THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

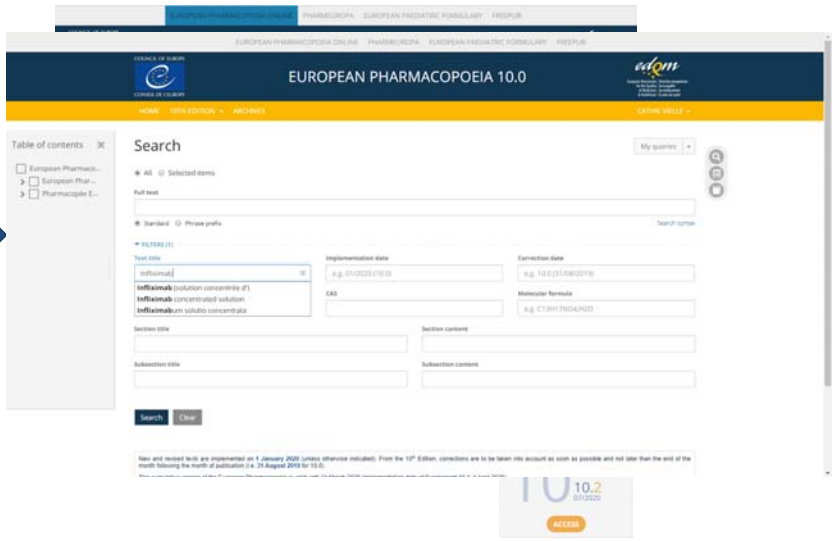
General concepts in the Ph. Eur.: theory and rationale

Cathie Vielle

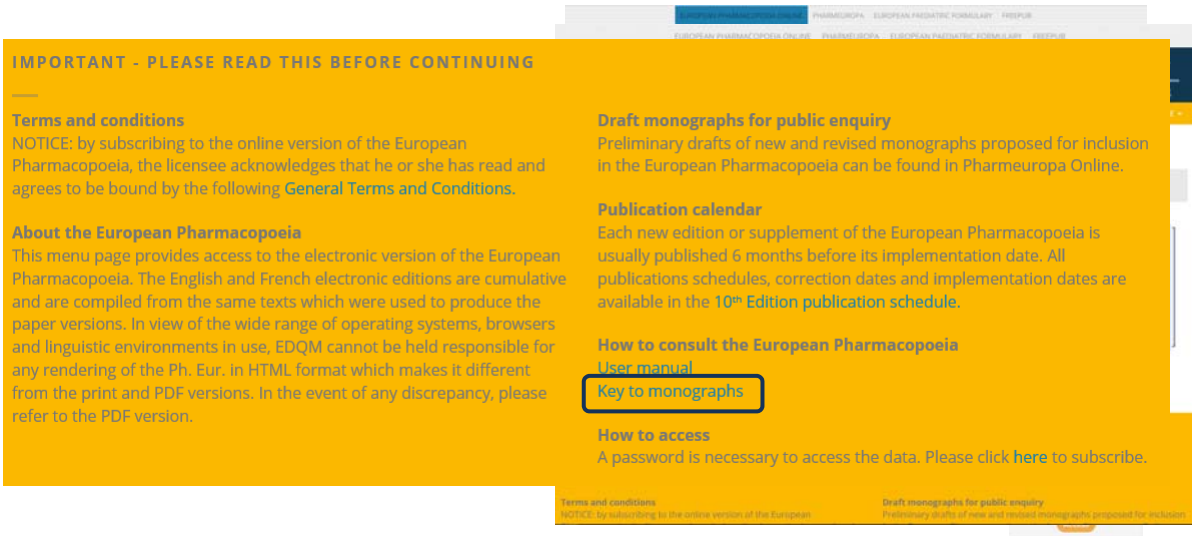
Head of European Pharmacopoeia Department

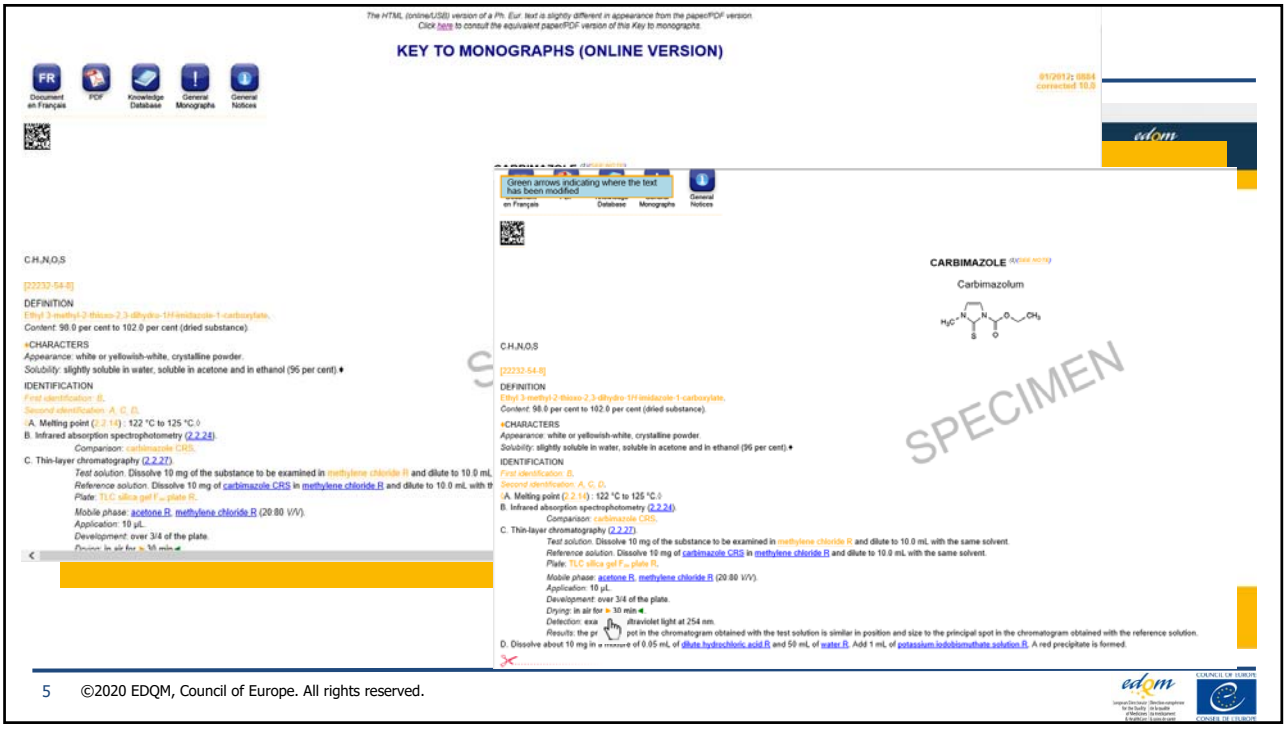
Where do you start … … when using the Ph. Eur.?

Sample to be tested

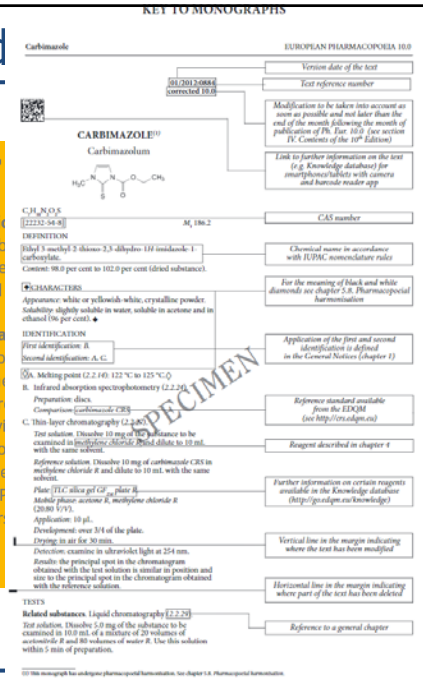


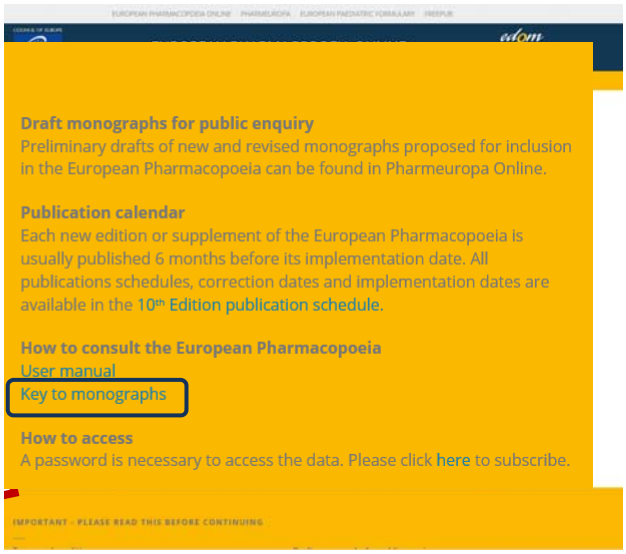
Where do you start … … when using the Ph. Eur.?





Where d en using the Ph. Eur.?





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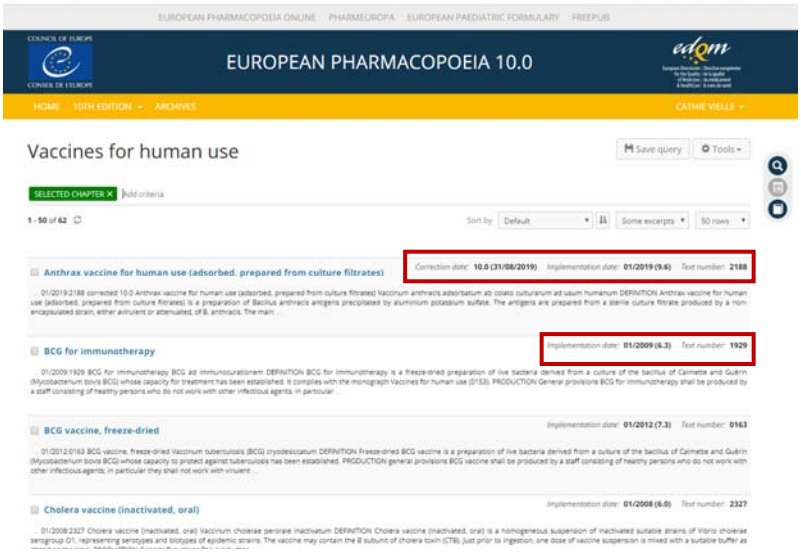
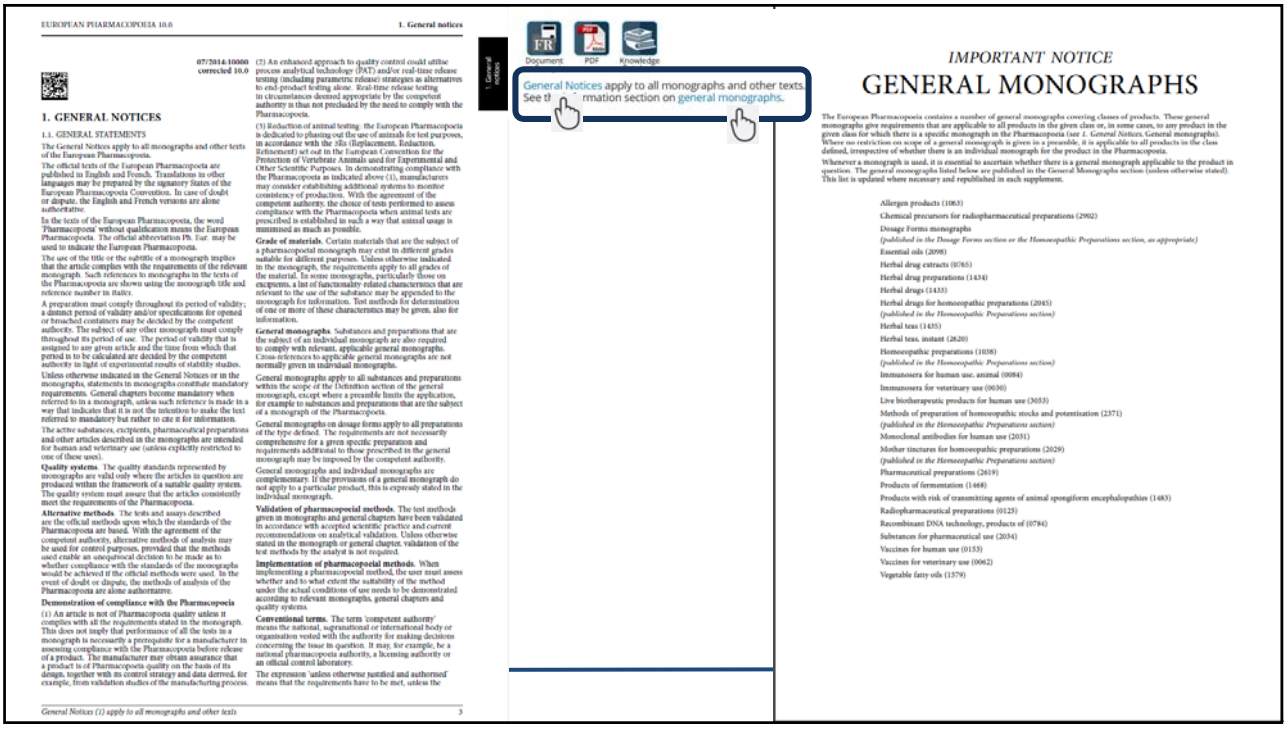


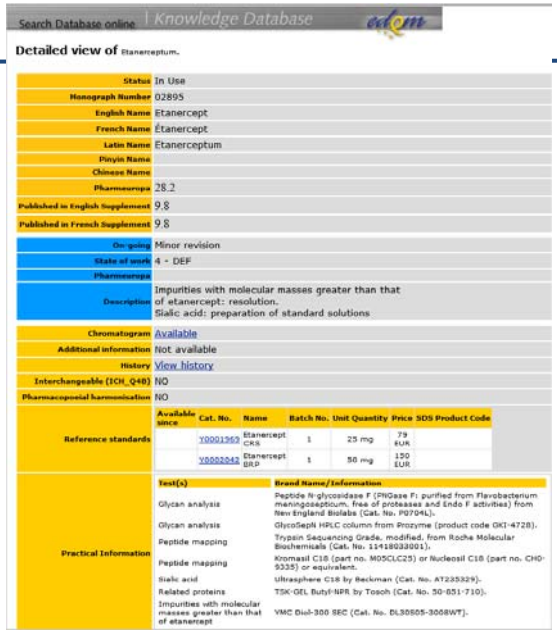
Where do you start … … when using the Ph. Eur.?

Sample to be tested

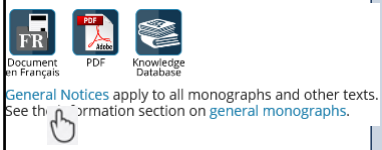


Knowledge database

General Notices apply to all monographs and other texts.
See the information section on general monographs.



The structure of the Ph. Eur.



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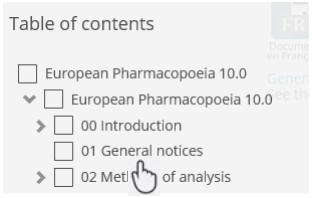

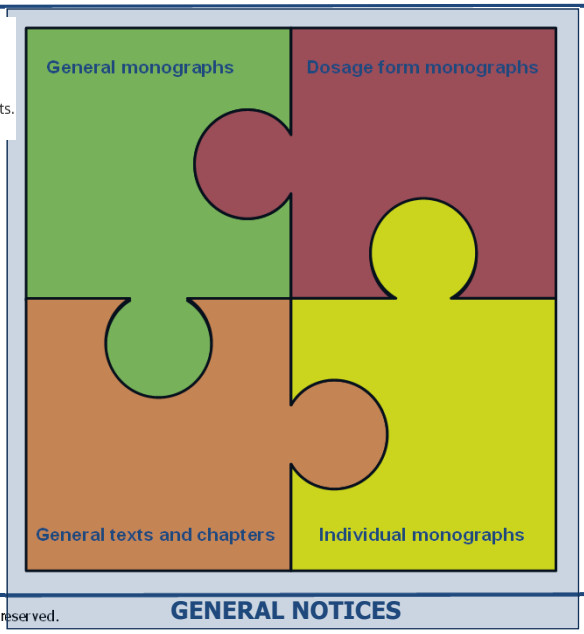

GENERAL NOTICES

General Notices

At the very beginning of the Ph. Eur. (page 3)

- address general issues
- aim at providing basic information to the user
- apply to **all** texts
- include rules to understand texts, conventional expressions

Essential reading before starting to use monographs and chapters


EUROPEAN PHARMACOPOEIA 10.0 — 1. General notices

1. GENERAL NOTICES

1.1. GENERAL STATEMENTS

The General Notices apply to all monographs and other texts of the European Pharmacopoeia.

The official texts of the European Pharmacopoeia are published in English and French. Translations in other languages may be prepared by the signatory States of the European Pharmacopoeia Convention. In case of doubt or dispute, the English and French versions are alone authoritative.

In the texts of the European Pharmacopoeia, the word 'Pharmacopoeia' without qualification means the European Pharmacopoeia. The official abbreviation Ph. Eur. may be used to indicate the European Pharmacopoeia.

The use of the title or the subtitle of a monograph implies that the article complies with the requirements of the relevant monograph. Such references to monographs in the texts of the Pharmacopoeia are shown using the monograph title and reference number in italics.

A preparation must comply throughout its period of validity; a distinct period of validity and/or specifications for opened or broached containers may be decided by the competent authority. The subject of any other monograph must comply throughout its period of use. The period of validity that is assigned to any given article and the time from which that period is to be calculated are decided by the competent authority in light of experimental results of stability studies.

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.

The active substances, excipients, pharmaceutical preparations and other articles described in the monographs are intended for human and veterinary use (unless explicitly restricted to one of these uses).

Quality systems. The quality standards represented by monographs are valid only where the articles in question are produced within the framework of a suitable quality system. The quality system must ensure that the articles consistently meet the requirements of the Pharmacopoeia.

Alternative methods. 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.

Demonstration of compliance with the Pharmacopoeia

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

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

(3) Reduction of animal testing: the European Pharmacopoeia is dedicated to phasing out the use of animals for test purposes, in accordance with the 3Rs (Replacement, Reduction, Refinement) principle. For this purpose, manufacturers may consider establishing additional systems to monitor consistency of production. With the agreement of the competent authority, the choice of tests performed to assess compliance with the Pharmacopoeia when animal tests are prescribed is established in such a way that animal usage is minimised as much as possible.

Grade of materials. Certain materials that are the subject of a pharmacopoeial monograph may exist in different grades suitable for different purposes. Unless otherwise indicated in the monograph, the requirements apply to all grades of the material. In some monographs, particularly those on excipients, a list of functionality-related characteristics that are relevant to the use of the substance may be appended to the monograph for information. Test methods for determination of one or more of these characteristics may be given, also for information.

General monographs. Substances and preparations that are the subject of an individual monograph are also required to comply with relevant, applicable general monographs. Cross-references to applicable general monographs are not normally given in individual monographs.

General monographs apply to all substances and preparations within the scope of the Definition section of the general monograph, except where a preamble limits the application, for example to substances and preparations that are the subject of a monograph of the Pharmacopoeia.

General monographs on dosage forms apply to all preparations of the type defined. The requirements are not necessarily comprehensive for a given specific preparation and requirements additional to those prescribed in the general monograph may be imposed by the competent authority.

General monographs and individual monographs are complementary. If the provisions of a general monograph do not apply to a particular product, this is expressly stated in the individual monograph.

Validation of pharmacopoeial methods. The test methods given in monographs and general chapters have been validated in accordance with accepted scientific practice and current recommendations on analytical validation. Unless otherwise stated in the monograph or general chapter, validation of the test methods by the analyst is not required.

Implementation of pharmacopoeial methods. When implementing a pharmacopoeial method, the user must assess whether and to what extent the suitability of the method under the actual conditions of use needs to be demonstrated according to relevant monographs, general chapters and quality systems.

Conventional terms. The term 'competent authority' means the national, supranational or international body or organisation vested with the authority for making decisions concerning the issue in question. It may, for example, be a national pharmacopoeia authority, a licensing authority or an official control laboratory.

The expression 'unless otherwise justified and authorised' means that the requirements have to be met, unless the

General Notices (1) apply to all monographs and other texts — 3

General Notices

Focus of this presentation

Structure of the text:

1.1. GENERAL STATEMENTS

1.2. OTHER PROVISIONS APPLYING TO GENERAL CHAPTERS AND MONOGRAPHS

1.3. GENERAL CHAPTERS

1.4. MONOGRAPHS

1.5. ABBREVIATIONS AND SYMBOLS

1.6. UNITS OF THE INTERNATIONAL SYSTEM (SI) USED IN THE PHARMACOPOEIA AND EQUIVALENCE WITH OTHER UNITS

1. GENERAL NOTICES:
1.1. GENERAL STATEMENTS

1.1. GENERAL STATEMENTS

EUROPEAN PHARMACOPOEIA 10.0 — 1. General notices

07/2014:10000
corrected 10.0

1. GENERAL NOTICES

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Quality systems. The quality standards represented by monographs are valid only where the articles in question are produced within the framework of a suitable quality system. The quality system must assure that the articles consistently meet the requirements of the Pharmacopoeia.

Alternative methods. 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.

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

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

Grade of materials. Certain materials that are the subject of a pharmacopoeial monograph may exist in different grades suitable for different purposes. Unless otherwise indicated in the monograph, the requirements apply to all grades of the material. In some monographs, particularly those on excipients, a list of functionality-related characteristics that are relevant to the use of the substance may be appended to the monograph for information. Test methods for determination of one or more of these characteristics may be given, also for information.

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Implementation of pharmacopoeial methods. When implementing a pharmacopoeial method, the user must assess whether and to what extent the suitability of the method under the actual conditions of use needs to be demonstrated according to relevant monographs, general chapters and quality systems.

Conventional terms. The term 'competent authority' means the national, supranational or international body or organisation vested with the authority for making decisions concerning the issue in question. It may, for example, be a national pharmacopoeia authority, a licensing authority or an official control laboratory.

The expression 'unless otherwise justified and authorised' means that the requirements have to be met, unless the competent authority authorises a modification or an exemption where justified in a particular case.

Statements containing the word 'should' are informative or advisory.

In certain monographs or other texts, the terms 'suitable' and 'appropriate' are used to describe a reagent, micro-organism, test method etc., if criteria for suitability are not described in the monograph, suitability is demonstrated to the satisfaction of the competent authority.

Medicinal product. (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings and/or animals; or (b) any substance or combination of substances that may be used in or administered to human beings and/or animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Herbal medicinal product. Any medicinal product, exclusively containing as active ingredients one or more herbal drugs or one or more herbal drug preparations, or one or more such herbal drugs in combination with one or more such herbal drug preparations.

Active substance. Any substance intended to be used in the manufacture of a medicinal product and that, when so used, becomes an active ingredient of the medicinal product. Such substances are intended to furnish a pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

Excipient (auxiliary substance). Any constituent of a medicinal product that is not an active substance. Adjuvants, stabilisers, antimicrobial preservatives, diluents, antioxidants, for example, are excipients.

Interchangeable methods. Certain general chapters contain a statement that the text in question is harmonised with the corresponding text of the Japanese Pharmacopoeia and/or the United States Pharmacopeia and that these texts are interchangeable. This implies that if a substance or preparation is found to comply with a requirement using an interchangeable method from one of these pharmacopoeias it complies with the requirements of the European Pharmacopoeia. In the event of doubt or dispute, the text of the European Pharmacopoeia is alone authoritative.

References to regulatory documents. Monographs and general chapters may contain references to documents issued by regulatory authorities for medicines, for example directives and notes for guidance of the European Union. These references are provided for information for users for the Pharmacopoeia. Inclusion of such a reference does not modify the status of the documents referred to, which may be mandatory or for guidance.

1.2. OTHER PROVISIONS APPLYING TO GENERAL CHAPTERS AND MONOGRAPHS

Quantities. In tests with numerical limits and assays, the quantity stated to be taken for examination is approximate. The amount actually used, which may deviate by not more than 10 per cent from that stated, is accurately weighed or measured and the result is calculated from this exact quantity. In tests where the limit is not numerical, but usually depends upon comparison with the behaviour of a reference substance in the same conditions, the stated quantity is taken for examination. Reagents are used in the prescribed amounts.

Quantities are weighed or measured with an accuracy commensurate with the indicated degree of precision. For weighings, the precision corresponds to plus or minus 5 units after the last figure stated (for example, 0.25 g is to be interpreted as 0.245 g to 0.255 g). For the measurement of volumes, if the figure after the decimal point is a zero or ends in a zero (for example, 10.0 mL or 0.50 mL), the volume is measured using a pipette, a volumetric flask or a burette, as appropriate; otherwise, a graduated measuring cylinder or a graduated pipette may be used. Volumes stated in microlitres are measured using a micropipette or microsyringe.

It is recognised, however, that in certain cases the precision with which quantities are stated does not correspond to the number of significant figures stated in a specified numerical limit. The weighings and measurements are then carried out with a sufficiently improved accuracy.

Apparatus and procedures. Volumetric glassware complies with Class A requirements of the appropriate International Standard issued by the International Organisation for Standardisation.

Unless otherwise prescribed, analytical procedures are carried out at a temperature between 15 °C and 25 °C.

Unless otherwise prescribed, comparative tests are carried out using identical tubes of colourless, transparent, neutral glass with a flat base; the volumes of liquid prescribed are for use with tubes having an internal diameter of 16 mm, but tubes with a larger internal diameter may be used provided the volume of liquid used is adjusted (2.1.5). Equal volumes of the liquids to be compared are examined down the vertical axis of the tubes against a white background, or if necessary against a black background. The examination is carried out in diffuse light.

Any solvent required in a test or assay in which an indicator is to be used is previously neutralised to the indicator, unless a blank test is prescribed.

Water-bath. The term 'water-bath' means a bath of boiling water unless water at another temperature is indicated. Other methods of heating may be substituted provided the temperature is near to but not higher than 100 °C or the indicated temperature.

Drying and ignition to constant mass. The terms 'dried to constant mass' and 'ignited to constant mass' mean that 2 consecutive weighings do not differ by more than 0.5 mg, the 2nd weighing following an additional period of drying or of ignition respectively appropriate to the nature and quantity of the residue.

Where drying is prescribed using one of the expressions 'in a desiccator' or 'in vacuo', it is carried out using the conditions described in chapter 2.2.32. *Loss on drying*.

Reagents. The proper conduct of the analytical procedures described in the Pharmacopoeia and the reliability of the results depend, in part, upon the quality of the reagents used. The reagents are described in general chapter 4. It is assumed that reagents of analytical grade are used; for some reagents, tests to determine suitability are included in the specifications.

Solvents. Where the name of the solvent is not stated, the term 'solution' implies a solution in water.

Where the use of water is specified or implied in the analytical procedures described in the Pharmacopoeia or for the preparation of reagents, water complying with the requirements of the monograph *Purified water* (0008) is used, except that for many purposes the requirements for bacterial endotoxins (*Purified water in bulk*) and microbial contamination (*Purified water in containers*) are not relevant. The term 'distilled water' indicates purified water prepared by distillation.

The term 'ethanol' without qualification means anhydrous ethanol. The term 'alcohol' without qualification means ethanol (96 per cent). Other dilutions of ethanol are indicated by the term 'ethanol' or 'alcohol' followed by a statement of the percentage by volume of ethanol (C_2H_5O) required.

Expression of content. In defining content, the expression 'per cent' is used according to circumstances with one of 2 meanings:

- per cent m/m (percentage, mass in mass) expresses the number of grams of substance in 100 g of final product;

Answer to a lot of questions!

Such as:

- What about alternative methods?
- What about waiving of tests?
- What does compliance mean?
- What is mandatory?
- What to do when implementing a method?
- Human and/or veterinary use?

And many more

Pre-requisite

Quality systems.

"The quality standards represented by monographs are valid only where the articles in question are produced within the framework of a suitable quality system. The quality system must assure that the articles consistently meet the requirements of the Pharmacopoeia."

Conventional terms: meanings

'competent authority': the national, supranational or international body / organisation vested with the authority for making decisions concerning the issue in question. May be a national pharmacopoeia authority, a licensing authority or an official control laboratory.

'unless otherwise justified and authorised' means that the requirements have to be met, unless the competent authority authorises a modification or an exemption where justified in a particular case.

Etc…

Flexibility in the Ph. Eur. **Alternative methods**

Alternative methods

- Ph. Eur. tests = reference methods, alone authoritative in cases of doubt or dispute.
- Compliance required, but alternative methods may be used: same pass/fail decision
- Users' responsibility to demonstrate their suitability. Approval of *competent authority* needed in any case

The EDQM does not decide if acceptable or not!

Flexibility in the Ph. Eur. **Waiving of tests**

Compliance ≠ Performance

↓ prerequisite

↓ not prerequisite

- In some cases, some tests may be omitted based on validation data or other suitable justification
- Tests for process-specific impurities may be omitted if it is demonstrated that they will not occur with the particular process used e.g. boron in salbutamol

Waiving of tests

"(1) *An article 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."*

Flexibility in the Ph. Eur. **PAT**

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

What does compliance mean?

- All **mandatory** parts of a **monograph**
  ("*Unless otherwise indicated in the General Notices or in the monographs, statements in monographs constitute mandatory requirements.*" Characters section, second identification test and storage section – not mandatory)
- Compliance throughout period of validity for preparations.
- A distinct period of validity and/or specifications for opened or broached containers may be decided by licensing authority for each preparation
- Compliance **until end of shelf-life** for all other items: API, excipients, …

What to do when implementing a method?

Ref: Ph. Eur. / General notices

- **Validation of pharmacopoeial methods**. The test methods given in monographs and general chapters have been validated in accordance with accepted scientific practice and current recommendations on analytical validation. Unless otherwise stated in the monograph or general chapter, validation of the test methods by the analyst is not required.
- **Implementation of pharmacopoeial methods**. When implementing a pharmacopoeial method, the user must assess whether and to what extent the suitability of the method under the actual conditions of use needs to be demonstrated according to relevant monographs, general chapters and quality systems.

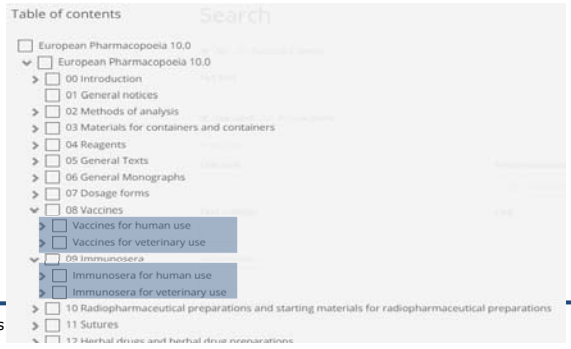
- **# Demonstration of suitability:** Each MAA still to provide to the competent authority demonstration that tests in the monograph are appropriate for the quality control of their product.

Reference to regulatory documents

- *"These references are provided for information for users for the Pharmacopoeia. Inclusion of such a reference does not modify the status of the documents referred to, which may be mandatory or for guidance."*

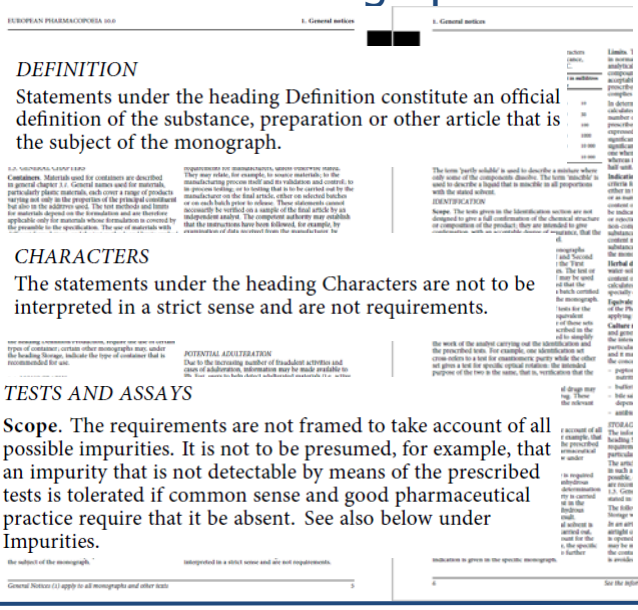
Human and veterinary use

- Unless otherwise stated, monographs cover human **and** veterinary use. Where a substance is used in both human and veterinary products, the same quality specification is applied.
- When the monograph title bears "for veterinary use" the substance is intended only for veterinary products.
- The Ph. Eur. structure also indicated whether human and/or veterinary use:



1. GENERAL NOTICES:
1.4. MONOGRAPHS

Section 1.4 Monographs



DEFINITION

Statements under the heading Definition constitute an official definition of the substance, preparation or other article that is the subject of the monograph.

CHARACTERS

The statements under the heading Characters are not to be interpreted in a strict sense and are not requirements.

TESTS AND ASSAYS

Scope. The requirements are not framed to take account of all possible impurities. It is not to be presumed, for example, that an impurity that is not detectable by means of the prescribed tests is tolerated if common sense and good pharmaceutical practice require that it be absent. See also below under Impurities.

IDENTIFICATION

Scope. 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 article conforms to the description on the label.

First and second identifications. Certain monographs have subdivisions entitled 'First identification' and 'Second identification'. The test or tests that constitute the 'First identification' may be used in all circumstances. The test or tests that constitute the 'Second identification' may be used in pharmacies provided it can be demonstrated that the substance or preparation is fully traceable to a batch certified to comply with all the other requirements of the monograph.

Certain monographs give two or more sets of tests for the purpose of the first identification, which are equivalent and may be used independently. One or more of these sets usually contain a cross-reference to a test prescribed in the Tests section of the monograph. It may be used to simplify the work of the analyst carrying out the identification and the prescribed tests. For example, one identification set cross-refers to a test for enantiomeric purity while the other set gives a test for specific optical rotation: the intended purpose of the two is the same, that is, verification that the correct enantiomer is present.

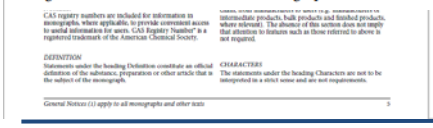
Section 1.4 Monographs

PRODUCTION

Statements under the heading Production draw attention to particular aspects of the manufacturing process but are not necessarily comprehensive. They constitute mandatory requirements for manufacturers, unless otherwise stated. They may relate, for example, to source materials; to the manufacturing process itself and its validation and control; to in-process testing; or to testing that is to be carried out by the manufacturer on the final article, either on selected batches or on each batch prior to release. These statements cannot necessarily be verified on a sample of the final article by an independent analyst. The competent authority may establish that the instructions have been followed, for example, by examination of data received from the manufacturer, by inspection of manufacture or by testing appropriate samples.

The absence of a Production section does not imply that attention to features such as those referred to above is not required.

Choice of vaccine strain, 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 o these characteristics are provided for information as example 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.



LABELLING

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.

STORAGE

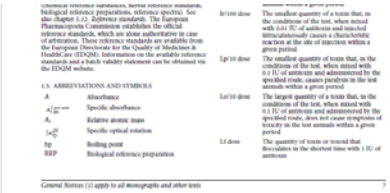
The information and recommendations given under the heading Storage do not constitute a pharmacopoeial requirement but the competent authority may specify particular storage conditions that must be met.

The articles described in the Pharmacopoeia are stored in such a way as to prevent contamination and, as far as possible, deterioration. Where special conditions of storage are recommended, including the type of container (see section 1.3. General chapters) and limits of temperature, they are stated in the monograph.

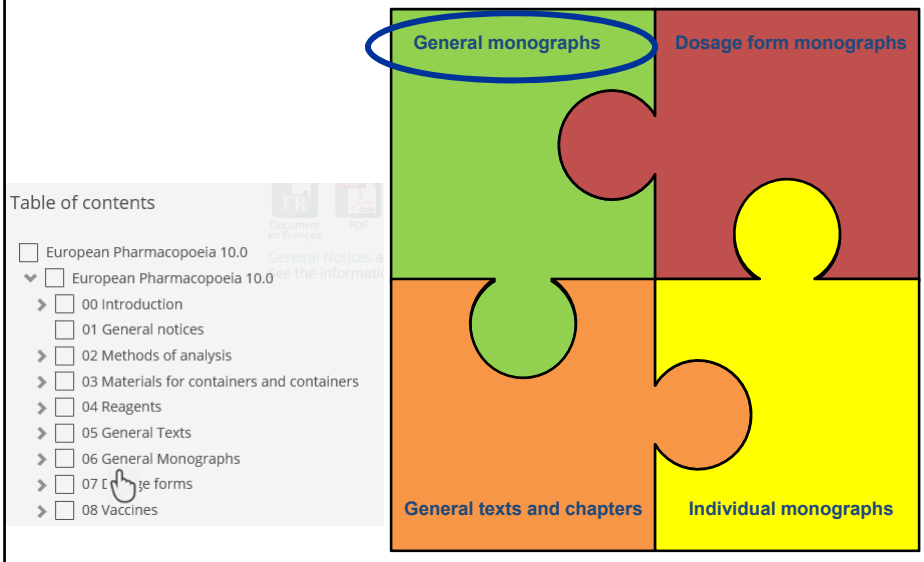
The following expressions are used in monographs under Storage with the meaning shown.

In an airtight container means that the product is stored in an airtight container (*3.2*). Care is to be taken when the container is opened in a damp atmosphere. A low moisture content may be maintained, if necessary, by the use of a desiccant in the container provided that direct contact with the product is avoided.

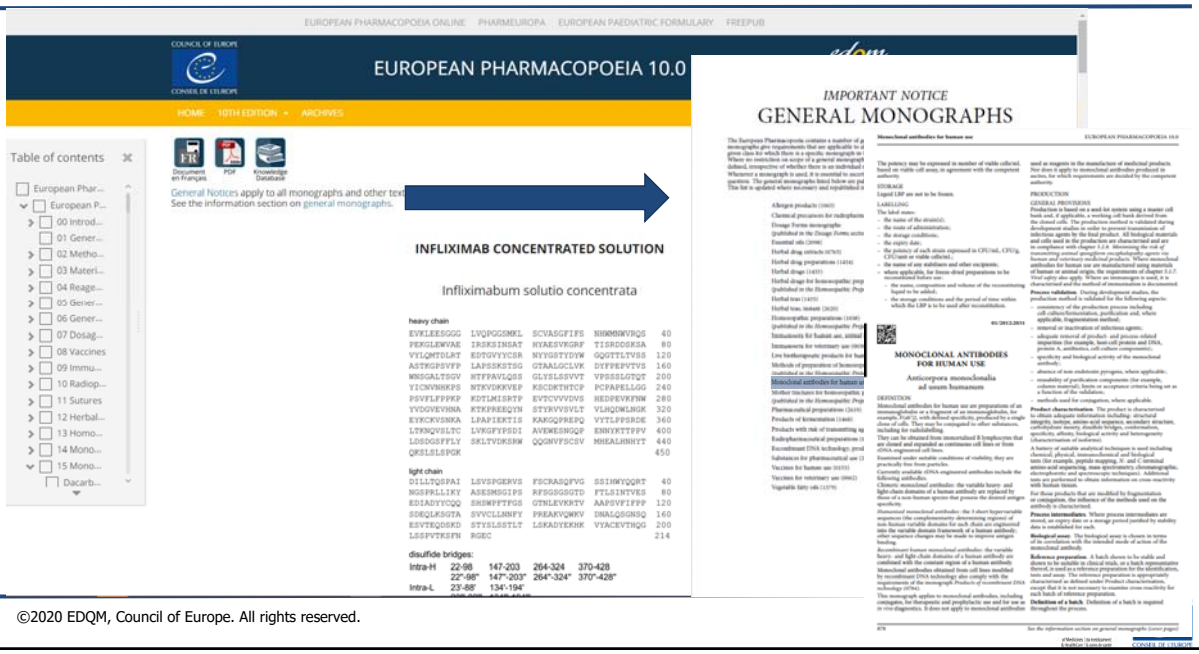
Protected from light means that the product is stored either in a container made of a material that absorbs actinic light sufficiently to protect the contents from change induced by such light, or in a container enclosed in an outer cover that provides such protection, or is stored in a place from which all such light is excluded.



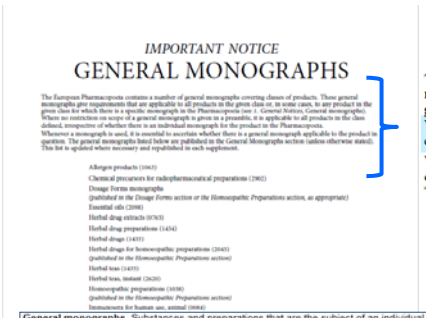
The structure of the Ph. Eur.



Important notice: General monographs



General monographs



The European Pharmacopoeia contains a number of general monographs covering classes of products. These general monographs give requirements that are applicable to all products in the given class or, in some cases, to any product in the given class for which there is a specific monograph in the Pharmacopoeia (see *1. General Notices*, General monographs). Where no restriction on scope of a general monograph is given in a preamble, it is applicable to all products in the class defined, irrespective of whether there is an individual monograph for the product in the Pharmacopoeia.

Whenever a monograph is used, it is essential to ascertain whether there is a general monograph applicable to the product in question. The general monographs listed below are published in the General Monographs section (unless otherwise stated). This list is updated where necessary and republished in each supplement.

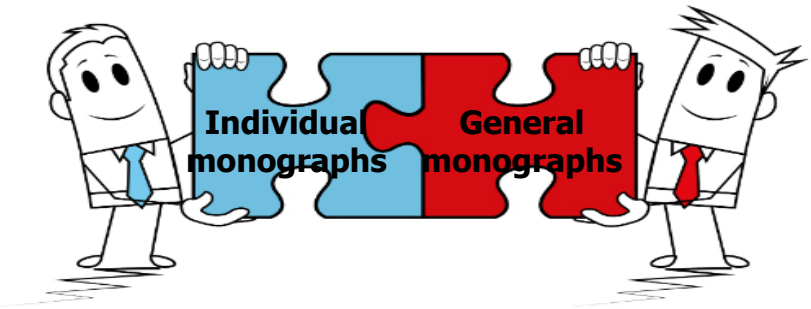
General monographs. Substances and preparations that are the subject of an individual monograph are also required to comply with relevant, applicable general monographs. Cross-references to applicable general monographs are not normally given in individual monographs.

General monographs apply to all substances and preparations within the scope of the Definition section of the general monograph, except where a preamble limits the application, for example to substances and preparations that are the subject of a monograph of the Pharmacopoeia.

General monographs on dosage forms apply to all preparations of the type defined. The requirements are not necessarily comprehensive for a given specific preparation and requirements additional to those prescribed in the general monograph may be imposed by the competent authority.

General monographs and individual monographs are complementary. If the provisions of a general monograph do not apply to a particular product, this is expressly stated in the individual monograph.

General vs. individual monographs



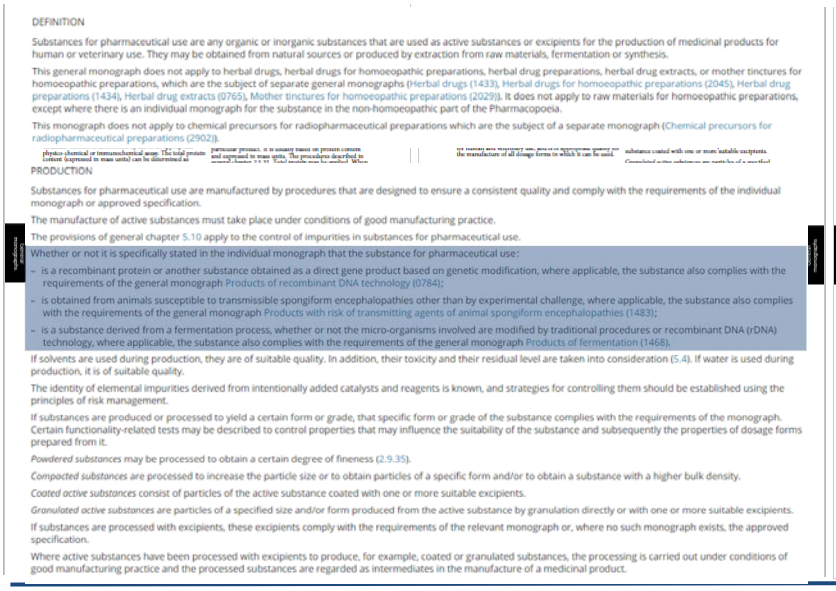
- Complementary
- One not overruling the other
- Exceptions are clearly indicated either in the general monograph or in the individual one

General monographs

- Deal with aspects that cannot be treated in each individual monograph
- "*General monographs apply to all substances and preparations within the scope of the Definition section of the general monograph, except where a preamble limits the application, for example to substances and preparations that are the subject of a monograph of the pharmacopoeia.*"
- No cross-reference in individual monographs: "*Whenever a monograph is used, it is essential to ascertain whether there is a general monograph applicable to the product in question.*"

CHECK WHICH GENERAL MONOGRAPH APPLIES!

Substances for pharmaceutical use



DEFINITION

Substances for pharmaceutical use are any organic or inorganic substances that are used as active substances or excipients for the production of medicinal products for human or veterinary use. They may be obtained from natural sources or produced by extraction from raw materials, fermentation or synthesis.

This general monograph does not apply to herbal drugs, herbal drugs for homoeopathic preparations, herbal drug preparations, herbal drug extracts, or mother tincture for homoeopathic preparations, which are the subject of separate general monographs (Herbal drugs (1433), Herbal drugs for homoeopathic preparations (2045), Herbal drug preparations (1434), Herbal drug extracts (0765), Mother tinctures for homoeopathic preparations (2029)). It does not apply to raw materials for homoeopathic preparations, except where there is an individual monograph for the substance in the non-homoeopathic part of the Pharmacopoeia.

This monograph does not apply to chemical precursors for radiopharmaceutical preparations which are the subject of a separate monograph (Chemical precursors for radiopharmaceutical preparations (2902)).

PRODUCTION

Substances for pharmaceutical use are manufactured by procedures that are designed to ensure a consistent quality and comply with the requirements of the individual monograph or approved specification.

The manufacture of active substances must take place under conditions of good manufacturing practice.

The provisions of general chapter 5.10 apply to the control of impurities in substances for pharmaceutical use.

Whether or not it is specifically stated in the individual monograph that the substance for pharmaceutical use:

- is a recombinant protein or another substance obtained as a direct gene product based on genetic modification, where applicable, the substance also complies with the requirements of the general monograph Products of recombinant DNA technology (0784);
- is obtained from animals susceptible to transmissible spongiform encephalopathies other than by experimental challenge, where applicable, the substance also complies with the requirements of the general monograph Products with risk of transmitting agents of animal spongiform encephalopathies (1483);
- is a substance derived from a fermentation process, whether or not the micro-organisms involved are modified by traditional procedures or recombinant DNA (rDNA) technology, where applicable, the substance also complies with the requirements of the general monograph Products of fermentation (1468).

If solvents are used during production, they are of suitable quality. In addition, their toxicity and their residual level are taken into consideration (5.4). If water is used during production, it is of suitable quality.

The identity of elemental impurities derived from intentionally added catalysts and reagents is known, and strategies for controlling them should be established using the principles of risk management.

If substances are produced or processed to yield a certain form or grade, that specific form or grade of the substance complies with the requirements of the monograph. Certain functionality-related tests may be described to control properties that may influence the suitability of the substance and subsequently the properties of dosage forms prepared from it.

Powdered substances may be processed to obtain a certain degree of fineness (2.9.35).

Compacted substances are processed to increase the particle size or to obtain particles of a specific form and/or to obtain a substance with a higher bulk density.

Coated active substances consist of particles of the active substance coated with one or more suitable excipients.

Granulated active substances are particles of a specified size and/or form produced from the active substance by granulation directly or with one or more suitable excipients.

If substances are processed with excipients, these excipients comply with the requirements of the relevant monograph or, where no such monograph exists, the approved specification.

Where active substances have been processed with excipients to produce, for example, coated or granulated substances, the processing is carried out under conditions of good manufacturing practice and the processed substances are regarded as intermediates in the manufacture of a medicinal product.

Pharmaceutical preparations

INTRODUCTION

This monograph is intended to be a reference source of standards in the European Pharmacopoeia on active substances, excipients and dosage forms, which are to be applied in the manufacture/preparation of pharmaceuticals, but not a guide on how to manufacture as there is specific guidance available covering methods of manufacture and associated controls.

It does not cover investigational medicinal products, but competent authorities may refer to pharmacopoeial standards when authorising clinical trials using investigational medicinal products.

DEFINITION

Pharmaceutical preparations are medicinal products generally consisting of active substances that may be combined with excipients, formulated into a dosage form suitable for the intended use, where necessary after reconstitution, presented in a suitable and appropriately labelled container.

Pharmaceutical preparations may be licensed by the competent authority, or unlicensed and made to the specific needs of patients according to legislation. There are 2 categories of unlicensed pharmaceutical preparations:

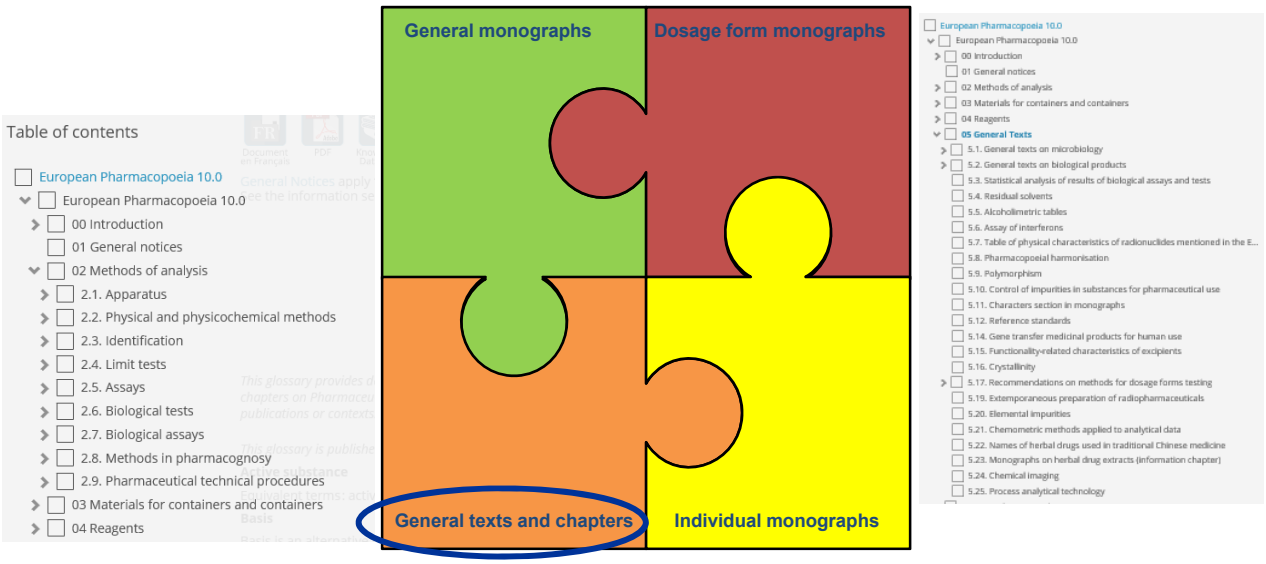
- extemporaneous preparations, i.e. pharmaceutical preparations individually prepared for a specific patient or patient group, supplied after preparation;
- stock preparations, i.e. pharmaceutical preparations prepared in advance and stored until a request for a supply is received.

In addition to this monograph, pharmaceutical preparations also comply with the General Notices and with the relevant general chapters of the Pharmacopoeia. General chapters are normally given for information and become mandatory when referred to in a general or specific 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.

Where relevant, pharmaceutical preparations also comply with the dosage form monographs (e.g. Capsules (0016), Tablets (0478)) and general monographs relating to pharmaceutical preparations (e.g. Allergen products (1063), Herbal teas (1435), Homoeopathic preparations (1038), Homoeopathic pillules, coated (2786), Homoeopathic pillules, impregnated (2079), Immunosera for human use, animal (0084), Immunosera for veterinary use (0030), Live biotherapeutic products for human use (3053), Monoclonal antibodies for human use (2031), Radiopharmaceutical preparations (0125), Vaccines for human use (0153), Vaccines for veterinary use (0062)).

More examples – specific to bio products – to come soon!

The structure of the Ph. Eur.



Why general chapters?

Analytical methods:

- Editorial convenience: avoid repeating standard methods in each monograph
- Provide standard methods that can be used when there is no monograph
- Give general requirements for equipment, equipment qualification or calibration

General chapters

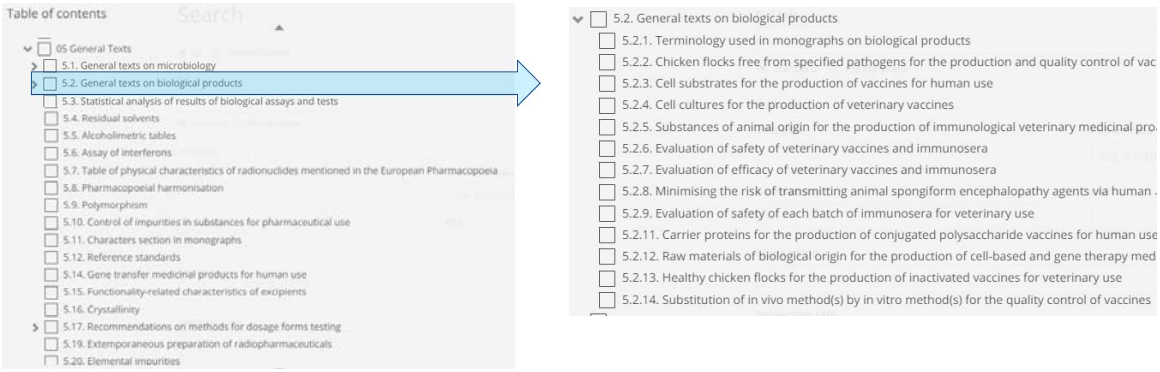
Section 2: Methods of analysis

- *Different subsections such as Subsection 2.6.: Biological tests or Subsection 2.7.: Biological assays*

General chapters

Section 5: General texts

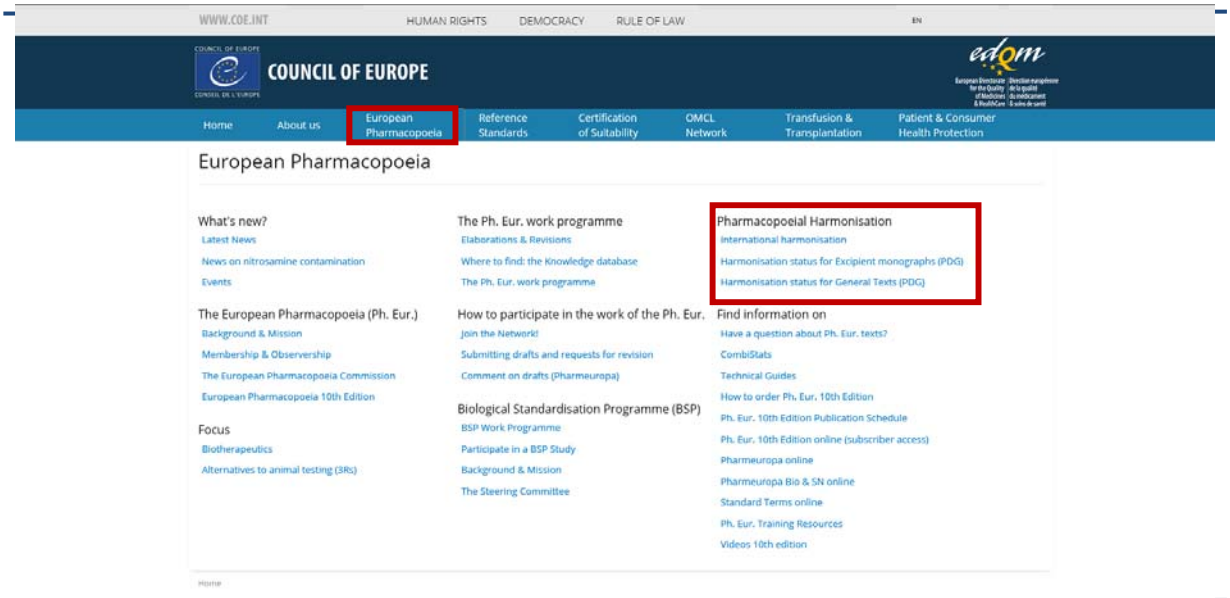
- *Different subsections such as Subsection 5.2 General texts on biological products*



General chapters

- Not mandatory "*per se*"
- When referred to in a monograph, they become part of the standard
- Can be used for substances not covered by monographs → may need validation
- Some general chapters are not referred to in any monograph (*5.8*): useful guidance, can be referred to in applications

Example of Chapter 5.8 _ New EDQM webpage on IH



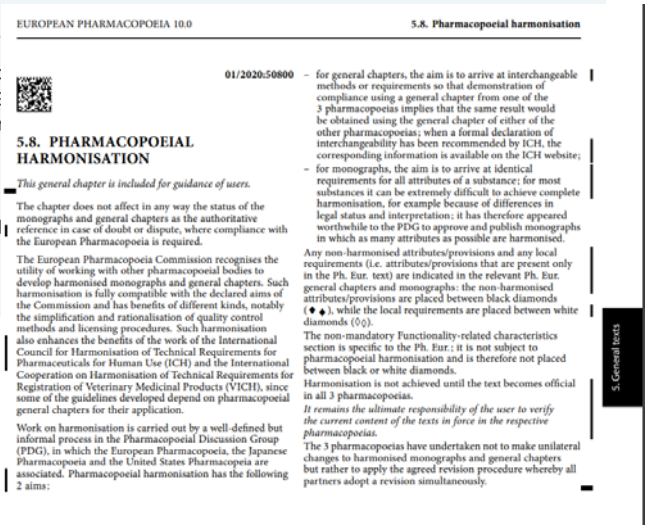
Revision of Ph. Eur. chapter 5.8 as of 10th Edition

Information on texts harmonised by th

General chapter 5.8 *Pharmacopoeia harmonisation* p
and how information is included in harmonised Ph. E
need this information in order to understand and co

Details about the status of individual texts and agree
the tables and documents linked below.

- Harmonisation status for General Texts is availabl
- Harmonisation status for Excipients monographs



EUROPEAN PHARMACOPOEIA 10.0 — 5.8. Pharmacopoeial harmonisation

01/2020:50800

5.8. PHARMACOPOEIAL HARMONISATION

This general chapter is included for guidance of users.

The chapter does not affect in any way the status of the monographs and general chapters as the authoritative reference in case of doubt or dispute, where compliance with the European Pharmacopoeia is required.

The European Pharmacopoeia Commission recognises the utility of working with other pharmacopoeial bodies to develop harmonised monographs and general chapters. Such harmonisation is fully compatible with the declared aims of the Commission and has benefits of different kinds, notably the simplification and rationalisation of quality control methods and licensing procedures. Such harmonisation also enhances the benefits of the work of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), since some of the guidelines developed depend on pharmacopoeial general chapters for their application.

Work on harmonisation is carried out by a well-defined but informal process in the Pharmacopoeial Discussion Group (PDG), in which the European Pharmacopoeia, the Japanese Pharmacopoeia and the United States Pharmacopeia are associated. Pharmacopoeial harmonisation has the following 2 aims:

– for general chapters, the aim is to arrive at interchangeable methods or requirements so that demonstration of compliance using a general chapter from one of the 3 pharmacopoeias implies that the same result would be obtained using the general chapter of either of the other pharmacopoeias; when a formal declaration of interchangeability has been recommended by ICH, the corresponding information is available on the ICH website;

– for monographs, the aim is to arrive at identical requirements for all attributes of a substance; for most substances it can be extremely difficult to achieve complete harmonisation, for example because of differences in legal status and interpretation; it has therefore appeared worthwhile to the PDG to approve and publish monographs in which as many attributes as possible are harmonised.

Any non-harmonised attributes/provisions and any local requirements (i.e. attributes/provisions that are present only in the Ph. Eur. text) are indicated in the relevant Ph. Eur. general chapters and monographs: the non-harmonised attributes/provisions are placed between black diamonds (♦ ♦), while the local requirements are placed between white diamonds (◊◊).

The non-mandatory Functionality-related characteristics section is specific to the Ph. Eur.; it is not subject to pharmacopoeial harmonisation and is therefore not placed between black or white diamonds.

Harmonisation is not achieved until the text becomes official in all 3 pharmacopoeias.

It remains the ultimate responsibility of the user to verify the current content of the texts in force in the respective pharmacopoeias.

The 3 pharmacopoeias have undertaken not to make unilateral changes to harmonised monographs and general chapters but rather to apply the agreed revision procedure whereby all partners adopt a revision simultaneously.

5. General texts

COUNCIL OF EUROPE

Home | About us | European Pharmacopoeia | Reference Standards | Certification of Suitability | OMCL Network | Transfusion & Transplantation | Patient & Consumer Health Protection

Home > European Pharmacopoeia > Pharmacopoeial Harmonisation > Harmonisation status for General Texts (PDG)

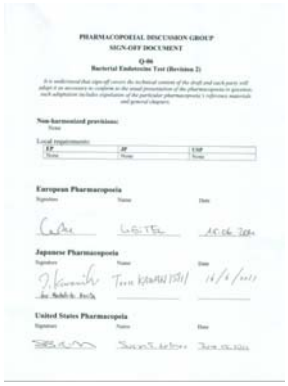
Harmonisation status for General Texts (PDG)

The following table summarises the sign-off coversheets for all general texts under the Pharmacopoeial Discussion Group (PDG) work plan. These coversheets provide detailed helpful information about harmonised parts and local requirements for all individual texts having undergone harmonisation by the PDG. Information is updated after each PDG meeting.

EP HARMONISATION STATUS FOR GENERAL TEXTS (as of 30 October 2019)

PDG#	Ph. Eur. general texts name (Ph. Eur. number)	Coordinating pharmacopoeia	Elaboration/Revision/Correction	Sign-off document	On-going work
B-01	Amino acid analysis (2.2.56)	USP	Revision 1	B01_Rev1_2016_10_Sign-off	–
B-02	Capillary electrophoresis (2.2.47)	Ph. Eur.	Correction 3	B02_Corr3_2018_12_Sign-off	Revision 1 on-going (Stage 1)
B-03	Isoelectric focusing (2.2.54)	USP	Elaboration	B03_2002_09_Sign-off	–
B-04	Total protein (2.5.33)	USP	Suppressed from the PDG work programme in Sept. 2017	–	–
B-05	Peptide mapping (2.2.55)	Ph. Eur.	Elaboration	B05_2002_09_Sign-off	Revision 1 on-going (Stage 2)
B-06	Electrophoresis (2.2.31)	Ph. Eur.	Revision 1	B06_1999_09_Sign-off	–
G-01	Particle-size distribution estimation by analytical sieving (2.9.38)	USP	Revision 1	G01_Rev1_2007_05_Sign-off	–
G-02	Bulk density and tapped density of powders (2.9.34)	Ph. Eur.	Revision 3	G02_Rev3_2013_11_Sign_off	Revision 4 on-going (Stage 2)
G-03	Conductivity (2.2.38)	USP	Correction 1	G03_2019-10_Corr1_Sign-off	–
G-04	Gas pycnometric density of solids (2.9.23)	Ph. Eur.	Elaboration	G04_2007_05_Sign-off	–
G-05	Powder flow (2.9.36)	USP	Elaboration	G05_2004_06_Sign-off	Revision 1 on-going (Stage 2)
G-06	Friability of uncoated tablets (2.9.7)	USP	Elaboration	G06_2004_02_Sign-off	–
					Elaboration

Until Ph. Eur. 9.8 | As of 10th Edition | ICH Q4B



PHARMACOPOEIAL DISCUSSION GROUP
SIGN-OFF DOCUMENT
Q-06
Bacterial Endotoxins Test (Revision 2)

Non-harmonised provisions:

Local requirements:

EP	JP	USP
None	None	None

European Pharmacopoeia

Japanese Pharmacopoeia

United States Pharmacopeia

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

EVALUATION AND RECOMMENDATION OF PHARMACOPOEIAL TEXTS FOR USE IN THE ICH REGIONS ON BACTERIAL ENDOTOXINS TEST GENERAL CHAPTER Q4B ANNEX 14

Current Step 4 version
dated 18 October 2012

Q4B Annex 14 Bacterial Endotoxins Test General Chapter

The ICH Harmonised Annex was finalised under Step 4 in October 2012. This annex is the result of the Q4B process for Bacterial Endotoxins Test General Chapter. It contains the Interchangeability Statement from Health Canada, Canada.

Date of Step 4: 18 October 2012

Status: Step 5

Implementation status:

ANVISA, Brazil - Implemented; Date: 1 November 2010; Reference: RDC 49/2010

EC, Europe - Implemented; Date: 1 November 2012; Reference: CHMP/ICH/529759/2010

FDA, United States - Implemented; Date: 1 October 2013; Reference: Vol. 78, No. 205, p. 63221-2

HSA, Singapore - Not applicable

Health Canada, Canada - Implemented; Date: 29 May 2015; Reference: File #: 16-106255-956

MFDS, Republic of Korea - Implemented; Date: 1 December 2012; Reference: Korean Pharmacopoeia - Bacterial Endotoxins Test, [MFDS Notification No.2011-75,02 March 2011]

MHLW/PMDA, Japan - Implemented; Date: 1 March 2013; Reference: PFSB/ELD Notification No. 0301-1

NMPA, China - In the process of implementation; Reference: Chinese Pharmacopoeia (2015 edition) volume IV, General Chapter 1143 Test for bacterial endotoxin

Swissmedic, Switzerland - Implemented; Date: 18 October 2012; Reference: ICH website

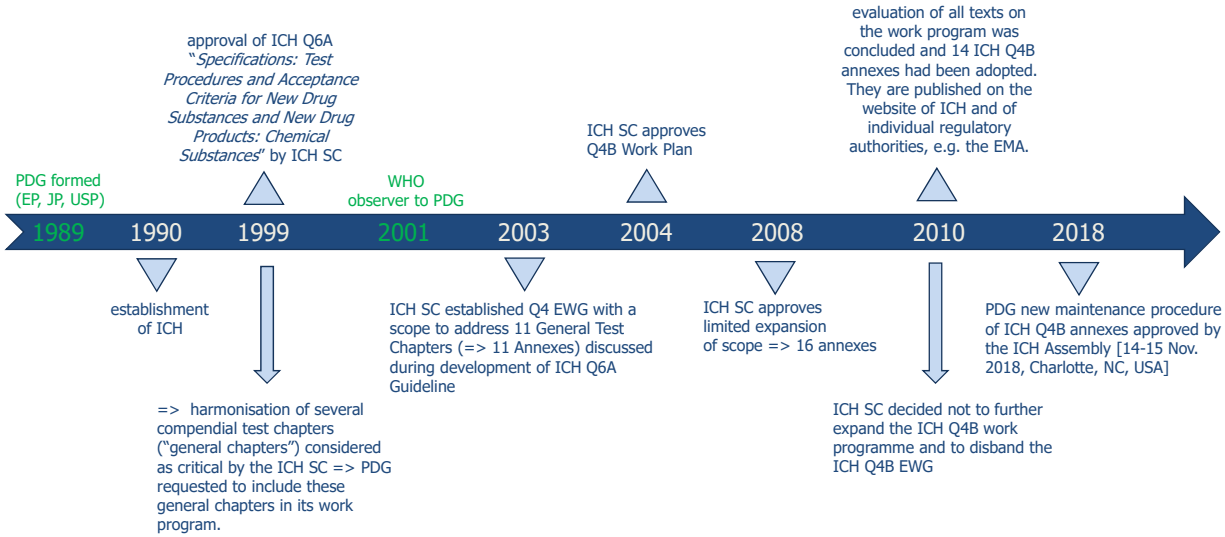
TFDA, Chinese Taipei - Implemented; Date: 12 December 2016; Reference: 1. Chinese Pharmacopoeia 2. Public Announcement for " List for ICH Guidelines Adopted."

Guideline
Q4B Annex 14

Other documents
Q4B Frequently Asked Questions (FAQs)

As far as the Q4B annexes are concerned…

Why a new maintenance procedure? Some history

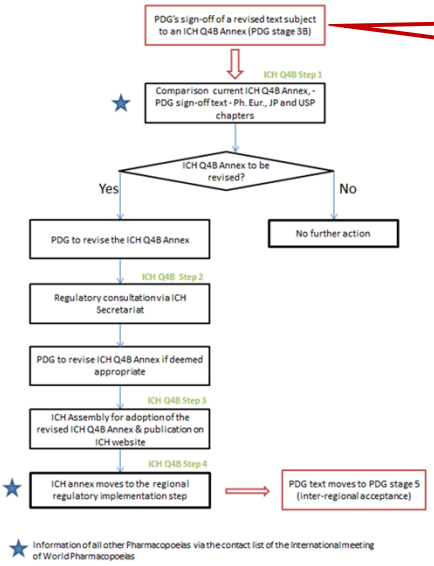


PDG Chapter ⇔ ICH Q4B Annex

CP	PDG Number	PDG Name	Q4B Annex
JP	Q-10	Residue on Ignition	Q4B Annex 1R1 Residue on Ignition/Sulphated Ash
EP	Q-08	Extractable Volume	Q4B Annex 2R1 Test for Extractable Volume of Parenteral Preparations
EP	Q-09	Particulate Contamination	Q4B Annex 3R1 Test for Particulate Contamination: Sub-Visible Particles
EP	Q-05a	Test for Specified Microorganism	Q4B Annex 4AR1 Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests
EP	Q-05b	Microbial Enumeration	Q4B Annex 4BR1 Microbiological Examination of Non-Sterile Products: Tests for Specified Micro-Organisms
EP	Q-05c	Limits for Non-sterile Products	Q4B Annex 4CR1 Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use
USP	Q-02	Disintegration	Q4B Annex 5R1 Disintegration Test
USP	Q-03/04	Uniformity of Content/Mass	Q4B Annex 6 Uniformity of Dosage Units
USP	Q-01	Dissolution	Q4B Annex 7R2 Dissolution Test
EP	Q-11	Sterility Test	Q4B Annex 8R1 Sterility Test
USP	G-06	Tablet Friability	Q4B Annex 9R1 Tablet Friability
EP	B-06	Polyacrylamide Gel Electrophoresis	Q4B Annex 10R1 Polyacrylamide Gel Electrophoresis
EP	B-02	Capillary Electrophoresis	Q4B Annex 11 Capillary Electrophoresis
USP	G-01	Analytical Sieving	Q4B Annex 12 Analytical Sieving
EP	G-02	Bulk Density and Tapped Density	Q4B Annex 13 Bulk Density and Tapped Density of Powders
JP	Q-06	Bacterial Endotoxins	Q4B Annex 14 Bacterial Endotoxins Test

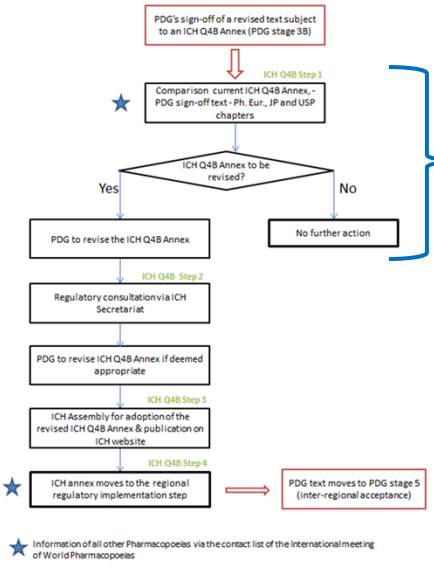
Added by ICH SC to Q4 EWG scope in Nov. 2008

Future Maintenance process of the ICH Q4B Annexes



As with the former ICH Q4B process, the need to revise a Q4B annex would be triggered by PDG's sign-off of a revised text subject to Q4B. Potentially non-harmonised and/or local requirements are highlighted in the sign-off coversheet.

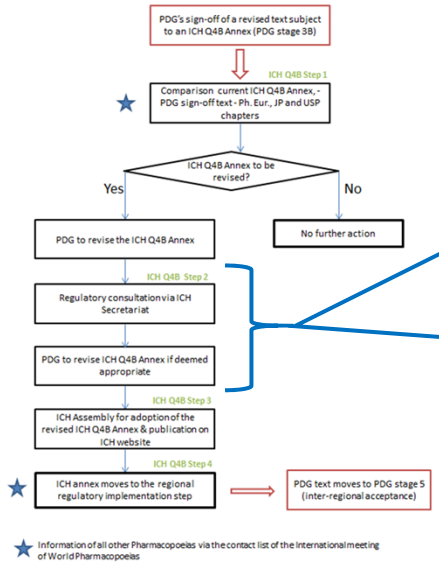
Future Maintenance process of the ICH Q4B Annexes



Step 1:

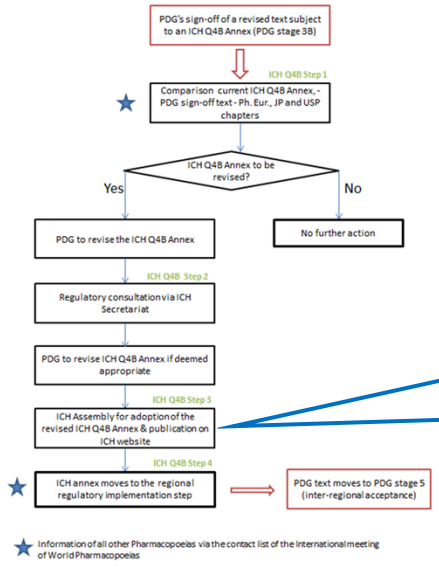
- PDG compares the corresponding current ICH Q4B Annex, the PDG sign-off text as well as the corresponding Ph. Eur., JP and USP chapters as published in the respective Pharmacopoeias. All other pharmacopoeias are informed of the ongoing review via the contact list of the **International meeting of World Pharmacopoeias (IMWP)**.
- Based on this review, the PDG prepares a revised Q4B annex, which is submitted to the ICH Secretariat for proceeding to Step 2. Depending on the case, revision could be limited to an update on the pharmacopoeial reference texts (i.e. updated versions of the pharmacopoeia).

Future Maintenance process of the ICH Q4B Annexes



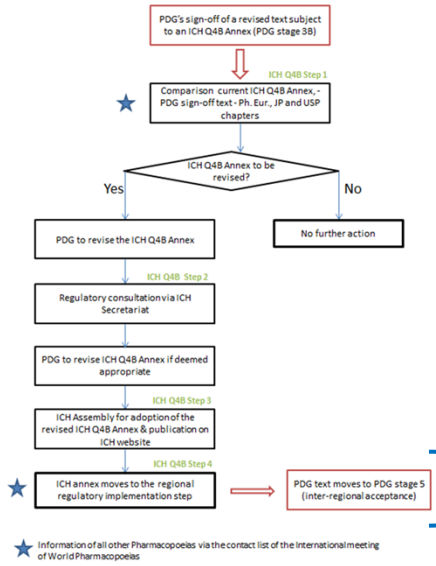
Step 2 (*former ICH Q4B Step 3*):
The draft Q4B annex is submitted to the ICH Secretariat to initiate regulatory consultation (generally for 3 months). The regulatory consultation and discussion should focus on the Q4B Outcome in the annex, i.e. regulatory interchangeability; comments on the harmonised pharmacopoeial text itself are not expected. Comments will be evaluated by PDG and the annex revised by PDG, where necessary.

Future Maintenance process of the ICH Q4B Annexes



Step 3 (*former ICH Q4B Step 4*):
PDG submits the revised annex to the ICH Assembly for adoption and publication on the ICH website.

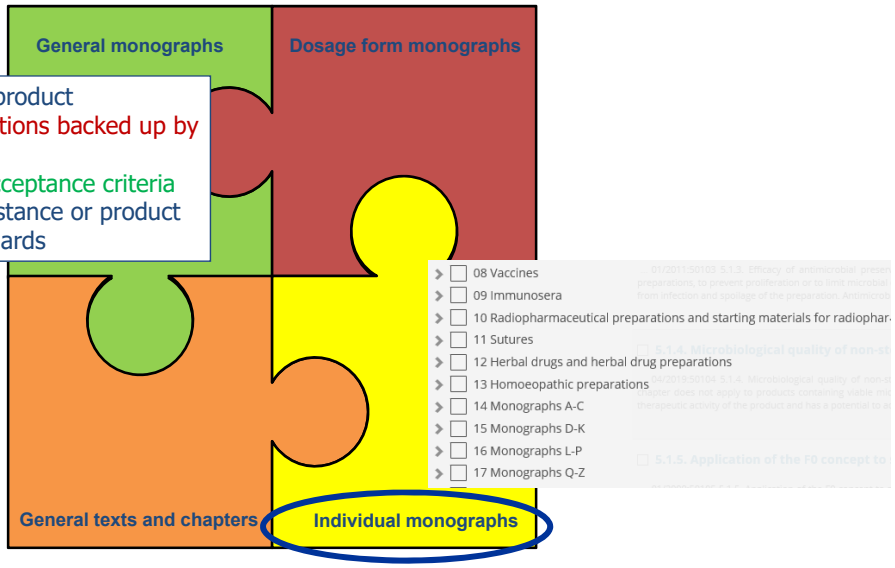
Future Maintenance process of the ICH Q4B Annexes



Step 4 (*former ICH Q4B Step 5*):
The annex moves to the regional regulatory implementation step. The corresponding PDG chapter moves to PDG stage 5 (inter-regional acceptance). All other pharmacopoeias are informed via the contact list of the **International meeting of World Pharmacopoeias (IMWP)**.

The structure of the Ph. Eur.

- Specifications for individual product
- Based on approved specifications backed up by batch data
- Analytical procedures and acceptance criteria to demonstrate that the substance or product meets required quality standards



Concrete examples – specific to bio products – to come soon!

Thank you for your attention

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