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

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"The European Pharmacopoeia"
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Where do you start ... when using the Ph. Eur.?

Sample of e.g. Omeprazole to be tested

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The structure of the Ph. Eur.

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 – 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?
  • Why two identification tests ... sometimes?
  • Human and/or veterinary use?

And many more

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...
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!
**Alternative methods**

*Example:*

- You may replace an existing HPLC method (impurities or assay) by an alternative one, provided the alternative method is cross-validated against the official one and leads to the same pass/fail decision.

- Not possible to replace a selective HPLC assay by a volumetric titration [since the same pass/fail cannot be obtained].

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**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 e.g. Levamisole for veterinary use.
Section 1.4 Monographs

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.

The structure of the Ph. Eur.

Table of contents
- European Pharmacopoeia 13.0
- European Pharmacopoeia 10.0
  - 01 General notices
  - 02 Methods of analysis
  - 03 Materials for containers and containers
  - 04 Reagents
  - 05 General Texts
  - 06 General Monographs
  - 07 Other forms
  - 08 Vaccines
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 General Notices, General monographs). Where no restriction on scope of a general monograph is given in a particular 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 when necessary and republished in each supplement.
General monographs

Two types:

- General monographs on classes of substances
  
  *e.g.* Products of fermentation, Allergen products, Herbal drugs, Essential oils, Monoclonal antibodies for human use, etc.

- General monographs on dosage forms
  
  *e.g.* capsules, tablets, parenteral preparations, eye preparations, etc.

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.”
General monographs

• 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!

General vs. individual monographs

• Complementary
• One not overruling the other
• Exceptions are clearly indicated either in the general monograph or in the individual one
Two key examples

<table>
<thead>
<tr>
<th>Example 1</th>
<th>Example 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description of the method used for the analysis of the compound</td>
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<tr>
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The structure of the Ph. Eur.

Section 7 Dosage forms

- 1st text published in there:

This glossary provides definitions and/or explanations of terms that may be found in, or used in association with, the general monographs on dosage forms and the corresponding chapters on Pharmaceutical technical procedures (2.9), but that are not defined within them. Where relevant, reference is made to other equivalent terms that may be found in other publications or contexts.

This glossary is published for information.
Section 7 Dosage forms

- Contain requirements common to all dosage forms of the type defined e.g. sterility, uniformity of dosage units, dissolution ...

- Classified by pharmaceutical form/route of administration e.g. Tablets, Preparations for inhalation ...

- Applied during licensing

- Framework specification: extra tests and acceptance criteria are proposed by manufacturer and approved by competent authority

One example: Tablets

- Apply to all categories of tablets of oral use

- In addition
  - Specific to this category of tablets of oral use
The structure of the Ph. Eur.

Table of contents
- European Pharmacopoeia 10.0
  - 00 Introduction
  - 01 General notices
    - 01.1 General notices
    - 01.2 Merits of analysis
    - 01.3 Etiquette of the company and company
    - 01.4 Raw materials
  - 02 Dosage form monographs
  - 03 General monographs
    - 03.1 Physical and physicochemical methods
    - 03.2 Chemical analysis
    - 03.3 Pharmacology
    - 03.4 Materials for containers and containers
  - 04 General texts and chapters
  - 05 Individual monographs

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

• 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 (2.4.30 EG and DEG in ethoxylated substances): useful guidance, can be referred to in applications

General texts

• Are often published for information and guidance.
• Aspects that cannot be treated in each individual monograph ≠ standard methods
• Become mandatory when referred to in a monograph
Examples

• **5.10. Control of impurities in substances for pharmaceutical use** referred to in general monograph *Substances for pharmaceutical use* (2034) ➔ chapter 5.10 applies to all APIs (whether or not an individual monograph exists in the Ph. Eur.)

Where a substance for pharmaceutical use not described in an individual monograph of the Pharmacopoeia is used in a medicinal product prepared for the special needs of individual patients, the need for compliance with the present general monograph is decided in the light of a risk assessment that takes account of the available quality of the substance and its intended use.

**PRODUCTION**

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

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

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

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**Examples**

• **5.10. Control of impurities in substances for pharmaceutical use** referred to in general monograph *Substances for pharmaceutical use* (2034) ➔ chapter 5.10 applies to all APIs (whether or not an individual monograph exists in the Ph. Eur.)

• **5.4 Residual solvents** referred to in general monograph 2034 ➔ chapter 5.4 applies to APIs and excipients covered by 2034

Where a substance for pharmaceutical use not described in an individual monograph of the Pharmacopoeia is used in a medicinal product prepared for the special needs of individual patients, the need for compliance with the present general monograph is decided in the light of a risk assessment that takes account of the available quality of the substance and its intended use.

**Residual solvents** are limited according to the principles defined in chapter 5.4, using general method 2.4.24 or another suitable method. Where a quantitative determination of a residual solvent is carried out and a test for loss on drying is not carried out, the content of residual solvent is taken into account for calculation of the assay content of the substance, the specific optical rotation and the specific absorbance.
Examples

• 5.10. Control of impurities in substances for pharmaceutical use referred to in general monograph *Substances for pharmaceutical use (2034)* chapter 5.10 applies to all APIs (whether or not an individual monograph exists in the Ph. Eur.)

• 5.4 Residual solvents referred to in general monograph *2034* chapter 5.4 applies to APIs and excipients covered by *2034*

• 5.20 Elemental impurities reproduces the essentials of ICH Q3D guideline, is referred to in general monographs *2619 Pharmaceutical preparations* and *2034 Substances for pharmaceutical use* for ex.

The structure of the Ph. Eur.

- **Product specific**
  - Active substances:
    - Paracetamol (0049)
    - Rosuvastatin calcium (2631)
    - Sitagliptin phosphate monohydrate (2778)
  - Finished products:
    - Sitagliptin tablets (2927)
- **Dosage form monographs**
  - 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
Thank you for your attention

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