

# General Concepts in the European Pharmacopoeia

Anne-Sophie Bouin  
European Pharmacopoeia Department,  
EDQM, Council of Europe

# 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**



# 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.

# 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”
- Medicines legislation in Europe makes monographs obligatory standards (2001/83/EC, 2001/81/EC)
- Monographs may be accepted as suitable standards even when not obligatory

# What does compliance mean?

Compliance with a monograph:

- All mandatory parts of a monograph
- Compliance until time of use for raw materials
- 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



# 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*

# 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

- 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



# 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

- Apply to all relevant products
- No cross-reference in individual monographs

**CHECK WHICH GENERAL  
MONOGRAPHS APPLY!**



# 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



# Specific monographs

# Specific monographs

Requirement for a substance consists of:

Specific monograph + general  
monograph(s)

Whole set of requirements defining quality

# TITLE

- INNs used almost universally (modified to indicate salt)
- Titles now include **degree of hydration**
- Use in labelling required
- Molecular formula and mass: do not have to be checked!



# DEFINITION

- **Chemical nomenclature**
- **Assay limits**
  - LC assay: reflect assay variability and purity (eg:, 96.0-102.0% means 2% assay variability and 3.0% total impurities)
  - Microbiological assay: minimum activity (IU/mg, as is)
  - Biological assay: specific activity (eg: IU/mg)
- **Solvent-free substance is implied even where not stated** (see *Substances for Pharmaceutical Use, residual solvents*)



# Scope

- May include statements on scope (eg route of synthesis)
- Monograph applies to **all grades**, unless otherwise stated
- Special grades may be mentioned in body of monograph (parenteral etc.)

# Use of excipients

- Definition indicates where applicable that additives can be used (antioxidants, etc).
- See *Substances for Pharmaceutical Use*:  
“Processing with addition of excipients is permitted only where this is specifically stated in the Definition of the individual monograph.”
- Indication on the label

# PRODUCTION SECTION

- Instructions to manufacturers
  - May relate to source materials, manufacturing process, its validation and control or to in-process testing
  - Cannot necessarily be verified by independent analyst
  - Compliance established by competent authorities
- > e.g. by examination of data or inspection



# CHARACTERS

- Not analytical requirements, do not have to be checked
- Useful information for the analyst (solubility, hygroscopicity)
- Polymorphism, where known, is mentioned (see also *5.9 Polymorphism*)
- Physical properties may be mentioned (melting point, refractive index, density)



# IDENTIFICATION

First and Second identifications/alternative identifications: defined in General Notices

- First identification alone is always sufficient, Second is never mandatory
- Alternative identifications are equivalent

# TESTS

- To detect: organic impurities, inorganic impurities, volatiles
- Methods:
  - Physical and physico-chemical
  - Chemical
  - Chromatographic...

# Basis for impurities control

- Specifications and batch analysis data for approved products
- Specified impurities are those in specifications for approved products
- Specified impurities are qualified at or above the level indicated in the monograph

# Template for requirements

- Limits for:
  - Specified impurities
  - Unspecified impurities
  - Total impurities
- Impurities section
  - Specified impurities
  - Other detectable impurities
- If the Impurities section is not divided, all the impurities listed are specified

# Other Detectable Impurities

- Specific Ph.Eur. category
- Impurities sections in monographs may have a list of ODIs
  - **Analytical information only:** the impurity is *detected* by the monograph method
  - ODIs are limited in the monograph by the limit for “unspecified impurities” (or *Substances for Pharmaceutical Use*)

# IMPURITIES SECTION

- Gives impurities that are **known** to be detected by monograph tests
- Usually controlled by related substances test, but may be other tests
- **Not necessarily exhaustive**
- Based on information obtained and verified during elaboration

# Directive 2003/63/EC

“ However, where a starting material in the European Pharmacopoeia ... has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described.”



# Monograph revision

- Impurities control has to be updated for newly authorised products/sources:

“[Where] a monograph ... [may] be insufficient ... the competent authorities shall inform the European Pharmacopoeia. The marketing authorisation holder shall provide the European Pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.”



# Residual solvents

- Dealt with in *Substances for Pharmaceutical Use* and general chapter 5.4 *Residual solvents*
- Specific monographs do not include a test for residual solvents, *except*:



# Residual solvents

- Class 1 solvents are always named and limited in monographs
- Class 3 solvents are **only** named and limited in monographs when they exceed 0.5% (impact on assay results)
- Class 2 solvents are **NOT** named and limited in monographs: chapter 5.4 applies



# ASSAY

- Ph.Eur. policy prefers unspecific but **precise assay (titration)** provided related substances test is sufficiently characteristic and searching
- Well-defined salts: normally only the pharmacologically active part is determined by titration
- For chromatographic assays chapter 2.2.46 defines repeatability requirements



# STORAGE

- Section is **not mandatory**
- Competent authority decides on storage - may decide to make Ph. Eur. mandatory
- Product has to be stored so as to ensure compliance with monograph
- Conventional expressions defined in General Notices

# LABELLING

- Covered by national and international regulations
- Ph Eur indicates labelling items needed for application of monographs

For example, nominal values (especially excipients)



# LABELLING

- “Labelling” is interpreted in broad sense
- Not just what is read on container
- Information provided with the product is also included in “labelling”: package, leaflet, certificate of analysis



# FUNCTIONALITY-RELATED CHARACTERISTICS

- Monographs on excipients
- Section is **not mandatory**
- Tests are linked to use (lubricant, filler, etc.)
- Section provides information on important parameters



**Thank you for your attention !**