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

General Notices, General Chapters, and General Monographs

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General Notices
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
Quiz: what is repeated at least 3000 times in the Ph. Eur.?

- A: Test for heavy metals
- B: Reference to BSE/TSE
- C: Reference to General Notices
- D: « Unless otherwise justified and authorised »
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Typical questions that are answered in the General Notices

- Do specifications apply throughout shelf-life?
- Are alternative methods allowed?
- The monograph specifies 1.000 g to be weighed for the test, what is the tolerance?
- Is Solubility a mandatory requirement?
- Is the Second Identification compulsory?
Alternative methods

• Ph. Eur. tests are reference methods, essential in cases of dispute
• Compliance is required, but alternative methods may be used as long as they lead to the same pass/fail result. It is the responsibility of the user to demonstrate their suitability. Approval of the competent authority is necessary in many cases.
Quiz: The monograph specifies 1.000 g to be weighed for the test (test with a numerical limit)

• A: You must weigh between 0.9995 and 1.0005 g
• B: You may weigh a quantity between 0.9 and 1.1 g, but with a tolerance of +/- 0.5 mg
• C: You must weigh exactly 1.000 g
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Quiz: The monograph specifies 1.0 g to be weighed for a comparative test (sulphates, chlorides, etc…)

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Quiz: The monograph specifies 1.0 ml of a solution to use for a test

• A: You have to use between 0.95 ml and 1.05 ml

• B: You have to sample the solution with a pipette, a volumetric flask or a burette

• C: You have to use a balance for the determination
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Sample size

- Accuracy defined by the number of significant figures: 1.000 g ⇒ ± 0.5 mg
- For test/assay with calculated result, amount to be used is within 10% (absorbance, water, loss on drying etc.)
- For comparative tests (sulphates, chlorides, etc.) amount defined by number of significant figures: 1.0 g ⇒ 0.95-1.04 g
Quiz: I have demonstrated that my process does not generate an impurity for which a test is prescribed in the monograph

• A: Compliance with Ph. Eur. necessitates the verification that the test is performed on each batch to verify that the level of the impurity is below the specific limit

• B: The test does not need to be carried out at all
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Quiz: The monograph prescribes a test for sterility

• A: A sterility test is to be used for compliance to Ph. Eur.

• B: I have demonstrated by appropriate equipment validation and in process controls that my process will consistently lead to a sterile product. With the agreement of the competent authority a sterility test can be omitted.
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- B: I have demonstrated by appropriate equipment validation and in process controls that my process will consistently lead to a sterile product. With the agreement of the competent authority a sterility test can be omitted.
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
Waiving of tests

• « The manufacturer may obtain assurance that a product is of Pharmacopoeia quality from data derived, for example, from validation studies of the manufacturing process and from in-process controls. Parametric release in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia. »
Legal status of monographs

- Monographs are “official standards”
- Mandatory at the same date in 36 states (CoE) and the EU, legally binding quality standard (2001/83/EC, 2001/81/EC)
- Monographs may be accepted as suitable standards even when not obligatory
Quiz: Reference to regulatory documents

• A: When the Ph. Eur. refers to a regulatory document (e.g. EU note for guidance) it becomes mandatory.

• B: Reference to a regulatory document does not change its original status
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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, 6th edition
Quiz: Do Ph. Eur. specifications apply throughout shelf-life?

- A: Yes, specifications apply until time of use for raw materials and throughout period of validity for preparations.
- B: No, Ph. Eur. requirements are for release only.
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What does compliance mean?

- Compliance with a **monograph**
- All mandatory parts of a monograph
- 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
What must comply?

• Mandatory for all substances for pharmaceutical use
• Ingredients (incl. excipients) of final formulation
• Components of solvents, buffers etc in or used to make up final formulation
• Solvents used for purification? If a monograph exists, then compliance will usually be required
• Reagents? Not usually needed for upstream use
What is mandatory?

• “Unless otherwise indicated in the General Notices or in the monographs, statements in monographs constitute mandatory requirements.” (General Notices)

↔ Non mandatory parts of a monograph (e.g. Characters, Storage) are clearly indicated as such in the General Notices (ex: 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) or in the monograph itself.
Quiz: Validation of Pharmacopoeial methods

• A: All methods of the Ph. Eur. need to be revalidated in order to check robustness

• B: Methods of the Ph. Eur. have been validated. Validation by the analyst is not required.
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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. »

General Notices, 6th edition
Validation (ctd)

• Even if Ph. Eur. methods have not to be revalidated by the users, a written risk analysis (e.g. using ICH Q9 Quality Risk Management) to assess which lab verification(s) of one or more tests prescribed in a monograph shall be performed, or not, may be expected by Regulators.
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.
General Chapters
Why general chapters?

• Analytical methods:
  – Editorial convenience: avoid repeating standard methods in each monograph
  – Provide standard methods that can be used where there is no monograph
  – Give general requirements for equipment, equipment verification
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 (2)

- Many have validity or equipment-verification requirements
- These requirements become part of monograph
Chromatographic separation techniques

2.2.46.

- 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
General chapters in section 5

not analytical methods

5.1 Preparation of sterile products / Microbiology
5.2 Production and QC of vaccines
5.3 Statistical Analysis
5.4 Residual solvents
...
5.9 Polymorphism
5.10 Control of impurities (5.10)
Microbiological quality

- Microbiological examination of non-sterile products: total viable aerobic count (2.6.12)
- Microbiological examination of non-sterile products: test for specified microorganisms (2.6.13)
- Microbiological quality of pharmaceutical preparations (5.1.4)
General Monographs
Why general monographs?

• Two types:
  – General monographs on classes of substances
  – General monographs on dosage forms
General monographs

• “Classes” defined by different criteria: production method, origin, risk factors
• Aspects that cannot be treated in each individual monograph
  – Residual solvents
  – TSE/BSE
  – Pesticides in herbals
  – etc.
General monographs (2)

• Apply to all products

• No cross-reference in individual monographs

CHECK WHICH GENERAL MONOGRAPH APPLIES!
Quiz: From general monographs and individual monographs which are the ones which have priority?

- A: General monographs overrule individual monographs
- B: Individual monographs overrule general monographs
- C: There is no such priority
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Complementarity of General & individual monographs

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

General notices, 6th edition
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