyde, ovalbumin, bovine serum albumin, total protein, pyrogens, the assay, etc.). A statement to this effect is then included under *Final lot*.

For live vaccines, a test for thermal stability may be required on the final lot to monitor the lot-to-lot consistency in heat-sensitivity of viral/bacterial particles in the product, as per the general monograph *Vaccines for human use (0153)*.

4.2.3. Identification

This section describes how to identify the product. For identification purposes, the main characteristic of the product is usually checked by appropriate methods such as the assay method which can also serve to identify the vaccine, or recognition of the antigens present in the vaccine by specific antibodies, etc.

4.2.4. Tests

A series of tests to be carried out on each batch (e.g., the content of antimicrobial preservatives, aluminium, free formaldehyde, bovine serum albumin, ovalbumin, water, a test for inactivation if applicable, for toxicity, sterility, pyrogens or bacterial endotoxins) is prescribed and limits are given, unless otherwise justified. The product must comply with these requirements throughout its shelf-life.

4.2.5. Assay or Live virus/bacteria concentration or (Poly)saccharide content

A potency test is included in each individual monograph, but it may sometimes be described in a separate chapter which is referred to in the individual monograph.

The aim of this test is to determine the capacity of a vaccine to induce the formation of specific antibodies against the pathogen, or to titrate the infective virus/live bacteria/antibodies against toxoids, or to determine the content of an antigen which is relevant to measure the efficacy of the vaccine, or to assess the protection of a vaccine, etc.

The expiry date can be calculated from the beginning of the assay or from the beginning of the first assay for a combined vaccine or from the date of filling.

4.2.6. Storage

This section is given for information. It gives information on storage conditions. The storage conditions are indicated by the manufacturer. They are validated by stability testing that shows that the vaccine will comply throughout the period of validity.

Unless otherwise indicated in an individual monograph, the storage of vaccines is expected to conform to that described in the general monograph *Vaccines for human use (0153)*.

4.2.7. Labelling

The requirements of the labelling statements described in the general monograph *Vaccines for human use (0153)* apply to all vaccines for human use. In some cases, additional information may be required for a particular vaccine. This information is included in the Labelling section of the individual monograph and is supplementary to the requirements of the general monograph.

The status of the labelling is defined in the *General Notices*:

In general, labelling of medicines is subject to supranational and national regulations and to international agreements. The statements under the heading *Labelling* are not therefore comprehensive and, moreover, for the purposes of the Pharmacopoeia only those statements that are necessary to demonstrate compliance or non-compliance with the monograph are mandatory. Any other labelling statements are included as recommendations. When the term 'label' is used in the Pharmacopoeia, the labelling statements may appear on the container, the package, a leaflet accompanying the package, or a certificate of analysis accompanying the article, as decided by the competent authority. (Ph. Eur. 9th Edition)

5. Structure and content of the general monograph on animal immunosera for human use

The provisions of the general monograph *Immunosera for human use, animal (0084)* apply to all animal immunosera for human use, including those for which there is no individual monograph.

The general monograph provides a detailed overview of the requirements and points to be addressed by manufacturers for the preparation and testing of batches of all immunosera. Unlike vaccines for human use, the majority of the requirements, including the tests to be conducted on batches of products, are described in the general monograph and there are only a small number of individual monographs with limited additional information, mostly about the potency assay.

Although the contents are different, the information provided for sections such as Definition, Storage and Labelling can be interpreted in a similar manner in the general monographs *Immunosera for human use, animal (0084)* and *Vaccines for human use (0153)*.

The pharmacopoeial requirements for immunosera and the tests to be carried out are those described in the general monograph *Immunosera for human use, animal (0084)* and those described in the relevant individual monograph where one exists.

5.1. Definition

This section defines the scope of the general monograph.

5.2. Production

General provisions

This section describes requirements and other aspects of the manufacturing process, which may relate, for example, to source materials, to the manufacturing process itself and to its validation and control, as well as to in-process requirements that are common to all immunosera for human use and which enable the consistency of the manufacturing process to be demonstrated.

Animals

This section describes requirements for the selection, housing, feeding, sanitary control, and monitoring of animals used for the production of immunosera.

Conditions for use of antibiotics or vaccines are also described.

Immunisation

This section describes the preparation of the antigens used for the immunisation of animals, and the immunisation process.

Collection of blood or plasma

Requirements for the collection of blood from immunised animals (premises, collection session) are described in this section.

Tests to be carried out on the collected plasma or sera prior to purification are given: test for contaminating viruses, potency, protein content.

Purification and viral inactivation

This section indicates some of the chemical or physical methods which can be used to purify the immunoglobulins and approaches to avoid contamination of the product, the formation

of protein aggregates and the generation of additional components that may compromise the quality and safety.

Only an intermediate product that complies with the requirement for purity of the general monograph may be used in the preparation of the final bulk.

Final bulk

In accordance with the general monograph, if an antimicrobial preservative is added in the final bulk, its content should be determined.

A test for sterility (2.6.7) is described in this section.

Only a final bulk that complies with the requirements of this section may be used in the preparation of the final lot.

Final lot

The term 'final lot' applies to the final bulk product aseptically distributed into sterile tamper-proof containers.

Only a final lot that complies with each of the tests described under Identification, Tests (where applicable), and Assay/Potency may be released for use. The general monograph allows that certain tests may be omitted if they have been carried out with satisfactory results on the final bulk (tests for osmolality, protein content, molecular-size distribution, antimicrobial preservative, stabiliser, purity, foreign proteins and albumin).

5.3. Identification

This section describes how to identify the immunoserum. The tests given in the Identification section are not designed to give a full confirmation of the chemical structure or composition of the product; they are intended to give confirmation, with an acceptable degree of assurance that the product conforms to the description on the label.

5.4. Characters

The statements under this section are not to be interpreted in a strict sense and are not requirements.

5.5. Tests

A series of tests to be carried out on each batch of the final lot (e.g., content of antimicrobial preservatives, albumin, stabiliser, phenol, water, the determination of molecular-size distribution, the test for sterility, pyrogens, etc.) is prescribed and limits are given, unless otherwise justified. The product must comply with these requirements throughout its shelf-life.

5.6. Assay

Where appropriate, requirements for carrying out the assay are described in the individual monograph.

5.7. Storage

Unless otherwise indicated in an individual monograph, the storage of immunosera is expected to conform to that described in the general monograph *Immunosera for human use, animal (0084)*.

5.8. Labelling

The labelling statements described in the general monograph *Immunosera for human use, animal (0084)* apply to all immunosera for human use. Where appropriate, additional information may be required for a particular immunoserum. This information is included in the Labelling section of the individual monograph and is supplementary to the requirements of the general monograph.

The status of the labelling is defined in the *General Notices*:

In general, labelling of medicines is subject to supranational and national regulation and to international agreements. The statements under the heading *Labelling* are not therefore comprehensive and, moreover, for the purposes of the Pharmacopoeia only those statements that are necessary to demonstrate compliance or non-compliance with the monograph are mandatory. Any other labelling statements are included as recommendations. When the term 'label' is used in the Pharmacopoeia, the labelling statements may appear on the container, the package, a leaflet accompanying the package, or a certificate of analysis accompanying the article, as decided by the competent authority. (Ph. Eur. 9th Edition)

6. Style guide for the elaboration of individual monographs on vaccines for human use

6.1. Standardised text for drafting monographs on vaccines for human use

The following section provides the main examples of the structure and the phrases and terms that should be used by rapporteurs when drafting monographs on vaccines for human use. Examples are given for monographs for different types of products but which are drafted to suit the majority of the products of that type (e.g. live viral vaccines). The standard layout given in these examples should be used as far as possible when drafting a monograph. It is, however, accepted and expected that, in some cases, there will be reasons for adopting a different approach or adding sections to reflect requirements that are different from the norm and which reflect the particular characteristics of a product type.

6.2. Title of individual monographs

Preferred format: Disease name + 'vaccine' + (type) (live, inactivated, adsorbed, virosome, etc.) + (route of administration [if not parenteral]) (oral, nasal, etc.)

The term 'rDNA' is added in brackets where the vaccine antigen(s) is (are) manufactured by rDNA technology. Likewise, the phrase 'prepared in cell cultures' is added where the vaccine viral strain(s) is (are) grown in cell cultures.

Examples: *Measles vaccine (live)*; *Tetanus vaccine (adsorbed)*; *Influenza vaccine (surface-antigen, inactivated)*; *Influenza vaccine (surface antigen, inactivated, prepared in cell culture)*; *Rotavirus vaccine (live, oral)*.

Note: the preferred format above is not always suitable. Vaccines against *Neisseria meningitidis* are not referred to as meningitis vaccine since there are several causal agents of meningitis. In such cases, the title specifies the name of the micro-organism. For example, polysaccharide and conjugate vaccines are described as such in the title.

Polysaccharide-based vaccines

- Non-conjugate vaccines
 - *Meningococcal polysaccharide vaccine*
 - *Pneumococcal polysaccharide vaccine*
 - *Typhoid polysaccharide vaccine*
- Conjugate vaccines
 - *Haemophilus type b conjugate vaccine*
 - *Meningococcal group C conjugate vaccine*
 - *Pneumococcal polysaccharide conjugate vaccine (adsorbed)*

Viral vaccines

- Live vaccines
 - *Measles vaccine (live)*
 - *Mumps vaccine (live)*
 - *Rubella vaccine (live)*
 - *Varicella vaccine (live)*
 - *Poliomyelitis vaccine (oral)*
 - *Yellow fever vaccine (live)*
- Inactivated vaccines
 - *Hepatitis A (inactivated)*
 - *Poliomyelitis vaccine (inactivated)*
 - *Tick-borne encephalitis vaccine (inactivated)*
- Component-based vaccines
 - *Hepatitis B vaccine (rDNA)*
 - *Human Papillomavirus vaccine (rDNA)*

Bacterial vaccines

- Live vaccines
 - *Typhoid vaccine (live, oral, strain, Ty21a)*
 - *BCG vaccine, freeze-dried*
- Inactivated vaccines
 - *Cholera vaccine (inactivated, oral)*
- Toxoid vaccines (and other component-based vaccines)
 - *Diphtheria vaccine (adsorbed), Tetanus vaccine (adsorbed), Pertussis vaccine (acellular, component adsorbed)*

6.3. Definition

This section defines the scope of the monograph. The composition of the product is briefly stated.

6.4. Production

The general monograph *Vaccines for human use (0153)* contains the following sub-chapters (listed as seen in the general monograph):

- General provisions
- Substrates for propagation
- Seed lots/cell banks
- Culture media
- Propagation and harvest
- Control cells
- Control eggs
- Purification
- Inactivation
- Carrier proteins
- Test for sterility of intermediates prior to final bulk
- Stability of intermediates
- Final bulk, including various elements of the formulation of the vaccine such as possible addition of adjuvants and anti-microbial preservatives (for antimicrobial preservatives, the amount is not less than 85 per cent and not greater than 115 per cent of the intended amount). The expected concentration is confirmed.
- Final lot, including various elements and parameters to be checked at the final lot stage such as appearance, degree of adsorption, stability and expiry date. The absence of overdose is confirmed.
- Appearance
- Animal tests

Typically, individual vaccine monographs contain the following sub-sections (*lists provided as examples and are not exhaustive*):

Viral vaccines (live)

- General provisions
- Substrates for virus propagation
- Seed lots
- Virus propagation and harvest
- Final bulk vaccine
- Final lot

Viral vaccines (inactivated)

- General provisions
- Substrates for virus propagation
- Seed lot
- Virus propagation and harvest
- Inactivation
- Purification
- Final bulk vaccine
- Final lot

Bacterial vaccines (inactivated)

- General provisions
- Seed lots
- Propagation and harvest
- Purification
- Inactivation
- Final bulk vaccine
- Final lot

Bacterial vaccines (live)

General provisions

- Choice of vaccine strain
- Seed lots
- Propagation and harvest
- Final bulk vaccine
- Final lot

Polysaccharide-based vaccines (non-conjugate vaccines)

- General provisions
- Seed lots
- Culture and harvest
- Purified polysaccharides
- Final bulk vaccine
- Final lot

Polysaccharide-based vaccines (conjugate vaccines)

- General provisions
- Seed lots
- Purified polysaccharides
- Carrier protein
- Bulk conjugate
- Final bulk vaccine
- Final lot

Combined vaccines

The General provisions section is included. For production of the components, a reference is made to the corresponding sections of the monographs on the single-component vaccines.

6.5. Tests

The general monograph *Vaccines for human use (0153)* contains the following tests (listed as seen in the general monograph):

- pH
- Adjuvant
- Aluminium
- Calcium
- Free Formaldehyde
- Phenol
- Water
- Extractable volume
- Bacterial endotoxins

Typically, individual vaccine monographs may contain the following tests (*list provided as example and is not exhaustive*):

- Residual pertussis toxin for vaccines containing acellular pertussis component
- Residual infectious virus
- Sterility (for inactivated vaccines)/Bacterial and fungal contamination (for live vaccines)
- Pyrogens/Bacterial endotoxins
- Total protein content, where relevant
- Free saccharide for conjugate vaccines
- Distribution of molecular size/ molecular weight , for polysaccharide vaccines
- Ovalbumin content, where a vaccine is produced in eggs
- Bovine serum albumin, where a vaccine is produced in cell cultures
- Host cell and vector DNA
- Host cell protein
- Residual reagents
- Vesicle size (viroosomal vaccines)
- etc.

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