

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



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.?

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How to consult the European Pharmacopoeia

User manual

Key to monographs

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KEY TO MONOGRAPHS (ONLINE VERSION)

Document en Français PDF Knowledge Database General Monographs General Notices

CH₃N₃O₅

[2232-64-8]

DEFINITION
Ethyl 3-methyl-2-thioxo-2,3-dihydro-1H-imidazole-1-carboxylate.
Content: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS
Appearance: white or yellowish-white, crystalline powder.
Solubility: slightly soluble in water, soluble in acetone and in ethanol (96 per cent).

IDENTIFICATION
First identification: B.
Second identification: A, C, D.
A. Melting point (2.2.14): 122 °C to 125 °C.
B. Infrared absorption spectrophotometry (2.2.24).
Comparison: carbimazole CRS.
C. Thin-layer chromatography (2.2.27).
Test solution: Dissolve 10 mg of the substance to be examined in methylene chloride R and dilute to 10.0 mL.
Reference solution: Dissolve 10 mg of carbimazole CRS in methylene chloride R and dilute to 10.0 mL with R.
Plate: TLC silica gel F₂₅₄ plate R.
Mobile phase: acetone R, methylene chloride R (20:80 V/V).
Application: 10 µL.
Development: over 3/4 of the plate.
Drying: in air for 30 min.

CARBIMAZOLE (CODE: ACTY)
Carbimazolium
CCOC(=O)N1C=NC(S1)=N

CH₃N₃O₅

[2232-64-8]

DEFINITION
Ethyl 3-methyl-2-thioxo-2,3-dihydro-1H-imidazole-1-carboxylate.
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Comparison: carbimazole CRS.
C. Thin-layer chromatography (2.2.27).
Test solution: Dissolve 10 mg of the substance to be examined in methylene chloride R and dilute to 10.0 mL with the same solvent.
Reference solution: Dissolve 10 mg of carbimazole CRS in methylene chloride R and dilute to 10.0 mL with the same solvent.
Plate: TLC silica gel F₂₅₄ plate R.
Mobile phase: acetone R, methylene chloride R (20:80 V/V).
Application: 10 µL.
Development: over 3/4 of the plate.
Drying: in air for 30 min.
Detection: examine in ultraviolet light at 254 nm.
Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.
D. Dissolve about 10 mg in a mixture of 0.5 mL of dilute hydrochloric acid R and 50 mL of water R. Add 1 mL of potassium iodobismuthate solution R. A red precipitate is formed.

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Where do I find the Key to Monographs?

Important - Please read this before continuing

Terms and conditions of use
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About the European Pharmacopoeia
This menu page provides information on the European Pharmacopoeia and its editions. The monographs and are compiled from paper versions. In view of the linguistic environment, any rendering of the text from the print and refer to the PDF version.

Key to Monographs

Carbimazole
EUROPEAN PHARMACOPOEIA 10.0
Version date of the test
Test reference number
Modification to be taken into account as soon as possible and not later than the end of the month following the month of publication of Ph. Eur. 10.0 (see section IV, Contents of the 10th Edition)
Link to further information on the test (e.g. Knowledge database) for smartphone/tablets with camera and barcode reader app
CAS number
Chemical name in accordance with IUPAC, nomenclature rules
For the meaning of black and white diamonds see chapter 5.8, Pharmaceutical harmonisation
Application of the first and second identification is defined in the General Notices (chapter 1)
Reference standard available from the EDQM (see <http://www.edqm.eu>)
Reagent described in chapter 4
Further information on certain reagents available in the Knowledge database (<http://knowledge.edqm.eu>)
Vertical line in the margin indicating where the text has been modified
Horizontal line in the margin indicating where part of the text has been deleted
Reference to a general chapter

en using the Ph. Eur.?

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

EUROPEAN PHARMACOPOEIA 10.0

Vaccines for human use

1: 50 of 42

Sort by: Default

Some excerpts

50 rows

Anthrax vaccine for human use (adsorbed, prepared from culture filtrates)

Correction date: 10.0 (31/08/2019) Implementation date: 01/2019 (9.6) Test number: 2188

01/2019:2188 corrected 10.0 Anthrax vaccine for human use (adsorbed, prepared from culture filtrates) Vaccinum anthracis adsorbatum ab cocto culturae et alium humanum DEFINITION Anthrax vaccine for human use (adsorbed, prepared from culture filtrates) is a preparation of Bacillus anthracis antigens precipitated by aluminium potassium sulfate. The antigens are prepared from a sterile culture filtrate produced by a non-encapsulated strain, either avirulent or attenuated, of B. anthracis. The main

BCG for immunotherapy

Implementation date: 01/2009 (6.3) Test number: 1929

01/2009:1929 BCG for immunotherapy BCG ad immunisationem DEFINITION BCG for immunotherapy is a freeze-dried preparation of live bacteria derived from a culture of the bacillus of Calmette and Guérin (Mycobacterium bovis BCG) whose capacity to protect against tuberculosis has been established. It complies with the monograph Vaccines for human use (01/13). PRODUCTION General provisions BCG for immunotherapy shall be produced by a staff consisting of healthy persons who do not work with other infectious agents, in particular

BCG vaccine, freeze-dried

Implementation date: 01/2012 (7.3) Test number: 0163

01/2012:0163 BCG vaccine, freeze-dried Vaccinum tuberculosis (BCG) cryodesiccatum DEFINITION Freeze-dried BCG vaccine is a preparation of live bacteria derived from a culture of the bacillus of Calmette and Guérin (Mycobacterium bovis BCG) whose capacity to protect against tuberculosis has been established. PRODUCTION General provisions BCG vaccine shall be produced by a staff consisting of healthy persons who do not work with other infectious agents, in particular they shall not work with virulent

Cholera vaccine (inactivated, oral)

Implementation date: 01/2008 (6.6) Test number: 2327

01/2008:2327 Cholera vaccine (inactivated, oral) Vaccinum cholerae peroris inactivatum DEFINITION Cholera vaccine (inactivated, oral) is a homogeneous suspension of inactivated vibrio strains of Vibrio cholerae serogroup O1, representing serotypes and biotypes of epidemic strains. The vaccine may contain the B subunit of cholera toxin (CTB). Just prior to ingestion, one dose of vaccine suspension is mixed with a suitable buffer as

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

EUROPEAN PHARMACOPOEIA 10.0

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

01/2020:2928

INFLIXIMAB CONCENTRATED SOLUTION

Infliximabum solutio concentrata

Heavy chain

EVPLSDSDG LVGPGDSHGL ICYAGGPTFS SNNNNWQDQ 40
 EKSLKSLGK EKASLISAT NYAGYVGRF TIRKGGGSA 80
 VYLGKSLDT KDFGVYVGR NYGUYVGRF QKYLTVYGR 120
 ATGKGVYVY LAFSGKSTG GTALGKGLV DFFGVYVGR 160
 NKKALTSYD STFVAVLGR GLYLSGVYT VYSGKSTGQ 200
 YVGNKGVYV STFVAVLGR KSCGVYVGR FCKVAVLGR 240
 KVTSLFVGR KSTLALSTG EYTCVYVGR KGVGVYVGR 280
 YVGVGVYV KTFVGVYV EYTCVYVGR KGVGVYVGR 320
 EYGVGVYV LAFVGVYV KGVGVYVGR KGVGVYVGR 360
 LKGVGVYV LVGVGVYV KGVGVYVGR KGVGVYVGR 400
 LKGVGVYV EYTCVYVGR KGVGVYVGR KGVGVYVGR 440
 KGVGVYVGR 480

Light chain

KVLLGVYV LKGVGVYV EYTCVYVGR KGVGVYVGR 40
 KGVGVYV KGVGVYV EYTCVYVGR KGVGVYVGR 80
 KGVGVYV KGVGVYV EYTCVYVGR KGVGVYVGR 120
 KGVGVYV KGVGVYV EYTCVYVGR KGVGVYVGR 160
 KGVGVYV KGVGVYV EYTCVYVGR KGVGVYVGR 200
 KGVGVYV KGVGVYV EYTCVYVGR KGVGVYVGR 240
 KGVGVYV KGVGVYV EYTCVYVGR KGVGVYVGR 280
 KGVGVYV KGVGVYV EYTCVYVGR KGVGVYVGR 320
 KGVGVYV KGVGVYV EYTCVYVGR KGVGVYVGR 360
 KGVGVYV KGVGVYV EYTCVYVGR KGVGVYVGR 400
 KGVGVYV KGVGVYV EYTCVYVGR KGVGVYVGR 440
 KGVGVYV KGVGVYV EYTCVYVGR KGVGVYVGR 480

Sample to be tested



07/2014:10000
corrected 10.0**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 regulatory 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, or defined period of validity and/or specifications for opened or unopened 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 when 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 as 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 a part 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 utilize 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.

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 relevant section of the general monograph, except where a possible limit to 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 laboratory.

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



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

IMPORTANT NOTICE**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 monograph, 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 when necessary and republished in each supplement.

Allergen products (1083)
Chemical precursors for radiopharmaceutical preparations (2902)
Dosage Forms monographs
(published in the Dosage Forms section or the Homoeopathic Preparations section, as appropriate)
Essential oils (2098)
Herbal drug extracts (0763)
Herbal drug preparations (1434)
Herbal drugs (1433)
Herbal drugs for homoeopathic preparations (2043)
(published in the Homoeopathic Preparations section)
Herbal teas (1435)
Herbal teas, instant (2620)
Homoeopathic preparations (1038)
(published in the Homoeopathic Preparations section)
Immunoassays for human use (0044)
Immunoassays for veterinary use (0030)
Live biotechnological products for human use (2053)
Methods of preparation of homoeopathic stocks and potentisation (2371)
(published in the Homoeopathic Preparations section)
Monoclonal antibodies for human use (2051)
Mother tinctures for homoeopathic preparations (2026)
(published in the Homoeopathic Preparations section)
Pharmaceutical preparations (2619)
Products of fermentation (1446)
Products with risk of transmitting agents of animal spongiform encephalopathies (1483)
Radiopharmaceutical preparations (0125)
Recombinant DNA technology, products of (0784)
Substances for pharmaceutical use (2034)
Vaccines for human use (0153)
Vaccines for veterinary use (0062)
Vegetable fatty oils (1379)

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

3

Knowledge database

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

Search Database online

Knowledge Database

**Detailed view of Etanerceptum.**

Status	In Use																											
Monograph Number	02895																											
English Name	Etanercept																											
French Name	Étanercept																											
Latin Name	Etanerceptum																											
Pharmacopoeia	28.2																											
Published in English Supplement	9.8																											
Published in French Supplement	9.8																											
On-going	Minor revision																											
State of work	4 - DEF																											
Pharmaceutic																												
Description	Impurities with molecular masses greater than that of etanercept: resolution. Sialic acid: preparation of standard solutions																											
Chromatogram	Available																											
Additional information	Not available																											
History	View history																											
Interchangeable (ICH_Q4B)	NO																											
Pharmaceutical harmonisation	NO																											
Reference standards	<table><tr><th>Available since</th><th>Cat. No.</th><th>Name</th><th>Batch No.</th><th>Unit</th><th>Quantity</th><th>Price</th><th>SDS</th><th>Product Code</th></tr><tr><td></td><td>Y0001350</td><td>Etanercept CRS</td><td></td><td>1</td><td>25 mg</td><td>79 EUR</td><td></td><td></td></tr><tr><td></td><td>Y0002042</td><td>Etanercept USP</td><td></td><td>1</td><td>50 mg</td><td>120 EUR</td><td></td><td></td></tr></table>	Available since	Cat. No.	Name	Batch No.	Unit	Quantity	Price	SDS	Product Code		Y0001350	Etanercept CRS		1	25 mg	79 EUR				Y0002042	Etanercept USP		1	50 mg	120 EUR		
Available since	Cat. No.	Name	Batch No.	Unit	Quantity	Price	SDS	Product Code																				
	Y0001350	Etanercept CRS		1	25 mg	79 EUR																						
	Y0002042	Etanercept USP		1	50 mg	120 EUR																						
Test(s)	Brand Name(s) / Information Glycan analysis Glycan analysis Peptide mapping Peptide mapping Sialic acid Related proteins Impurities with molecular masses greater than that of etanercept Ultraphere C18 by Beckman (Cat. No. AT235329). TSK-GEL Butyl-NR6 by Tosoh (Cat. No. 30-051-710). VME Duo-300 SEC (Cat. No. DL30055-3008WT).																											
Practical Information																												

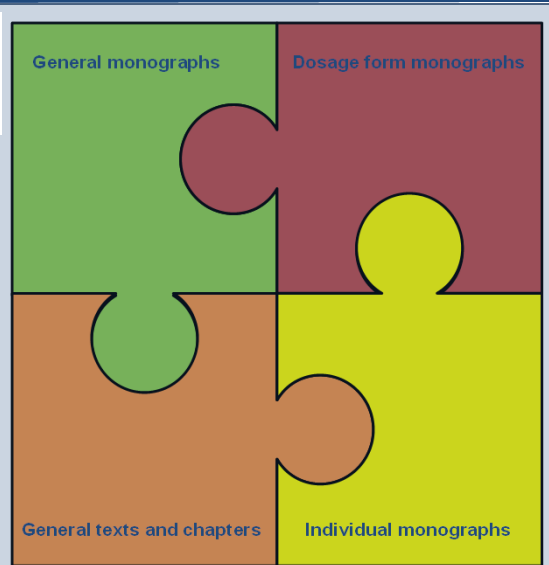
The structure of the Ph. Eur.



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

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- > ☐ 02 Methods of analysis



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



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



1. GENERAL NOTICES

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In the texts of the European Pharmacopoeia, the word "Pharmacopoeia" includes qualification names 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 text of the Pharmacopoeia are alone using the monograph title and reference number in full.

A preparation must comply throughout its period of validity with the requirements of the monograph and specifications for period of validity. 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, preparations in monographs contain no preservatives. General chapters bearing mandatory when referred to in a monograph, unless such reference is made in a way that indicates that it is not the intention to refer to the monograph in mandatory but rather to cite it for information.

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

Quality systems. The quality standards represented by monographs are valid only when the article in question is produced within the framework of a suitable quality system. The quality system must ensure that the article consistently meets the requirements of the monograph.

Alternative methods. The tests and assays described as the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authorities, alternative methods may be used for control purposes, provided that the methods used result in equivalent results to the official methods. 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 a test of Pharmacopoeia quality unless it complies with all the requirements stated in the monograph. This does not imply the performance of all the tests in a monograph is necessarily a prerequisite for a manufacturer to accept 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.

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

(2) An enhanced approach to quality control could utilize process analytical technology (PAT) online and time release testing (including potentially relevant) 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 minimized 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, particular grades are specified, or an insufficiently defined characteristic that is relevant to the use of the substance may be applied to the monograph for information. But articles for demonstration 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 noted in the individual monograph.

Validation of pharmaceutical 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 pharmaceutical methods. When implementing a pharmaceutical 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 criteria.

Conventional terms. The terms "competent authority" mean the national, regional or international body or organization vested with the authority for making decisions concerning the tests in question. It may, for example, be a national pharmaceutical authority, a licensing authority or an official control laboratory. The expression "unless otherwise justified and authorized" means that the requirements have to be met, unless the

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

1. General notices

EUROPEAN PHARMACOPOEIA 10.0

competent authority authorize a modification or an exception, where justified in a particular case.

Arguments concerning the word "should" are informative or advisory. In certain monographs in other texts, the terms "suitable" and "appropriate" are used to describe a request, minor exception, test method or, 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. Additives, solvents, antimicrobial preservatives, diluents, antioxidants, for example, are excipients.

Interchangeable methods. Certain general chapters contain a method that the user is expected to implement with the corresponding test of the European Pharmacopoeia and/or the United States Pharmacopoeia and that these tests are interchangeable. This implies that if a substance or preparation is found to comply with the method 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.

Reference to regulatory documents. Monographs and general chapters of the Pharmacopoeia are subject to revision and may be replaced by regulatory authorities for medicinal, 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 is to be taken for examination in 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. Weighing, the precision corresponds to plus or minus 3 units after the last figure stated (the 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 (the example, 10.0 mL or 0.30 mL), the volume is

measured using a pipette, a volumetric flask or a burette, or appropriate, where fitted, a graduated measuring cylinder or a graduated pipette may be used. Volumes stated in micro litres are measured using a micropipette or microburette.

It is recognized, 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 suitably improved accuracy.

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

Unless otherwise prescribed, comparative tests are carried out using identical values of reference, impure, standard glass with a flat base, the volume of liquid prescribed are for use with tubes having an internal diameter of 10 mm. But tubes with a larger internal diameter may be used provided the volume of liquid used is adjusted (11.0). Liquid volumes of the liquids to be compared are contained 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 standardized to the indicator, unless a black 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.

When drying is prescribed using one of the expressions "to constant mass" and "ignited to constant mass", these conditions described in the Pharmacopoeia and the suitability of the results depend on 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.

Substances. Where the name of the substance is not stated, the term "substance" implies a substance in water. When 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 (2000) is used, except that for many purposes the requirements for bacterial endotoxins (Particular notice in bulk) and microbial contamination (Particular notice in bulk) are not relevant. The term "distilled water" indicates purified water prepared by distillation.

The term "ethanol" without qualification means anhydrous ethanol. The term "ethanol" without qualification means ethanol (96 per cent). Other dilutions of ethanol are indicated by the term "ethanol" or "diluted" followed by a statement of the percentage by volume of ethanol (C₂H₅O) required.

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

1. per cent w/w (percentage, mass to mass) expresses the number of grams of substance in 100 g of final product, measured using a pipette, a volumetric flask or a burette, or appropriate, where fitted, a graduated measuring cylinder or a graduated pipette may be used. Volumes stated in micro litres are measured using a micropipette or microburette.

See the information section on general monographs (cover pages)

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 \neq **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?

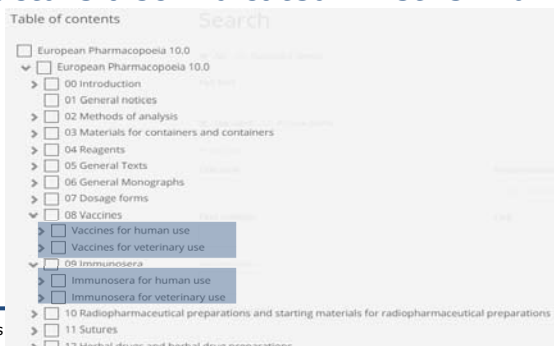
- **Validation of pharmacopoeial methods.** The test methods given in monographs and general chapters have been validated in accordance with accepted scientific practice and current recommendations on analytical validation. **Unless otherwise stated in the monograph or general chapter, validation of 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:



The screenshot shows the 'Table of contents' for the European Pharmacopoeia 10.0. It is a hierarchical list with expandable/collapsible icons (chevrons) next to each item. The items are: European Pharmacopoeia 10.0, 00 Introduction, 01 General notices, 02 Methods of analysis, 03 Materials for containers and containers, 04 Reagents, 05 General Texts, 06 General Monographs, 07 Dosage forms, 08 Vaccines, 09 Immunoserum, 10 Radiopharmaceutical preparations and starting materials for radiopharmaceutical preparations, 11 Sutures, and 12 Herbal drugs and herbal drug preparations. The '08 Vaccines' and '09 Immunoserum' sections are expanded, showing sub-items for 'human use' and 'veterinary use'.

Section	Sub-section
European Pharmacopoeia 10.0	
00 Introduction	
01 General notices	
02 Methods of analysis	
03 Materials for containers and containers	
04 Reagents	
05 General Texts	
06 General Monographs	
07 Dosage forms	
08 Vaccines	Vaccines for human use Vaccines for veterinary use
09 Immunoserum	Immunoserum for human use Immunoserum for veterinary use
10 Radiopharmaceutical preparations and starting materials for radiopharmaceutical preparations	
11 Sutures	
12 Herbal drugs and herbal drug preparations	

1. GENERAL NOTICES:

1.4. MONOGRAPHS

Section 1.4 Monographs

EUROPEAN PHARMACOPOEIA 10.0

1. General notices

1. General notices

DEFINITION

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

1.4.1. Substances and preparations

Containers, materials used for containers are described in general chapter 1.2. General notices and for materials, particularly plastic materials, each cover a range of products having not only the properties of the principal constituent but also in the address used. The test methods and limits for materials depend on the formulation and are described applicable only for materials whose formulation is covered by the monograph. The use of appropriate words

requirements on containers, where necessary, must, they may exist, for example, to ensure materials in the manufacturing process that are in relation and control, as to 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 as a sample of the final article by an independent analyst. The competent authority may establish that the manufacturer has been followed, for example, by examination of data received from the manufacturer for

The term 'batch' is used to describe a mixture where only one of the components varies. The term 'batch' is used to describe a liquid that is suitable in all proportions with the stated solvent.

IDENTIFICATION

Notes: 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

substance, in the form in which it is presented, corresponds to the description given in the monograph.

1.4.2. Substances and preparations

Containers, materials used for containers are described in general chapter 1.2. General notices and for materials, particularly plastic materials, each cover a range of products having not only the properties of the principal constituent but also in the address used. The test methods and limits for materials depend on the formulation and are described applicable only for materials whose formulation is covered by the monograph. The use of appropriate words

CHARACTERS

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

1.4.3. Substances and preparations

Containers, materials used for containers are described in general chapter 1.2. General notices and for materials, particularly plastic materials, each cover a range of products having not only the properties of the principal constituent but also in the address used. The test methods and limits for materials depend on the formulation and are described applicable only for materials whose formulation is covered by the monograph. The use of appropriate words

requirements on containers, where necessary, must, they may exist, for example, to ensure materials in the manufacturing process that are in relation and control, as to 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 as a sample of the final article by an independent analyst. The competent authority may establish that the manufacturer has been followed, for example, by examination of data received from the manufacturer for

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

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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.

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.

1.4.4. Substances and preparations

Containers, materials used for containers are described in general chapter 1.2. General notices and for materials, particularly plastic materials, each cover a range of products having not only the properties of the principal constituent but also in the address used. The test methods and limits for materials depend on the formulation and are described applicable only for materials whose formulation is covered by the monograph. The use of appropriate words

requirements on containers, where necessary, must, they may exist, for example, to ensure materials in the manufacturing process that are in relation and control, as to 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 as a sample of the final article by an independent analyst. The competent authority may establish that the manufacturer has been followed, for example, by examination of data received from the manufacturer for

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

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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 of 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.

CAS registry numbers are included for information in monographs, where applicable, to provide convenient access to useful information for users. CAS Registry Number® is a registered trademark of the American Chemical Society.

DEFINITION

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

CHARACTERISTICS

The statements under the heading Characteristics are not to be interpreted as a strict name and are test requirements.

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

1. General notices

EUROPEAN PHARMACOPOEIA 10.0

Stability. In statements of stability in the Characteristics section, the terms used have the following significance, related to a temperature between 15 °C and 25 °C.

Descriptor term	Approximate values of relative or absolute per cent of active
Very stable	More than 99
Stable	More than 90
Slightly stable	More than 80
Not stable	More than 70
Highly unstable	More than 60
Very highly unstable	More than 50
Practically unstable	More than 40

The term 'practically stable' is used to describe a mixture where only one of the components degrades. The term 'stable' is used to describe a liquid that is stable to all proportions with the stated solvent.

IDENTIFICATION

Notes. 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

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.

practice requires that it be stated, test also below under 'Impurities'.

Calculation. Where the result of a test or assay is required to be calculated with reference to the dried or anhydrous substance or on some other specified basis, the determination of loss on drying, water content or other property is carried out by the method prescribed in the relevant test in the monograph. The result (dried substance) or anhydrous substance (etc.) figure is printed in parentheses after the result.

Where a quantitative determination of a residual solvent is required and a test for loss on drying is not carried out, the content of residual solvent is taken into account for the calculation of the assay content of the substance, the specific optical rotation and the specific absorbance. No further indication is given in the specific monograph.

Limits. The limits prescribed are based on data obtained in normal analytical practice; they take account of normal analytical errors, of acceptable variations in manufacture and accompanying need of deterioration to an extent considered acceptable. No further information is to be applied in the limits prescribed to determine whether the article being examined complies with the requirements of the monograph.

In determining compliance with a numerical limit, the calculated result of a test or assay is first rounded to the number of significant figures stated, when otherwise prescribed. The limits, regardless of whether the values are expressed as percentages or as absolute values, are considered significant to the last digit shown (for example 100 indicates 1 significant figure). The last figure of the result is rounded by one when the part rejected is equal to or exceeds one half unit, whereas it is not rounded when the part rejected is less than a half unit.

Indication of permitted limit of impurities. The acceptance criteria for related substances are expressed in monographs either in terms of percentage of peak area (compared to total or to material peak). For comparative tests, the appropriate content of impurity related, or the ratio of impurities, may be indicated to facilitate interpretation only. Acceptance or rejection is determined on the basis of compliance or non-compliance with the stated test. If the use of a reference

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.

Intermediate reference standards, master reference standards, biological reference preparations, reference spectra, first and second reference standards, The European Pharmacopoeia (Ph. Eur.) defines reference standards, which are used as reference standards in the assay of substances. These reference standards are available from the European Directorate for the Quality of Medicines & HealthCare (EDQM). Information on the available reference standards and a batch release statement can be obtained via the EDQM website.

1.5. ABBREVIATIONS AND SYMBOLS

A Abbreviations

A₁ Specific absorbance

A₂ Relative density

A₃ Specific optical rotation

bp Boiling point

ESP Biological reference preparation

10/100 dose The smallest quantity of a test that, in the conditions of the test, when mixed with 10.0 EC of antimicrobial and incubated with 10.0 EC of the test article within a given period.

10/10 dose The smallest quantity of a test that, in the conditions of the test, when mixed with 10.0 EC of antimicrobial and incubated with 10.0 EC of the test article within a given period.

10/10 dose The smallest quantity of a test that, in the conditions of the test, when mixed with 10.0 EC of antimicrobial and incubated with 10.0 EC of the test article within a given period.

10/10 dose The quantity of test or tested that dissolves in the shortest time with 10.0 EC of antimicrobial.

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

The structure of the Ph. Eur.

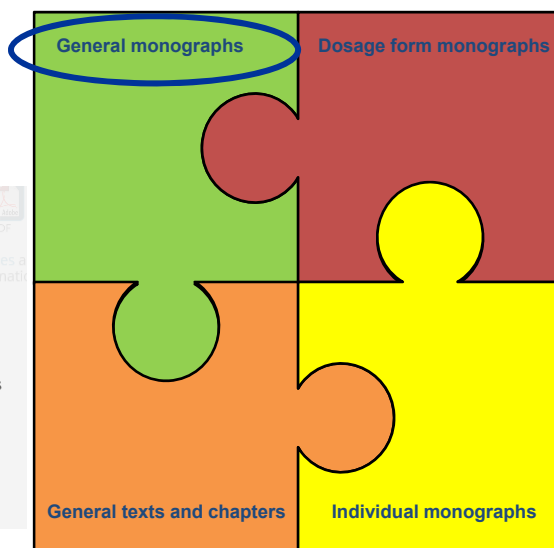


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➤ ☐ 00 Introduction

➤ ☐ 01 General notices

➤ ☐ 02 Methods of analysis

➤ ☐ 03 Materials for containers and containers

➤ ☐ 04 Reagents

➤ ☐ 05 General Texts

➤ ☐ 06 General Monographs

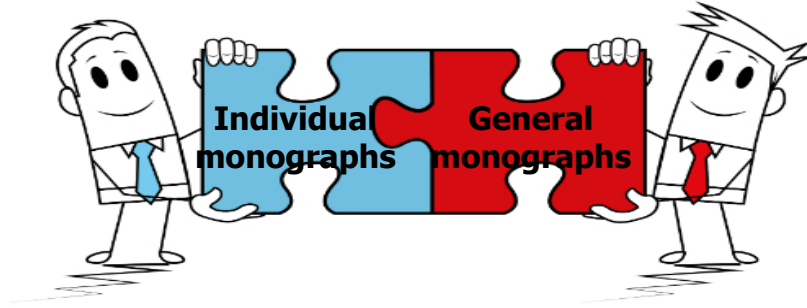
➤ ☒ 07 Dosage forms

➤ ☐ 08 Vaccines

[illegible]

<p>IMPORTANT NOTICE</p> <p>GENERAL MONOGRAPHS</p> <p>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). When 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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Product with risk of transmitting agents or other significant microorganisms (1301)</p> <p>Recombinant DNA technology: products of (1674)</p> <p>Substances for pharmaceutical use (1304)</p> <p>Vaccines for human use (1317)</p> <p>Vaccines for veterinary use (1682)</p> <p>Vegetable fatty oils (1376)</p>	<p>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). When 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.</p> <p>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.</p>
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General vs. individual monographs



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

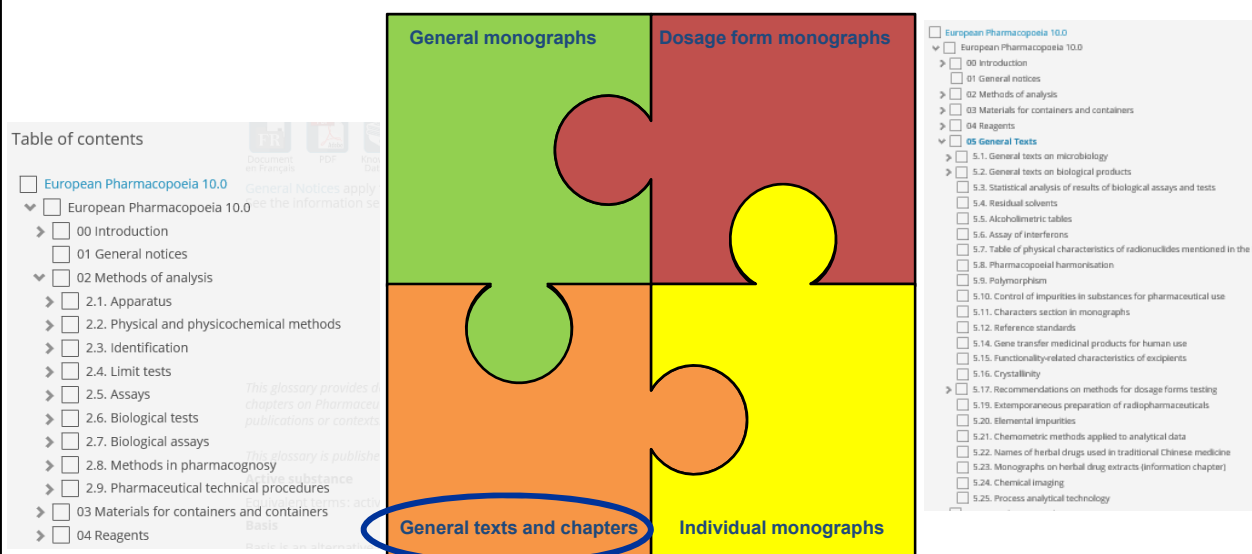
General monographs

- 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!

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

The structure of the Ph. Eur.



Why general chapters?

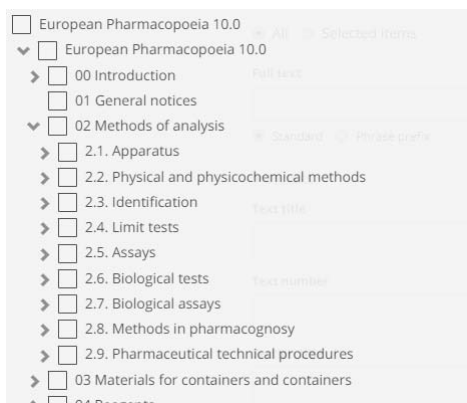
Analytical methods:

- 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*



The screenshot shows a web-based navigation menu for the European Pharmacopoeia 10.0. The menu is organized into a tree structure with expandable/collapsible arrows. The 'Methods of analysis' section is expanded, showing various subsections. To the right of the menu, there are search filters: 'All' and 'Selected items' at the top, and 'Full text', 'Standard', 'Phrase prefix', 'Text title', and 'Text number' below. The menu items include: European Pharmacopoeia 10.0, 00 Introduction, 01 General notices, 02 Methods of analysis, 2.1. Apparatus, 2.2. Physical and physicochemical methods, 2.3. Identification, 2.4. Limit tests, 2.5. Assays, 2.6. Biological tests, 2.7. Biological assays, 2.8. Methods in pharmacognosy, 2.9. Pharmaceutical technical procedures, 03 Materials for containers and containers, and 04 Reagents.

- ☐ European Pharmacopoeia 10.0
- ▼ ☐ European Pharmacopoeia 10.0
 - ☐ 00 Introduction
 - ☐ 01 General notices
 - ▼ ☐ 02 Methods of analysis
 - ☐ 2.1. Apparatus
 - ☐ 2.2. Physical and physicochemical methods
 - ☐ 2.3. Identification
 - ☐ 2.4. Limit tests
 - ☐ 2.5. Assays
 - ☐ 2.6. Biological tests
 - ☐ 2.7. Biological assays
 - ☐ 2.8. Methods in pharmacognosy
 - ☐ 2.9. Pharmaceutical technical procedures
 - ☐ 03 Materials for containers and containers
 - ☐ 04 Reagents

General chapters

Section 5: General texts

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

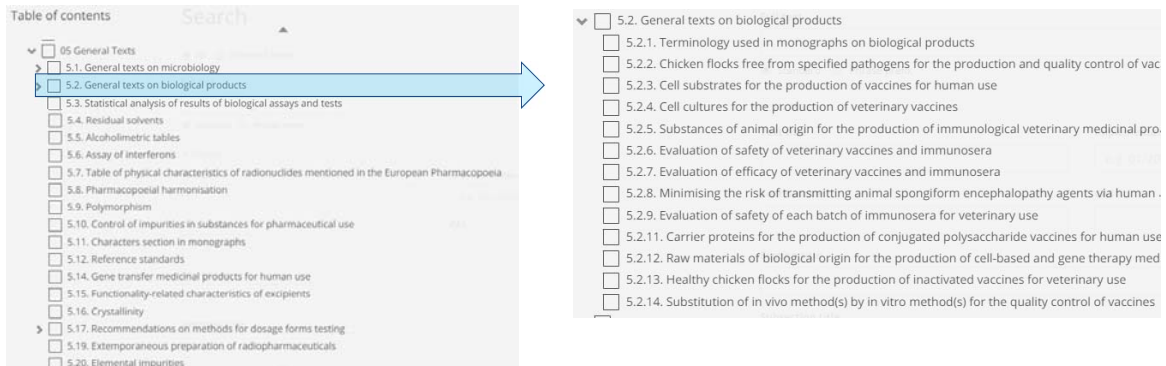


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General chapters

- 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

WWW.COE.INT HUMAN RIGHTS DEMOCRACY RULE OF LAW EN

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of Medicines
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European Pharmacopoeia

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PHOTOP

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

Information on texts harmonised by the

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

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

- ▶ Harmonisation status for General Texts is available
- ▶ Harmonisation status for Excipients monographs

EUROPEAN PHARMACOPOEIA 10.0

5.8. Pharmacopoeial harmonisation



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 Pharmacopoeia 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.

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

The diagram illustrates the transition from the original ICH Q4B Annex 14 (left) to the 10th edition (right). The original version is a dense, multi-column document. The 10th edition is a more structured, single-column document with a clear title and a table of contents. The 10th edition is titled "ICH HARMONISED TECHNICAL OVERVIEW" and "EVALUATION AND RECOMMENDATION OF PHARMACOPOEIAL TEXTS FOR USE IN THE ICH REGION". It includes a table of contents and a list of countries/regions that have implemented the standard.

ICH HARMONISED TECHNICAL OVERVIEW

EVALUATION AND RECOMMENDATION OF PHARMACOPOEIAL TEXTS FOR USE IN THE ICH REGION

ON BACTERIAL ENDOTOXINS TEST

GENERAL CHAPTER

Q4B ANNEX 14

Current Step 4 version
Issued 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 project for Bacterial Endotoxins Test General Chapter. It contains the inspection quality. (Statement from Health Canada, Canada)

Date of Step 4: 18 October 2012

Current Step 4:

Implementation status:

ANVISA, Brazil - Implemented: Date: 1 November 2013, Reference: RDC 162/2013

EC, Europe - Implemented: Date: 1 November 2012, Reference: Commission Directive 2012/232/EU

FDA, United States - Implemented: Date: 1 October 2013, Reference: Vol. 76, No. 20, p. 6522-2

HSA, Singapore - Not applicable

Health Canada, Canada - Implemented: Date: 29 May 2016, Reference: File # 13-0255-993

MOH, Republic of Korea - Implemented: Date: 1 December 2012, Reference: Korean Pharmacopoeia - Bacterial Endotoxins Test, JACS Notification No.2012-020-2012

MOH, China - In the process of implementation, Reference: Chinese Pharmacopoeia 2015 edition volume 10, General Chapter 143, Test for bacterial endotoxin

Swissmedic, Switzerland - Implemented: Date: 18 October 2012, Reference: CH-Pharm

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

Guideline

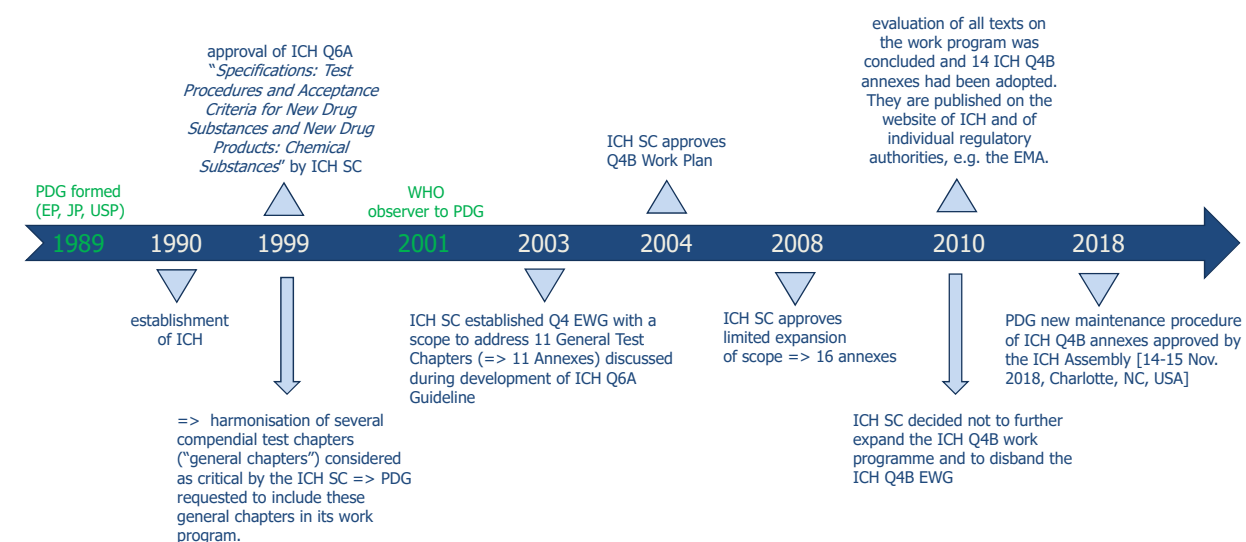
Q4B Annex 14

Other documents

Q4B Frequently Asked Questions (FAQs)

As far as the Q4B annexes are concerned...

Why a new maintenance procedure? Some history

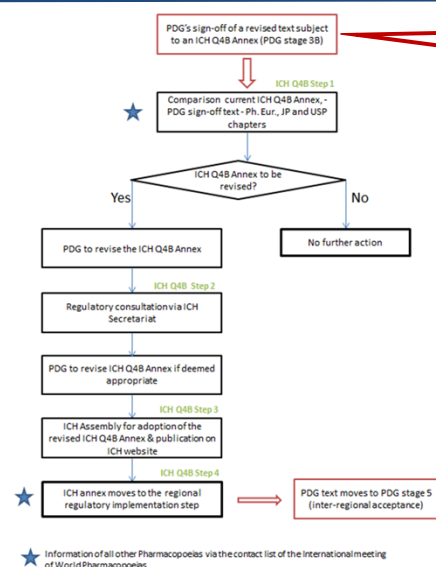


PDG Chapter ↔ ICH Q4B Annex

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

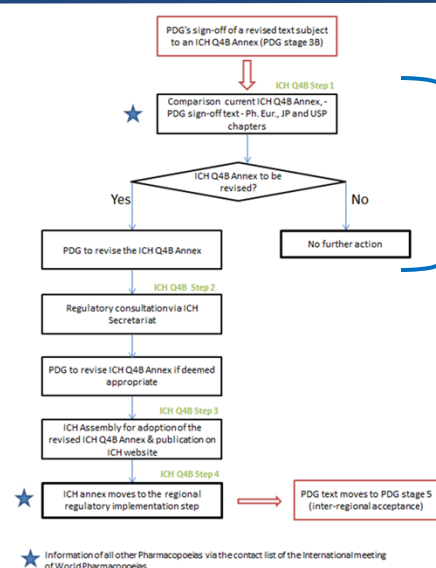
Added by ICH SC to Q4 EWG scope in Nov. 2008

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.

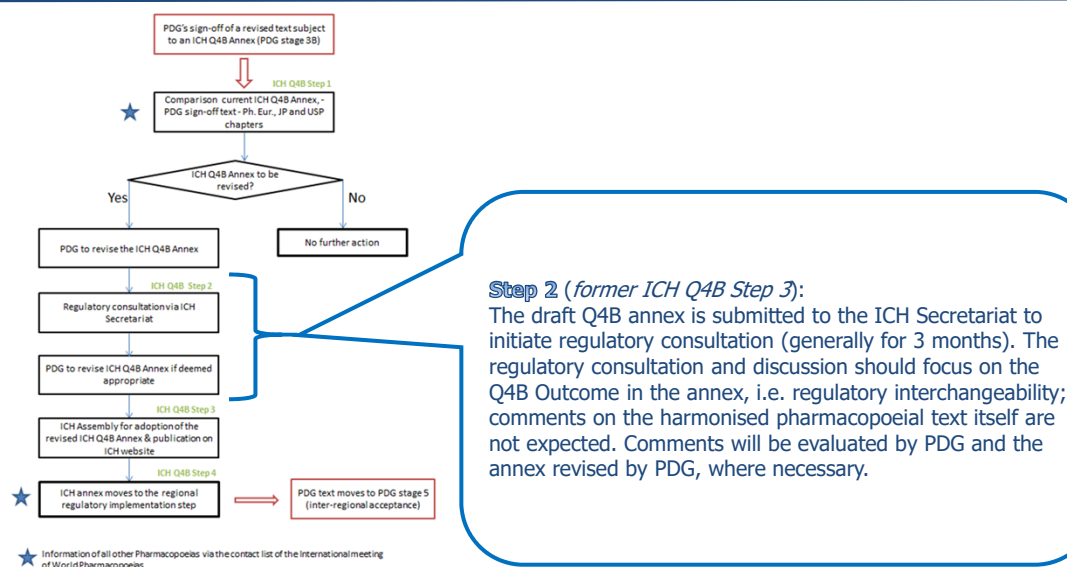
Future Maintenance process of the ICH Q4B Annexes



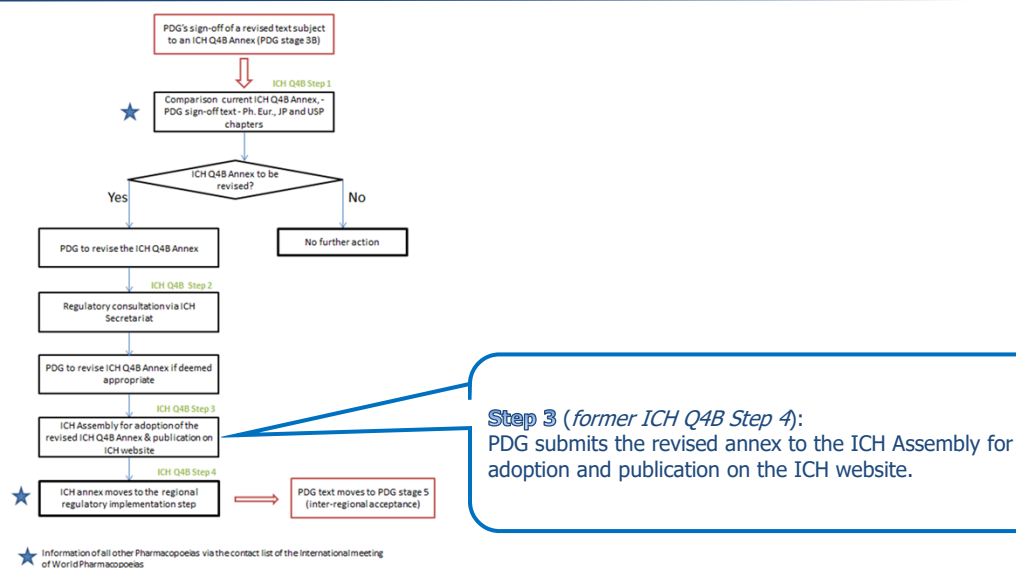
Step 1:

- 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).

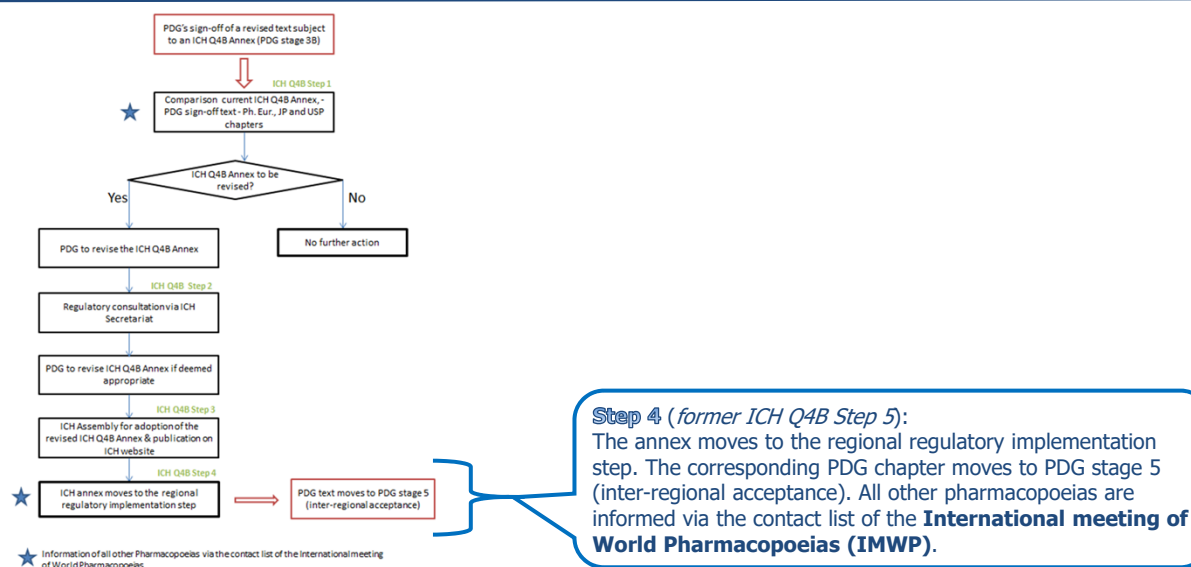
Future Maintenance process of the ICH Q4B Annexes



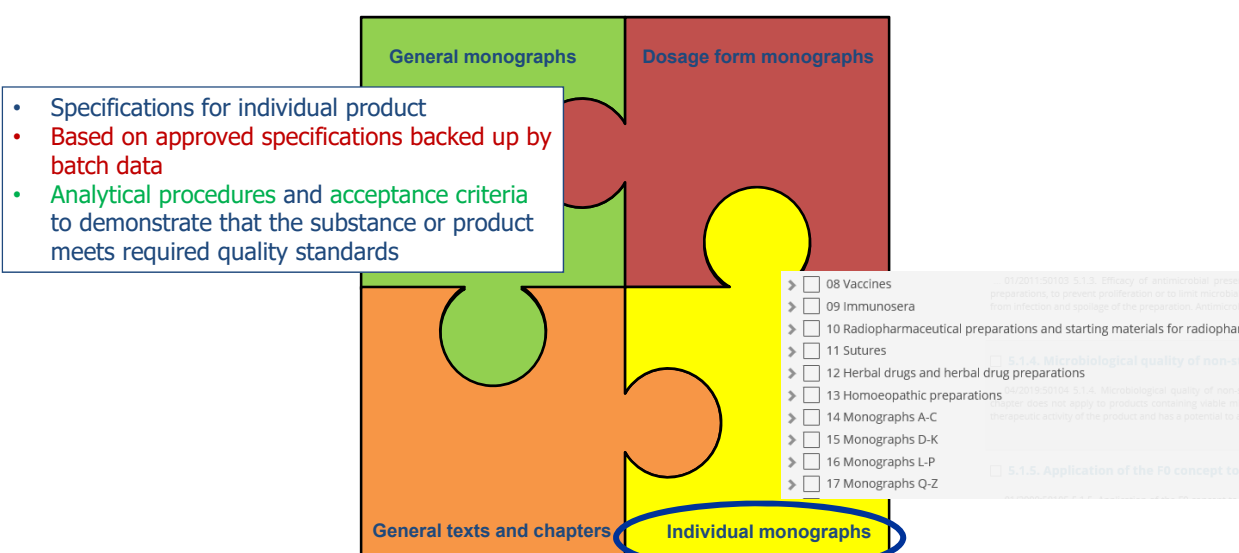
Future Maintenance process of the ICH Q4B Annexes



Future Maintenance process of the ICH Q4B Annexes



The structure of the Ph. Eur.



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

Thank you for your attention



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