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.

[Important - please read this before continuing]

Terms and conditions
NOTICE: by subscribing to the online version of the European Pharmacopoeia, the licensee acknowledges that he or she has read and agrees to be bound by the following General Terms and Conditions.

About the European Pharmacopoeia
This menu page provides access to the electronic version of the European Pharmacopoeia. The English and French electronic editions are cumulative and are compiled from the same texts which were used to produce the paper versions. In view of the wide range of operating systems, browsers and linguistic environments in use, EDQM cannot be held responsible for any rendering of the Ph. Eur. in HTML format which makes it different from the print and PDF versions. In the event of any discrepancy, please refer to the PDF version.

Draft monographs for public enquiry
Preliminary drafts of new and revised monographs proposed for inclusion in the European Pharmacopoeia can be found in Pharmaeuropa Online.

Publication calendar
Each new edition or supplement of the European Pharmacopoeia is usually published 6 months before its implementation date. All publications schedules, correction dates and implementation dates are available in the 10th Edition publication schedule.

How to consult the European Pharmacopoeia
User manual
Key to monographs

How to access
A password is necessary to access the data. Please click here to subscribe.
KEY TO MONOGRAPHS (ONLINE VERSION)

CHAMSA

DEFINITION
Content: 1 HCl, 2 ethanol, 9:1, calculated with respect to 100 g of substance.

EXPERIMENTAL
A. Solubility: in water, in ethanol (96% v/v), in methanol, in acetone, in diethylether, in chloroform, in methylene chloride, in ethyl acetate, in isopropanol, in toluene, in n-hexane.

B. Identification
C. TLC: in system A, Rf 0.52 to 0.55. In system B, Rf 0.52 to 0.57.

CARBARZOL PE

DEFINITION
Content: 1 HCl, 2 ethanol, 9:1, calculated with respect to 100 g of substance.

EXPERIMENTAL
A. Solubility: in water, in ethanol (96% v/v), in methanol, in acetone, in diethylether, in chloroform, in methylene chloride, in ethyl acetate, in isopropanol, in toluene, in n-hexane.

B. Identification
C. TLC: in system A, Rf 0.52 to 0.55. In system B, Rf 0.52 to 0.57.

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

Sample of e.g. Omeprazole to be tested

Draft monographs for public enquiry
Preliminary drafts of new and revised monographs proposed for inclusion in the European Pharmacopoeia can be found in Pharmeuropa Online.

Publication calendar
Each new edition or supplement of the European Pharmacopoeia is usually published 6 months before its implementation date. All publications schedules, correction dates and implementation dates are available in the 10th Edition publication schedule.

How to consult the European Pharmacopoeia
User manual
Key to monographs

How to access
A password is necessary to access the data. Please click here to subscribe.
Where do you start ... ... when using the Ph. Eur.?
Knowledge database

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

1.1. GENERAL STATEMENTS
1.1. GENERAL STATEMENTS

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?

- **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. MONOGRAPH

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.

**IDENITIFICATION**
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 of these characteristics are provided for information as examples of suitable methods. Subject to approval by the competent authority, other test methods may be used without validation against the method shown in the monograph.

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 (1.2). 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 dessicant 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.
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 product, it is applicable to all products in the class defined, irrespective of whether there is an individual monograph for 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 sections 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 should 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

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 control.

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: 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 required for supply in receipt.

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 normalized for information and become mandatory when referred to in a monograph or specific monograph, unless such reference is made in a way that indicates that it is not necessary to refer to the corresponding monograph or specific monograph.

Where relevant, pharmaceutical preparations also comply with the dosage form monographs (e.g. Capsules (0010), Tablets (1476)) and general monographs relating to pharmaceutical preparations (e.g. Anticancer products (1133), Parenterals (1410), Homoeopathic preparations (1129), Homoeopathic pills, coated (1276), Homoeopathic pills, uncoated (2070), Immunology for human use: animal (0034), Immunology for veterinary use (0039), Non-biopharmaceutical products for human use (1105), Non-biopharmaceutical products for veterinary use (0018)).

PRODUCTS OF FORMULATION

- Conventional preparations
- Stock preparations
- Customized preparations
- Radiolabelled preparations
- Vaccines for human use (0158)
- Vaccines for veterinary use (0936)
More examples – specific to bio products – to come soon!
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**

  - 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 the General chapter 5.8 *Pharmacopoeia harmonisation* 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 available
- Harmonisation status for Excipients monographs

---

**COUNCIL OF EUROPE**

---

**Harmonisation status for General Texts (PDG)**

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

<table>
<thead>
<tr>
<th>EP</th>
<th>Harmonisation Status</th>
<th>For General Texts (as of 30 October 2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.01</td>
<td>Amino-acids analysis (3.2.3a)</td>
<td>USP</td>
</tr>
<tr>
<td>5.03</td>
<td>Isotachophoresis (2.3.4)</td>
<td>USP</td>
</tr>
<tr>
<td>5.04</td>
<td>Titrision (2.2.32)</td>
<td>USP</td>
</tr>
<tr>
<td>5.05</td>
<td>High-performance liquid chromatography (2.2.34)</td>
<td>Ph. Eur</td>
</tr>
<tr>
<td>5.06</td>
<td>Spectrophotometry (2.2.31)</td>
<td>Ph. Eur</td>
</tr>
<tr>
<td>5.07</td>
<td>Particle size determination by air or laser light scattering (2.2.35)</td>
<td>USP</td>
</tr>
<tr>
<td>5.02</td>
<td>Amino-acids analysis (3.2.3a)</td>
<td>USP</td>
</tr>
<tr>
<td>5.04</td>
<td>Titrision (2.2.32)</td>
<td>USP</td>
</tr>
<tr>
<td>5.05</td>
<td>High-performance liquid chromatography (2.2.34)</td>
<td>Ph. Eur</td>
</tr>
<tr>
<td>5.06</td>
<td>Spectrophotometry (2.2.31)</td>
<td>Ph. Eur</td>
</tr>
<tr>
<td>5.07</td>
<td>Particle size determination by air or laser light scattering (2.2.35)</td>
<td>USP</td>
</tr>
</tbody>
</table>

---

©2020 EDQM, Council of Europe. All rights reserved.
As far as the Q4B annexes are concerned...
Why a new maintenance procedure? Some history

- **1989** PDG formed (EP, JP, USP)
- **1990** establishment of ICH
- **1999** approval of ICH Q6A "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" by ICH SC
- Evaluation of all texts on the work program was concluded and 14 ICH Q4B annexes had been adopted. They are published on the website of ICH and of individual regulatory authorities, e.g. the EMA.
- **2001** ICH SC approved Q4B Work Plan
- WHO observer to PDG
- **2003** ICH SC established Q4 EWG with a scope to address 11 General Test Chapters (=> 11 Annexes) discussed during development of ICH Q6A Guideline
- **2008** ICH SC approved Q4B Work Plan
- **2009** ICH SC approves limited expansion of scope => 16 annexes
- **2010** evaluation of all texts on the work program was concluded and 14 ICH Q4B annexes had been adopted. They are published on the website of ICH and of individual regulatory authorities, e.g. the EMA.
- **2018** PDG new maintenance procedure of ICH Q4B annexes approved by the ICH Assembly [14-15 Nov. 2018, Charlotte, NC, USA]
- **2018** ICH SC decided not to further expand the ICH Q4B work programme and to disband the ICH Q4B EWG

---

PDG Chapter ↔ ICH Q4B Annex

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

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

**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

Stay connected with the EDQM

EDQM Newsletter: https://go.edqm.eu/Newsletter
LinkedIn: https://www.linkedin.com/company/edqm/
Twitter: @edqm_news
Facebook: @EDQMCouncilofEurope