The European Pharmacopoeia

General methods, Control of impurities, FP monographs, Pharmacopoeial harmonisation

International workshop on the Chinese and the European Pharmacopoeias – The new editions

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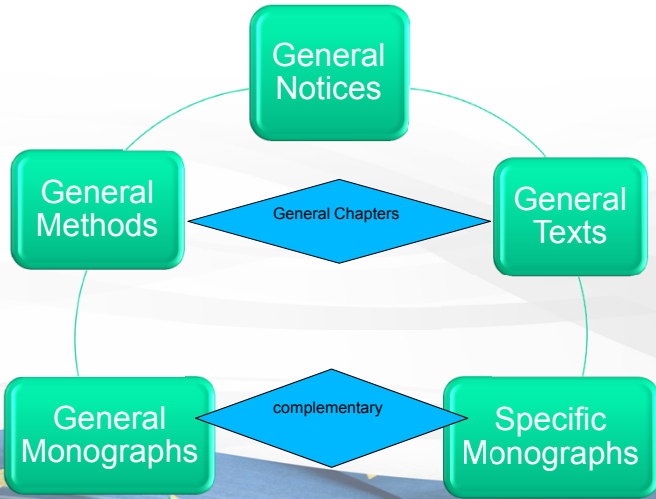
Which type of texts you find in the European Pharmacopoeia



General methods: why and how to use

Analytical methods:

- Editorial convenience: avoid repeating standard methods in each monograph
- Provide standard methods that can also be used where there is no monograph
- Provide general requirements for equipment, equipment qualification or calibration
- Provide general requirements for system suitability tests

General methods: why and how to use

- Not mandatory ***"per se"***
- Some general chapters are not referred to in any monograph (Raman spectroscopy): useful guidance
- When referred to in a monograph, they become part of the standard
- Can be used for substances not covered by monographs, may provide validation requirements
- Important elaboration/revision program currently ongoing

General Methods: Modernisation Program

- ✓ « Internal » harmonisation using a template
- ✓ To include recent techniques and produce a Pharmacopoeia which is scientifically state-of-the-art
- ✓ To improve existing methods to take into account recent progress in analytical technology and regulatory practice
- ✓ To suppress toxic reagents or materials
- ✓ To introduce and/or improve elements of equipment performance and qualification -> be more user-friendly
- ✓ To introduce and/or improve general system suitability tests
- ✓ International harmonisation within PDG (Pharmacopoeial Discussion Group)

General Methods

- Recently revised chapters:
  - Water: micro determination 2.5.32
  - Potentiometric titration 2.2.20
  - Approximate pH of solutions 2.2.4
  - Amperometric titration 2.2.19
  - Potentiometric determination of ionic concentration using ion-selective electrodes 2.2.36
  - Potentiometric determination of pH 2.2.3
  - Raman spectroscopy 2.2.48
  - Melting point 2.2.14
  - Standardisation of volumetric solutions 4.2.2

General Methods

- Underway:
- Chromatographic separation techniques 2.2.46
- Conductivity 2.2.38, Clarity and degree of opalescence 2.2.1
- X-Ray fluorescence spectrometry 2.2.37
- IR absorption spectrophotometry 2.2.24
- Loss on Drying, 2.2.32
- UV-VIS spectrophotometry 2.2.25

NEW: General methods working party co-ordinates the work on certain general chapters, e.g. elaborates a template on the structure of general chapters

General methods

Template proposal

- Principle of the technique
- Equipment
- Equipment performance/elements of qualification
- Procedure
- Validation requirements (if required)
- Additional information

General methods

- Example: Chromatographic separation techniques, 2.2.46

➢ Provides definitions and calculations of common parameters (peak, retention time, Rs etc)

➢ Defines permitted deviations to adjust chromatographic conditions, e. g. composition of mobile phase, column length, particle size etc. without re-validation

➢ Provides general system suitability parameter, not given in the individual monograph, e. g. minimum S/N ratio at reporting threshold, symmetry factor 0.8 to 1.5 -> become mandatory part of the monograph

→ is under revision within PDG, important changes

General texts

Are often published for information and guidance. They may also be subject to revision:

Examples:

➢ 5.4 Residual solvents

➢ 5.12 Reference standards

➢ 5.10 Impurities in substances for pharmaceutical use

➢ New: 5.21 Chemometric methods applied to analytical data

➢ Public enquiry: Chemical imaging

Control of impurities

Organic impurities	Inorganic impurities
Volatile impurities, Water and residual solvents	Special groups, e. g. genotoxic imps, inorganics subjected to Q3D

Control of impurities (cont.)

- **Inorganics:** are controlled by general tests like sulfated ash, heavy metals (2.4.8, now only for substances for verterinary use), specific tests like AAS, ICP or general chapter 2.4.20
- **Volatiles:** residual solvents are controlled according to general text 5.4 and general chapter 2.4.24. Class 3 solvents may be controlled by LOD (up to 0.5 %). Water is most often controlled by semi-micro determination, coulometry or loss on drying.
- **Genotoxic (DNA-reactive) impurities:**as from 1st January 2016 subjected to ICH M7. Control tests in monographs are in the test or production section.

Control of impurities (cont.)

- **Organic impurities:**

- Represent an essential part of the specific monograph
- Control strategy follows ICH Q3 A
- Principles are laid down in general monograph 2034 « Substances for pharmaceutical use »
- « Transparency list » at the end of a monograph: provides list of the impurities which are controlled by the test(s) described in the monograph
- Limits defined for « specified », « unspecified » and a total of impurities

Control of impurities (cont.)

Identification of impurities and quantification:

- Specified impurities must be identified in a chromatographic system: use of **reference standards**
- **Retention times and relative retentions are only given for information and are no system suitability requirements**
- Quantification is most often performed by external standard method and less often by peak area normalisation
- Consider response and correction factors
- New monographs describe **quantitative tests** and no longer limit tests

Control of impurities (cont.)

New technologies:

➢ Ph. Eur. follows a pragmatic approach

- Techniques should be « user-friendly », so that they can be applied by most of the control laboratories
- Sophisticated techniques are introduced where required for selectivity, sensitivity etc, not l'art pour l'art:

  e. g. UHPLC, LC-MS, ICP-MS

Monographs on „finished products"
- development for chemically defined actives

2012: Ph. Eur. Commission reconsidered its strategy

pilot phase initiated with examples of single-source and multi-source products

2014: strategy decided to widen the scope of Ph. Eur.
start with focus on single-source products
first monograph published in Pharmeuropa

2015: adopted and published in Ph. Eur. 8.7

2016: first monograph has come into force on April, 1st

Content of FP monograph

TITLE

DEFINITION

IDENTIFICATION

TESTS

RELATED SUBSTANCES

DISSOLUTION

ASSAY

IMPURITIES

Tests mandatory unless otherwise specified

Labelling is subject to supranational and national regulation and to international agreements: no intention to add additional requirements

Current focus

Follows critical assessment and discussions:

Takes into account usefulness of Ph. Eur. monograph and impact on registered products

- Single-source monographs on products that are potential future generics (Procedure 4)
- Immediate release dosage forms
- solid and liquid formulations
- Will be expanded subsequently
- Elaboration by P1 procedure possible on a case-by-case basis

Monographs of Finished Products

Work program:

- One monograph adopted: Sitagliptin tablets
- Two monographs currently published for enquiry
- 16 products have been added to the work program and are under elaboration
- More additions are foreseen

International Harmonisation

Three approaches:

- Pharmacopoeial Discussion Group (PDG): an informal structure (members: JP, Ph. Eur., USP + WHO as observer)
- Informal prospective harmonisation of API and FP monographs
- Elaboration of « Good Pharmacopoeial Practice » (GPhP) under the auspices of WHO

Objectives of the Harmonisation Activities

- Avoid redundant testing by suppliers and pharmaceutical industry to meet different standards
- Reduce the overall cost of pharmaceutical research world-wide by avoiding duplication of work (preparation of dossiers and studies)
- Reduce the time required for medicines to be made available to patients
- Facilitate free movement of goods

International Harmonisation

- PDG: set up in 1990, intended to elaborate a single set of global specifications for excipient monographs and general chapters

Current hot topics: Chromatography chapter, Chapter on determination of elemental impurities, cellulosics

- GPhP: Elaborated during 7 International meetings of World Pharmacopoeias, represents a kind of common technical guide as a basis for the elaboration of monographs