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

General Notices, General Chapters and General Monographs

Cathie Vielle
Head of European Pharmacopoeia Department

The structure of the Ph. Eur.
General Notices

Put at the very beginning of the Ph. Eur. (page 1), they address general issues and are aimed at providing the basic information to the user.

- Apply to all texts
- Rules to understand texts, conventional expressions

**Essential reading before starting to use**

**Monographs**
Conventional terms: meanings

Definition of conventional terms used in the Ph Eur provided such as:

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

- ‘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. (1/3)

Alternative methods

- Ph. Eur. tests: reference methods - essential in cases of dispute.
- alternative methods: same pass/fail result.
- Approval of the competent authority in many cases.
**Flexibility in the Ph.Eur. (2/3)**

**Waiving of tests**

- 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.

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**Flexibility in the Ph.Eur. (3/3)**

**Compliance ≠ Performance**

- performance of all tests is not a prerequisite
- compliance to the monographs is a prerequisite

⇒ need to know your product
What does compliance mean?

• Compliance with a **monograph**

• All **mandatory** parts of a monograph. ("Unless otherwise indicated in the General Notices or in the monographs, statements in monographs constitute mandatory requirements." General Notices => characters section, second identification test and storage section)

• Compliance **until time of use** for raw materials, ingredients.

• Compliance **throughout period of validity** for preparations.

• In-use compliance decided by licensing authority for each preparation.

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Validation of Ph. Eur. 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 if 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."
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."

General Notices, 9th edition
Identification

• For pharmaceutical industry (excipients, API, medicinal products), tests as described under First identification section shall be performed.

• Community and hospital pharmacies may only perform the tests as described under 2nd identification if all other tests (under Assay and Tests section) have been performed by the manufacturer of the excipient/API (and a respective CoA is available).

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.
Potential Adulteration

"Due to the increasing number of fraudulent activities and cases of adulteration, information may be made available to Ph. Eur. users to help detect adulterated materials (i.e. active substances, excipients, intermediate products, bulk products and finished products).

To this purpose, a method for the detection of potential adulterants and relevant limits, together with a reminder that all stages of production and sourcing are subjected to a suitable quality system, may be included in this section of monographs on substances for which an incident has occurred or that present a risk of deliberate contamination. The frequency of testing by manufacturers or by users (e.g. manufacturers of intermediate products, bulk products and finished products, where relevant) depends on a risk assessment, taking into account the level of knowledge of the whole supply chain and national requirements.

This section constitutes requirements for the whole supply chain, from manufacturers to users (e.g. manufacturers of intermediate products, bulk products and finished products, where relevant). The absence of this section does not imply that attention to features such as those referred to above is not required.

General Notices, 9th Edition
General chapters

Section 2: Methods of analysis

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

General chapters

Section 5: General texts

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

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

General chapters

• Many have validity or equipment-verification requirements.
• These requirements become part of monograph.
  • Ex. of Chromatographic separation techniques 2.2.46.:
    Covers:
    • LC, SEC, GC, TLC and SFC
    • System suitability: Peak symmetry, Repeatability (for assays), Limit of quantification
    • Adjustment of operating conditions
    ➔ Requirements apply wherever methods are prescribed in monographs
International Harmonisation

• Pharmacopoeial Discussion Group (PDG): an informal structure (members: JP, Ph. Eur., USP + WHO as observer)

• Chapter 5.8 Pharmacopoeial harmonisation:
  - included for guidance of users.
  - provides information on the degree of harmonisation of various general chapters and monographs
    • PDG procedure
    • PDG state of work

General Monographs
Why general monographs?

Two types:

- General monographs on classes of substances
- General monographs on dosage forms *(applied during licensing)*

General monographs

- “Classes” defined by different criteria: production method, origin, risk factors
- Aspects that cannot be treated in each individual monograph
- Apply to all products
- No cross-reference in individual monographs
Which has priority, a general monograph or an individual monograph?

- None ... Complementary
- Exceptions are clearly indicated either in the general monograph or in the individual one.

Examples of general monographs

- Immunosera for human use animal
- Immunosera for veterinary use
- Monoclonal antibodies for human use
- Pharmaceutical preparations
- Products of recombinant DNA technology
- Substances for pharmaceutical use
- Vaccines for human use
- Vaccines for veterinary use
General monographs on dosage forms

- Contain requirements common to all dosage forms of the type defined (tablets, capsules, parenteral preparations, etc.)
- Classified by pharmaceutical form/route of administration
- Applied during licensing
- Framework specification: acceptance criteria and extra tests are proposed by manufacturer and approved by competent authority

Thank you for your attention!