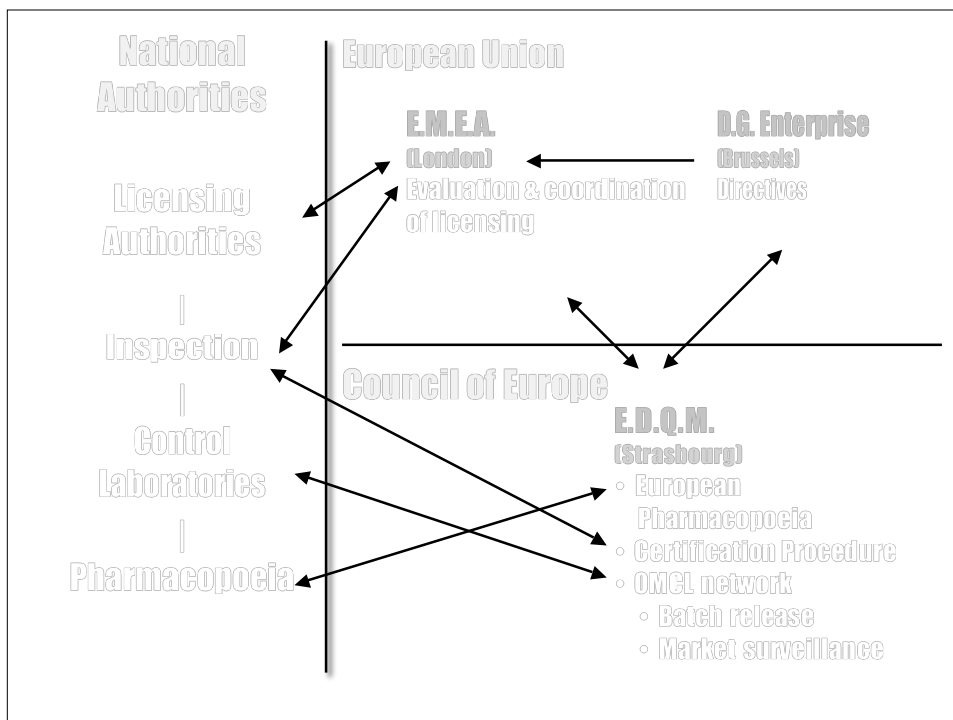


# An introduction to the European Pharmacopoeia

Dr Claude Coune  
Head of the Publications  
Department



## An international convention

- Signed in 1964
- Under the ægis of the Council of Europe, a Europe wide, inter-governmental organisation

## Member countries



## In the world



## Activities of EDQM

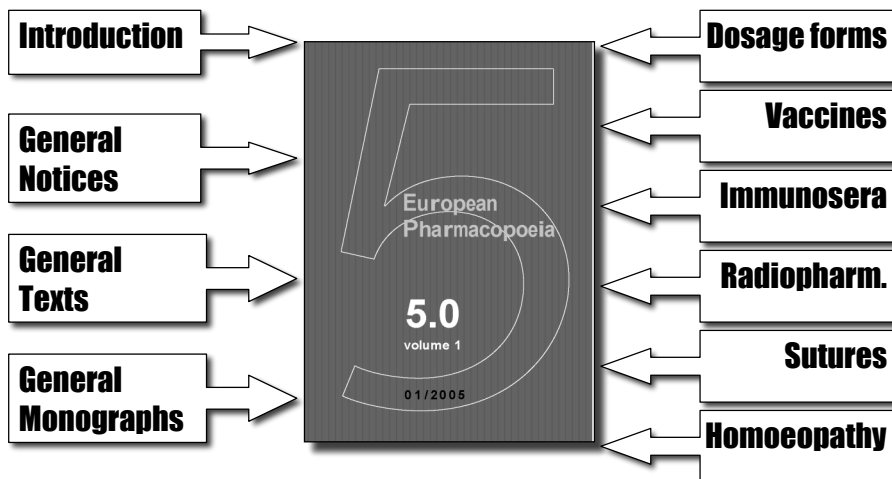
- The European Pharmacopoeia
- The Reference Standard (including Biologicals)
- The Network of Official Control Laboratories
  - Proficiency testing studies
- The Certification of suitability

## The European Pharmacopoeia

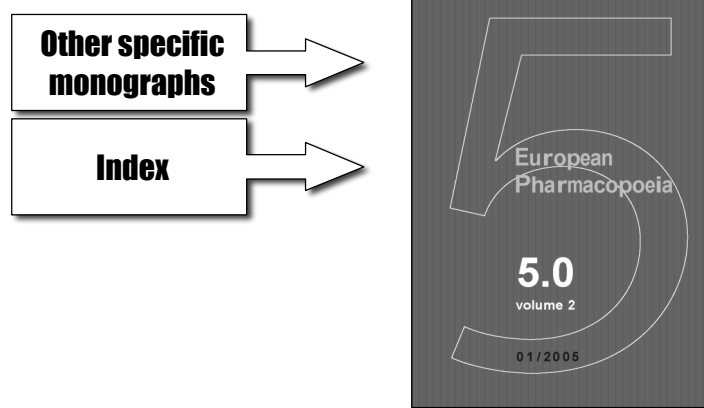
### The Convention

- Progressively elaborate a Pharmacopoeia which shall become common to the countries concerned...
- Take the necessary measures to ensure that the monographs...shall become the official standard applicable within the respective countries

## General organisation: Vol. 1



## General organisation: Vol. 2



## General Notices: what do I need to know?

- Many questions sent to EDQM can be answered just by knowing the General Notices
- Apply to all texts
- Rules to understand texts, conventional expressions
- **Essential reading before starting to use monographs**

## FAQs: answers are in General Notices

- Are the specifications for release or applicable throughout shelf-life?
- Can I use a method different from that in the monograph?
- If the monograph specifies 1.000 g for the test, what is the tolerance on the amount used?
- Do I have to check the solubilities given under Characters?
- Do I have to carry out the Second identification?

## General Chapters

### Why have general chapters?

- Analytical methods:
  - Editorial convenience : avoid repeating standard methods in each monograph
  - Provide standard methods that can be used where there is no monographs
  - Give general requirements for equipment, equipment verification

## General chapters in section 5

- Requirements that are not analytical methods
  - Preparation of sterile products
  - SPF flocks
  - Residual solvents
  - information chapters
  - Alcohol tables, radionuclides
  - Pharmacopoeial harmonisation
  - Polymorphism
  - Control of impurities (5.10)
  - Alternative methods in microbiology

## General Monographs

## Why have general monographs?

- There are two types:
  - General monographs on dosage forms
  - General monographs on classes of substances
- Monographs on specific dosage forms are not generally included in Ph Eur
- “Class” monographs give requirements that cannot be dealt with in specific monographs

## General monographs

- “Classes” defined by different criteria: production method, origin, risk factors
- Aspects that cannot be treated in each individual monograph
  - Residual solvents
  - Polymorphism
  - Pesticides in herbals
  - etc.

## General monographs (2)

- Apply to all products, **except** *Substances for Pharmaceutical Use*, which applies only where there is an individual monograph on the substance
- No cross-reference in individual monographs (removed for 4th Edn)
- Cross-references cannot be systematic and complete, therefore deleted
- CHECK WHICH GENERAL MONOGRAPH APPLIES!

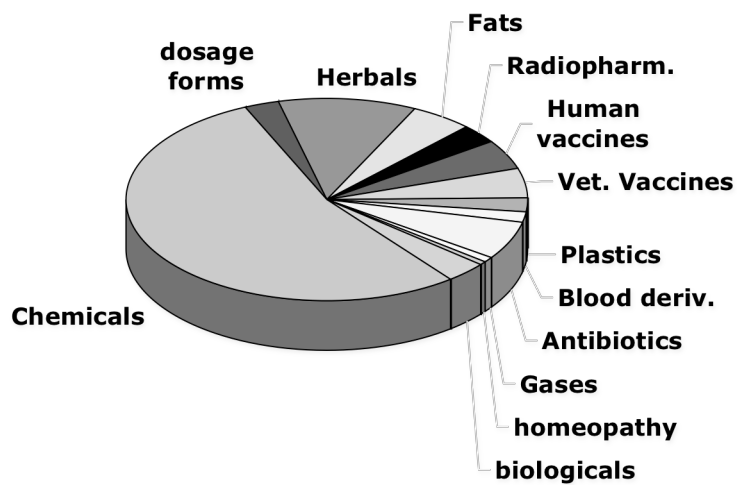
## Substances for Pharmaceutical Use

- Clarifies scope of individual monographs:
- Use of excipients, special grades/forms, polymorphism, residual solvents
- Applies to substances for which a specific monograph exists
- Competent authority can extend to other substances

# SPECIFIC MONOGRAPHS

A Guide Through The Different Sections

Contents of the European  
Pharmacopoeia  
1920 monographs



## Specific monographs

- Requirement for a substance consists of:
  - Specific monograph + general monograph(s)
- Whole set of requirements define quality

## TITLE

- INNs used almost universally (modified to indicate salt)
- Titles now include degree of hydration
- Use in labelling required

## DEFINITION

- Chemical nomenclature
- Assay limits
  - LC assay: reflect assay variability and purity (eg.: 92-102% means 2% assay variability and 6% 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*)

## PRODUCTION

- Instructions to manufacturers
- Cannot necessarily be verified by independent analyst
- > Examination of data, 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)
- *5.11 Characters section in monographs*: methods used for checking by EDQM

## IDENTIFICATION

- Not aimed to give a full confirmation of the chemical structure or composition
- Intended to give confirmation, with an acceptable degree of assurance, that the article conforms to the description on the label

## IDENTIFICATION (2)

- First and Second identifications: defined in General Notices
- First identification alone is always sufficient, Second is never mandatory
- Use of Second identification depends on competent authority
- First identification always has to be carried out at some point (upstream)

## TESTS

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

## Basis for impurities control

- Specifications for approved products 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 cited are specified

## Other detectable impurities (ODIs)

- Specific EP 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*)

## Which Ph.Eur texts to consult?

- Specific monograph
- General monograph on *Substances for Pharmaceutical Use*
- General chapter *5.10 Control of impurities*
- Any other relevant general monograph (for example *Products with TSE Risk*)
- General chapter *5.4 Residual solvents*

## Substances for Pharmaceutical Use

- Related substances. Organic impurities in active substances are to be reported, identified wherever possible, and qualified as indicated in Table 2034.-1.

## Substances for Pharmaceutical Use (2)

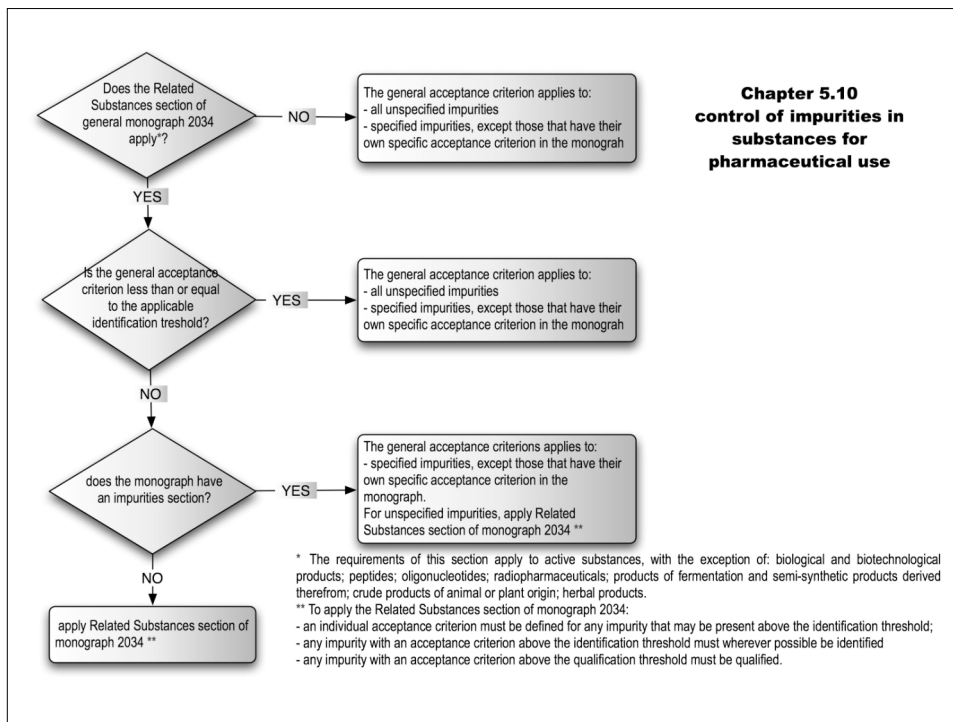
Use	Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
Human or human and veterinary	≤ 2 g/day	>0.05 per cent	>0.10 per cent or daily intake >1.0 mg (whichever lower)	>0.15 per cent or daily intake >1.0 mg (whichever lower)
Human or human and veterinary	> 2 g/day	>0.03 per cent	>0.05 per cent	> 0.05 percent
Veterinary only	Not applicable	>0.1 per cent	0.2 per cent	>0.5 per cent

## Requirements do not apply for

- biological and biotechnological products
- peptides
- oligonucleotides
- radiopharmaceuticals
- products of fermentation and semi-synthetic products derived there from
- crude products of animal or plant origin or herbal products

## General chapter 5.10

- Defines:
  - Basis for monographs and impurities control
  - Terminology
  - Interpretation of related substances tests
  - Other aspects of impurities control
- **ESSENTIAL READING!**



## 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.”

## Strategy for compliance

- Use state-of the-art methods for impurity control
- Know your product and its impurity profile
- Know your suppliers
- Request certificate of suitability to ensure smooth approval procedure
- Maintain liaison with Ph.Eur

## 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*:
  - Where a product has been approved with a limit higher than the one indicated in 5.4, option 1.
  - Class 1 solvents

## Residual solvents: recent news (November 2005)

- 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

- Well-defined salts: normally only the pharmacologically active part is determined by titration
- Ph.Eur. policy prefers unspecific but precise assay (titration) provided related substances test is sufficiently characteristic and searching
- 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)
- Informational items sometimes included

## Impurities

- 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

## Functionality-related characteristics

- New feature of monographs on excipients
- Section is not mandatory
- Tests are linked to use (lubricant, tablet compression, etc.)
- Section provides information on important parameters