

Technical Guide

for the elaboration of monographs on
vaccines and other immunological
human medicinal products

European Pharmacopoeia

European Directorate for the Quality of Medicines & HealthCare



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TABLE OF CONTENTS

1. PURPOSE OF THE GUIDE	5
2. STATUS AND SCOPE OF THE GUIDE	5
3. GENERAL INFORMATION	5
3.1. PHARMACOPOEIAL REQUIREMENTS	5
3.2. ALTERNATIVE METHODS	6
3.3. GENERAL CHAPTERS AND GENERAL MONOGRAPHS	7
3.4. SPECIFIC MONOGRAPHS	8
3.5. HOW MONOGRAPHS AND CHAPTERS ARE ELABORATED AND UPDATED	8
3.5.1. Inclusion of a new monograph or a new general chapter in the european pharmacopoeia	8
3.5.2. Revision of monographs and general chapters for immunosera and vaccines for human use	9
4. CONTENT OF THE MONOGRAPHS.....	10
4.1. STRUCTURE AND CONTENT OF THE MONOGRAPHS ON VACCINES FOR HUMAN USE	10
4.1.1. General points.....	10
4.1.2. Sections of the monographs on vaccines.....	11
4.2. SUMMARY OF THE CONTENT OF THE GENERAL MONOGRAPH ANIMAL IMMUNOSERA FOR HUMAN USE.....	14
5. STYLE GUIDE FOR THE ELABORATION OF SPECIFIC MONOGRAPHS ON VACCINES FOR HUMAN USE	16

EUROPEAN PHARMACOPOEIA GUIDE FOR THE ELABORATION OF MONOGRAPHS ON VACCINES AND OTHER IMMUNOLOGICAL HUMAN 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 vaccines and other immunological human medicinal products. This applies in particular to:

1. group of experts No. 15 (Vaccines and sera for human use);
2. authorities responsible for granting marketing authorisations for vaccines and immunosera for human use;
3. official Medicines Control Laboratories (OMCLs);
4. manufacturers of vaccines and immunosera for human use;
5. bodies that procure vaccines and immunosera for health services;
6. public and private analytical laboratories working for any of the above;
7. the Secretariat of the European Pharmacopoeia and any other department 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.

Certain 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 European Pharmacopoeia must be interpreted with reference to the *General Notices*. All users of the European Pharmacopoeia must be familiar with this text.

Statements in monographs are mandatory regulations 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 6th Edition)

As regards compliance with monographs, the General Notices state that: *“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’ from data derived, for example, from validation studies of the manufacturing process and from in-process controls. Parametric release in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia.” (Ph.Eur 6th Edition)*

As regards alternative methods, the General Notices state that: *“The tests and assays described are the official methods upon which the standards of the European 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 European Pharmacopoeia alone are authoritative.” (Ph.Eur 6th Edition)*

Special provisions apply to the section **Choice of Vaccine Strain and Choice of Vaccine composition**: *“The production section of a monograph may define the characteristics of a vaccine strain or vaccine composition. Unless otherwise stated, test methods given for verification of these characteristics are provided for information as examples of suitable methods. Subject to approval by the competent authority, other test methods may be used without validation against the method shown in the monograph.” (Ph.Eur 6th Edition)*

3.2 ALTERNATIVE METHODS

The test methods prescribed in monographs are the reference methods on which the quality standards are based. As indicated above under 3.1 Pharmacopoeial requirements, other methods of analysis may be used for a variety of reasons. Firstly, Pharmacopoeial methods have been chosen for application to all the relevant products that were available at the time of their elaboration. Other available methods can be used if it is demonstrated by validation that the alternative method is equivalent to the official method or more suitable, in accordance with the General Notices. Secondly, the methods have been developed for application in a variety of laboratories with standard equipment but this does not rule out the use of alternative, validated methods. Monographs are revised periodically to keep pace with progress in techniques but pending these revisions new methods can be used as alternatives, if validated and authorised by the competent authorities.

Use of Animals.

In accordance with the provisions of the *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (1986)* and the European Directive on the same principles, tests described in European Pharmacopoeia monographs must be carried out in such a way as to use the minimum number of animals for a

significant result and to cause the least pain, suffering, distress or lasting harm. Humane endpoints must be used wherever possible for all tests, even if it 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*).

3.3 GENERAL CHAPTERS AND MONOGRAPHS

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*.

The following general monographs apply to products for human use:

- *Vaccines for human use (0153)*;
- *Animal immunosera for human use (0084)*;

These monographs are published under the heading General monographs in the European Pharmacopoeia.

The following general chapters are published under the heading 2.6. Biological tests, 2.7. Biological assays, 5.1. General texts on microbiology 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:

- *Abnormal toxicity (2.6.9)*
- *Tests for extraneous agents in viral vaccines for human use (2.6.16)*
- *Test for neurovirulence of live virus vaccines (2.6.18)*
- *Test for neurovirulence of poliomyelitis vaccine (oral) (2.6.19)*
- *Assay of diphtheria vaccine (adsorbed) (2.7.6)*
- *Assay of pertussis vaccine (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)*
- *Viral safety (5.1.7)*
- *Cell substrates for the production of vaccines for human use (5.2.3)*

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/immunosera:

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

3.4 SPECIFIC MONOGRAPHS

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

3.5. HOW MONOGRAPHS AND CHAPTERS ARE ELABORATED AND UPDATED

3.5.1. Inclusion of a new monograph or a new general chapter in the European Pharmacopoeia

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

- the chair of the European Pharmacopoeia Commission,
- a delegation;
- the chair on behalf of the Group of experts;
- EDQM’s secretariat, for example, on the basis of information and data provided via the EDQM *Helpdesk* by a manufacturer or by a user of the European Pharmacopoeia.

It is the European Pharmacopoeia Commission which decides whether to accept the proposal, and if accepted, it adds the item to the work programme of the Group of experts (see the Rules of procedure of the European Pharmacopoeia Commission).

For many classes of medicinal substances or products, monographs are usually (but not always) included in the European Pharmacopoeia only when the 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 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.

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.

In general, the standards that are attained by vaccines that are already on the market are taken into consideration during the elaboration of a new monograph. Consequently, where there is sufficient information demonstrating that the product is of ‘Pharmacopoeial quality’, it will

not be necessary to retest these vaccines to show compliance with the requirements of subsections under Production when the monograph is finalised and published.

The drafted monograph is published in *Pharmeuropa* for public enquiry. All the interested parties have 3 months to send their comments to their National Pharmacopoeial Authority (NPA) which centralises all the comments from that country. NPAs then have 2 months to send the compiled comments to the EDQM's Secretariat. Manufacturers outside Europe and Paneuropean organisations have 3 months to send their comments to the EDQM's Secretariat via the EDQM *Helpdesk*. The EDQM's Secretariat makes a consolidated document from all these comments.

The consolidated comments are studied by the Group of experts at the meeting following the end of the consultation period.

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

If the text is adopted, it is published in the European Pharmacopoeia 6 months after the Commission session, and implemented 6 months later. If the text is not adopted, it will either go back to the Group of experts or no specific monograph on this particular product will be published in the European Pharmacopoeia.

3.5.2. Revision of monographs and general chapters for immunosera and vaccines for human use

Proposals to revise a text can be made by:

- the chair of the European Pharmacopoeia Commission;
- a delegation;
- the chair on behalf of Group of experts;
- the EDQM's secretariat, for example, on the basis of information and data provided via the EDQM *Helpdesk* by a manufacturer or by a user of the European Pharmacopoeia.

It is the European Pharmacopoeia Commission which 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, supported by data and documents.

During the revision of a monograph, the standards attained by vaccines that are already on the market will be 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 is published.

The revised monograph is published in *Pharmeuropa* for public enquiry. All the interested parties have 3 months to send their comments to their NPA which centralises all the comments of that country. NPAs then have 2 months to send the compiled comments to the EDQM's Secretariat. Manufacturers outside Europe and Paneuropean organisations have 3 months to send their comments to the EDQM's Secretariat via the EDQM Helpdesk. The EDQM's Secretariat makes a consolidated document from all these comments.

The consolidated comments are studied by the Group of experts at the meeting following the end of the consultation period.

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

If the revised text is adopted, it is published in the *European Pharmacopoeia* 6 months after the Commission session, and implemented 6 months later. Should the text not be adopted, it will either go back to the Group of experts or stay as it is.

4. CONTENT OF THE MONOGRAPHS

4.1 STRUCTURE AND CONTENT OF THE MONOGRAPHS ON VACCINES FOR HUMAN USE

4.1.1 General points

The pharmacopoeial requirements for vaccines and the tests to be carried out are those described in the General monograph on *Vaccines for Human Use (0153)* **and** those described in the relevant specific monographs where one exists.

The provisions of the general monographs apply to all vaccines/immunoserum, including those for which there is no specific monograph. The general monographs prescribe essential requirements which supplement and expand on requirements contained in the monographs on specific products (vaccines/immunoserum). The authors and users of specific monographs must be familiar with the contents of the relevant general monographs in order to be able to draft or use the specific monographs correctly. The requirements given in the general monographs are not usually repeated in the specific monographs, i.e., no reference is made to the general monograph in the specific monographs on vaccines/immunoserum, 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). Users of monographs should be aware, therefore, that if a general point from *Vaccines for Human Use (0153)* is included in one specific monograph but not in another, this does not mean that the point is not applicable to products covered by the latter monograph.

The specific monographs have to be used and applied, taking account of the explanations, guidance and requirements given in all the documents mentioned above, including the general monographs.

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

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

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

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

4.1.2 Sections of the monographs for vaccines

The various sections are mandatory, with the exception of the Storage section and, for some items, the Labelling section. Informational statements are identified by their content and drafting style. See also the General Notices.

The Definition section defines the scope of the monograph and its applicability to products on the market. In the specific monographs, the composition of the product is stated briefly. The monograph sets out the official standard for all products covered by this definition. If a new type of vaccine is developed against the same disease as a vaccine already covered by a European Pharmacopoeia monograph, either a new monograph is elaborated with a distinct title for the new type of vaccine or the existing monograph is revised, making appropriate changes to the definition and elsewhere, so that the European Pharmacopoeia monograph also covers the new product.

If a product is not covered by the scope of a specific monograph, the monograph is not applicable to this product. Only the general monograph on vaccines for human use applies in this case.

The Production section describes essential features of the manufacturing process. It follows more or less the sequence in time of the production of a vaccine. This section is primarily addressed to manufacturers and to provide advice. It contains information on points to be addressed for the production of the vaccine, the type of tests that it is expected will be conducted during development of the product, tests that may be conducted routinely in-process and tests that can be conducted on each batch by manufacturers, as part of the tests conducted to provide assurance that the product is of ‘Pharmacopoeia quality’.

General provisions

Abnormal toxicity. Where no animal safety test is included under Tests, the following paragraph is given under General provisions.

“The production method is validated to demonstrate that the product, if tested, would comply with the test for abnormal toxicity for immunosera and vaccines for human use (2.6.9)”.

The test for abnormal toxicity may be replaced by a test for specific toxicity as this is the case for example for the diphtheria and tetanus components. The following paragraph is then included in the monograph to replace the paragraph on a test for abnormal toxicity:

“The production method is validated to demonstrate that the product, if tested, would comply with the following test for specific toxicity of the diphtheria and tetanus components”.

These paragraphs imply that the test for abnormal toxicity (or an equivalent test) is carried out on a sufficient number of batches (usually 10) during the initial production phase and that such testing is repeated whenever there is a significant change in the production process. The number of batches to be tested and the need to resume testing following process modification are decided by the National Pharmacopoeial Authority.

Consistency of production has to be demonstrated for example by defining for each product suitable action or release limit(s).

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

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 specific 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 specific monograph.

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

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.

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, control cells from the production cell culture comply with an identification test and with the requirements for extraneous agents (2.6.16).

Purification and Inactivation for 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), it should be demonstrated that the purification process used consistently reduces the host cell DNA content. If a limit for residual DNA content is mentioned in a specific monograph, it applies to the vaccine concerned. The maximum limit of 10 ng per single human dose mentioned in chapter 5.2.3 applies to all vaccines for which there is no specific monograph and to vaccines for which the monograph does not mention a limit.

Inactivation is verified for inactivated vaccines (test for residual infectious virus).

Stability of intermediates is demonstrated.

Final bulk vaccine

If an adsorbent is added to a vaccine, it confers the appropriate physical form and adsorptive properties.

If an antimicrobial preservative is added to a vaccine, its content has to be determined.

A test for sterility / bacterial and fungal contamination (2.6.1) is carried out. The terms "bacterial and fungal contamination" are 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.

Final lot

This term applies to the final bulk vaccine aseptically distributed into sterile tamper-proof containers. The containers are closed so as to exclude microbial contamination and each container is inspected, either visually or mechanically.

Only a final lot that complies with each of the tests described under Identification, Tests and Assay may be released. Certain tests in the specific monograph may be omitted on the final lot if they have been carried out with satisfactory results upstream (for example, 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.

A test for thermal stability may be required at this stage of production (live vaccines).

IDENTIFICATION – This section describes how to identify the product. Where it is specified in a monograph, the assay can also serve to identify the vaccine.

TESTS – A series of batch tests (for example, 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, etc) is described and limits are given, unless otherwise justified. The product should comply with these requirements throughout its shelf-life.

ASSAY or LIVE VIRUS/BACTERIA CONCENTRATION or (POLY)SACCHARIDE CONTENT – A potency test is included in each specific monograph, but it is sometimes described in a separate chapter which is referred to in the specific monograph.

The expiry date is usually calculated from the beginning of the assay or from the beginning of the first assay for a combined vaccine.

STORAGE – This section is given for information. The storage conditions are indicated by the manufacturer; these have been validated by stability testing which showed that the vaccine will comply throughout the period of validity.

Unless otherwise indicated in a specific monograph, the storage of vaccines is expected to conform to that described in the general monograph.

LABELLING – The appropriate requirements of the labelling statements described in the general monograph apply to all vaccines for human use. In some cases, additional information may be necessary for a particular vaccine. This information is then included in the Labelling section of the specific monograph and this is supplementary to the requirements of the general monograph.

The status of 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 product, as decided by the competent authority”.

4.2 SUMMARY OF THE CONTENT OF THE GENERAL MONOGRAPH ON “ANIMAL IMMUNOSERA FOR HUMAN USE”

The general monograph *Animal immunosera for human use (0084)* contains, in a general but detailed way, the requirements and points that have to be addressed by manufacturers for the preparation and testing of batches of immunosera. There are only a few specific monographs for immunosera and these are relatively short documents as the bulk of the requirements are in the general texts.

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 2 general monographs *Animal immunosera for human use (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 on *Immunosera for human use, animal (0084)* **and** those described in the relevant specific monographs where one exists.

DEFINITION

— This section defines the scope of the general monograph.

PRODUCTION

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

IDENTIFICATION – This section describes which tests are used 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.

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

TESTS - A series of tests to be carried out on each batch is described. The product has to comply with these requirements throughout its shelf-life.

ASSAY – Where appropriate, carry out the assay as described in the specific monograph.

STORAGE – Unless otherwise indicated in a specific monograph, the storage of immunosera is expected to conform to that described in the general monograph.

LABELLING – The appropriate requirements of the labelling statements described in the general monograph apply to all immunosera for human use. Where appropriate, additional information may be necessary for a particular immunoserum. This information is then included in the specific monograph, in the Labelling section, and this is supplementary to the requirements of the general monograph.

The status of Labelling is defined in the General Notices: *“In general, labelling of medicines is subject to supranational and national regulation and to international agreements. The statements under the heading Labelling are not therefore comprehensive and, moreover, for the purposes of the Pharmacopoeia only those statements that are necessary to demonstrate compliance or non-compliance with the monograph are mandatory. Any other labelling statements are included as recommendations. When the term “label” is used in the Pharmacopoeia, the labelling statements may appear on the container, the package, a leaflet accompanying the package, or a certificate of analysis accompanying the product, as decided by the competent authority”* (Ph.Eur 6th Edition).

5. STYLE GUIDE FOR THE ELABORATION OF SPECIFIC MONOGRAPHS ON VACCINES FOR HUMAN USE

STANDARDISED TEXT FOR DRAFTING MONOGRAPHS

The following section of this guide provides the main examples of the structure and the phrases and terms that should be used by rapporteurs when drafting monographs. Examples are given for monographs for different types of products but which are drafted to suit the bulk 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.

TITLE OF SPECIFIC MONOGRAPHS

Preferred format: Disease name + “vaccine” + (type) (live, inactivated, adsorbed, virosome, etc.)

Examples:

Measles vaccine (live)

Tetanus vaccine (adsorbed)

Influenza vaccine (surface-antigen, inactivated)

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

◆ 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)
- Bacterial vaccine (whole-cell, inactivated)
- Pertussis vaccine (adsorbed)

◆ Bacterial toxoid vaccines (and other component-based vaccines)

- Diphtheria vaccine, Tetanus vaccines, Pertussis vaccine (acellular)

◆ Bacterial vaccines (live)

- Typhoid vaccine (live, oral, strain, Ty21a)
- BCG vaccine, freeze-dried

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

PRODUCTION — The general monograph on vaccines for human use has a number of sub-chapters:

General provisions

Substrates for micro-organism propagation

Seed lots

Culture media

Propagation and harvest

Control cells

Control eggs

Purification

Inactivation

Stability of intermediates

Final bulk, including various elements of the formulation of the vaccine such as possible addition of adjuvants and antimicrobial 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

The specific monographs also have a number of sub-sections:

Viral vaccines (live)

General provisions

Substrates for virus propagation

Seed lots

Virus propagation and harvest

Final bulk vaccine

Final lot

For Viral vaccines (inactivated)

General provisions

Substrates for virus propagation

Seed lots

Virus propagation and harvest

Inactivation

Purification

Final bulk vaccine

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.

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

IDENTIFICATION — The aim of this test is to be sure that the product is the one expected. For that purpose, the main characteristic is usually checked by appropriate methods such as the assay which can also serve to identify the vaccine, or inactivation of specific antibodies by the antigens present in the vaccine, etc.

TESTS — The general monograph on vaccines for human use has a number of tests:

pH

Adjuvant

Aluminium

Calcium

Free Formaldehyde

Phenol

Water

Extractable volume

The specific monographs also have a number of sub-sections:

Specific toxicity (of the pertussis component, for example)

Absence of residual pertussis toxin and irreversibility of pertussis toxoid 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, 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

ASSAY or LIVE VIRUS/BACTERIA CONCENTRATION or (POLY)SACCHARIDE CONTENT — The aim of this test is to determine the capacity of a vaccine to induce the formation of specific antibodies against the disease, 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.

STORAGE — If other storage conditions than those described in the general monograph apply, they are indicated in the specific monograph.

LABELLING — Only information that is not in the general monograph is mentioned in the specific monographs. This section states indications needed to perform the tests described in the specific monograph.