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 Notices
- General Methods
- General Chapters
- General Texts
- General Monographs
- Specific Monographs
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.

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**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 veterinary use), specific tests like AAS, ICP or general chapter 2.4.20
- **Volutiles**: 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

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

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