

**Up-date of the harmonization of
Pharmacopoeial Requirements in Europe.
Policy on General Monographs and
Impurities**

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Council of Europe & European Union

How to understand more

the philosophy behind the work ?

European regulatory framework



Council of Europe

- **Political intergovernmental organisation of 45 European pluralist democracies**
- **Developing multilateral conventions among them**
- **The European Pharmacopoeia convention (Public Health and exchanges of medicines)**
- **Headquarters in Strasbourg (France)**

European Union

- **15 countries → 25 in 2004**
- **From common market: facilitating free circulation for people, goods (e.g. medicines), services and finances**
- **To European Union: extending activities in Public Health area and protection of consumers**
- **Council of Ministers and Commission (Brussels), Parliament (Strasbourg), Court of Justice (Luxembourg)**

Regulations of Medicines in Europe (1)

Council of Europe

- **1964: Convention for the elaboration of a Eur. Pharmacopoeia (Ph. Eur.)**
8 Member States (MS)
(6 EU+U.K. + CH)

- **1974: Enlargement to other European countries (Nordic and Eastern countries)**

- **1992/1994: certification procedure**

European Union

- **1964: EU observer Ph. Eur. Commission**

- **1965: Directive 65/65**
Definition of medicines marketing autorisation (6 MS)

- **1969: 9 MS (U.K.+IRL+DK)**

- **1975: 75/318/EEC**

Implementation of the Ph. Eur. in the MA dossiers.

- **1992: NfG requirements for demonstration of suitability to Ph. Eur. Monographs**

Regulations of Medicines in Europe (2)

Council of Europe

- **1995: European OMCL Network**
- **1996: officialisation of EDQM (European Directorate for the Quality of Medicines)**
 - Ph. Eur.
 - OMCL Network
 - CEP
- **1999: Ph. Eur. and Certification TSE procedure**

European Union

- **1992: Contract EU Biological Standardisation Programme**
- **1994: EU signs the Ph. Eur. Convention**
- **1995: Contract EU/EDQM for the European Network of the OMCLs**
- **1997: Contract EMEA/EDQM for sampling testing C.A.P.**
- **1999: Dir. TSE risk**

The European Pharmacopoeia 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

Membership

- **31 MS + the European Union**
- **Ph. Eur. is recognised as the only official Pharmacopoeia in Europe and has to be used for international trade.**
- **16 observer countries + World Health Organisation**
- **Working languages: English and French**

Ph. Eur. MEMBER & OBSERVERSHIP (including EU)



European Pharmacopoeia

Legal status

- **Replace national monographs & texts**
- **Mandatory at the same date in 31 Member States**
- **Mandatory in European MA dossiers (at submission and during the validity of the MA) Dir 2003/63/EC, July 2003**
- **Demonstration of suitability required (API, TSE risks...): certification procedure Ph. Eur. is recognised as the preferred option)**

Implementation dates

	Adoption	Publication	Implementation
Suppl. 4.7	03/2003	Oct. 2003	April 2004
Suppl. 4.8	06/2003	Jan. 2004	July 2004
5th Edition	11/2003	Summer 2004	Jan. 2005

Ph. Eur. : Getting started

- **Proper in-house training of users in analytical methods/regulatory affairs**
- **Know the place of the Ph. Eur. in the overall structure of medicines regulations**
- **Be familiar with the whole of the Ph. Eur. not just the monograph you want to use**

Structure of the Ph. Eur.

- **General notices**
- **General chapter**
- **General monographs**
- **General monographs on dosage forms**
- **Monographs on active substances and excipients**

How to use the European Pharmacopoeia Interaction Ph. Eur. /CEP

General monographs
General chapter
(e.g. residual solvents
TSE risks)



Specific monographs
e.g. Ibuprofen
Mg Stearate



CEP
Confidential data

Revision/ Up-dating

What is mandatory ?

- **Mandatory unless otherwise indicated**
- **« Should » → informative or advisory (i.e. not mandatory)**
- **« This chapter/section is published for information and guidance »**

Why have general monographs

- **Editorial convenience (original reason)**
- **Now necessary for proper regulatory framework**
- **Deal with issues that cannot be dealt with in specific monographs, e.g.:**
 - **Residual solvents**
 - **Pesticides in herbal drugs**
- **Give general rules for preparations**

Types of general monographs

- **Classes of preparation: vaccines, immunosera, radiopharmaceuticals, etc.**
- **Nature of product: herbal drugs, substances for pharmaceutical use**
- **Method of manufacture: products of fermentation, products of recombinant DNA technology**
- **Dosage form monographs: tablets, parenteral preparations)**

Scope of general monographs

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

General vs specific monographs

- **The two types of monograph are complementary**
- **There is usually at least one general monograph to be consulted along with a specific monograph**
- **List of general monographs given in Ph. Eur. and Supplements**
- **User's responsibility to check**

Substances for Pharmaceutical use

2034

- **Clarifies scope of individual monographs:**
- **Use of excipients, special grades/forms, polymorphism, residual solvents**
- **Applies to substances for which a specific monograph exists**
- **Section on related substances gives a regulatory basis for dealing with new impurities**
- **Competent authority can extend to other substances**

Products of fermentation ¹⁴⁶⁸

- **Individual monographs need support of general monograph, especially for change control**
- **Applies to indirect gene products, especially antibiotics, some amino-acids**
- **Compliance assessed during certification**

Products with risk of transmitting agents of animal spongiform encephalopathies

1483

- **Implements chapter 5.2.8 which is a transcription of the CPMP/CVMP Note for Guidance 528**
- **Compliance with NfG is mandatory via EU directive**
- **Certification via monograph can be used to demonstrate compliance**
- **Applies to complete production chain**

Specific monographs

- **monograph has to be seen as a single entity**
- **Whole set of tests define quality**

Policy on impurities (historic)

- **June 2001** **The Future face of the European Pharmacopoeia. Current concerns in pharmaceutical analysis - Cannes (France)**
- **Dec. 2001** **Workshop with all parties: assessors, groups of experts, pharmaceutical manufacturers, suppliers of the Pharmaceutical Industry, OMCLs, Inspectors**
- **2002/2003** **Programme of actions for the 5th Edition**

Impurities seminar - Follow-up

- **Impurities section in monographs**
 - To be clarified, harmonized
- **Information chapter on impurities**
 - Policy
 - Terminology (to be harmonised with ICH)
 - Scope and use of impurities section
 - Identification of impurities
- **Description of chromatographic system**
- **Revision of technical guide**
- **Revision of general monograph « Substances for Pharmaceutical use »**

Impurities seminar - Follow-up ⁽²⁾

2002-2003 : actions taken

- **For the 5th Edition (June 2004)**
 - **General chapter on impurities: Pharmeuropa 15.3**
 - **Policy clarified in common by Ph. Eur. COM & QWP (EMEA)**
- **Immediate:**
 - **list of chromatographic system: on EDQM web site (www.pheur.org)**
- **Programme of revision for « old monographs »**

Aim of impurities control

- **Contribute to public health protection by describing products of acceptable quality**
- **Provide reliable and robust test methods as the basis of quality definition**
- **Cover all substances used in approved products in Ph. Eur. Member States**
- **Facilitate licensing procedures**

Policy on impurities

- **Presentation concerns organic chemicals**
- **Ph. Eur. now applies on the same approach as the ICH Q3A(R) guideline:**
 - **Individual limit for specified impurities**
 - **General limit for other impurities at reporting threshold**
 - **Limit for total impurities**
 - **Limits take account of safety data and batch data**
- **Policy defined in general monograph on *Substances for Pharmaceutical Use* and general chapter *5.10 Control of impurities in substances for pharmaceutical use.***

Methods for impurity control

- **General test (« Related substances »): liquid chromatography now the preferred method (also gas chromatography and electrophoresis)**
- **Thin-layer chromatography acceptable for specified impurity that cannot be conveniently controlled by general LC/GC test**
- **Ph. Eur. has revision programme to replace most general TLC tests by LC/GC**

The impurities section

- **Formally published for information (see General Notices)**
- **In practice, within the European regulatory system, status is somewhat stronger**
- **May be divided into « Specified impurities » and « Other detectable impurities »**
- **Where the list is not divided, impurities are « specified »**

The impurities section ⁽²⁾

- **Indicates impurities known to be controlled by the monograph at an acceptable level**
- **Section is not necessarily exhaustive**
- **Based on data generated during drafting of monograph**
- **Completed after publication with information from certification**

General chapter 5.10

- **Pre-publication in Pharmeuropa 15.2**
- **Publication in 5th Edition**
- **Gives detailed information on**
 - **Policy for impurities control in monographs**
 - **Interpreting the Related substances test**
 - **Scope of related substances tests and impurities section**
 - **Dealing with new impurities**

Specified impurities

- **Impurities that occur in substances from approved sources**
- **Individual limits included for specified impurities**
- **Limits in monographs are valid for these impurities**
- **By implication, specified impurities are qualified at the specified level (or greater)**

Other detectable impurities (ODI)

- **Impurities known to controlled at reporting treshold by monograph**
- **ODI do not occur in batches of approved sources above reporting treshold**
- **ODI may be impurities found in development batches but removed to below the reporting treshold by current purification procedures**
- **Included in section as useful information, e.g. for new sources**

Using the impurities section

- **Manufacturers have an obligation to define the impurity profile of their products in line with general Ph. Eur. Policy:**
 - **Reporting treshold**
 - **Identification treshold**
 - **Qualification treshold**

Using the impurities section ⁽²⁾

- **Where the profile is covered by the Impurities section, monograph provides adequate control**
- **Otherwise**
 - **Licensing authorities will require supplementary test(s) e.g. those on CEP**
 - **Monograph will need revision**

Residual solvents

- **Ph. Eur. has same policy as ICH guideline**
- **Three basic texts:**
 - **Substances for Pharmaceutical Use (general monograph)**
 - **5.4 Residual solvents (general chapter)**
 - **2.4.24 Identification and control of residual solvents (general method)**
- **Residual solvents mentioned on CEP**

Links with Certification

- **The Impurities section is a starting point for certification**
- **If the impurity profile of the source to be certified is covered by the section, CEP can be issued on that basis (general monograph(s) may require complementary tests (e.g. residual solvents))**
- **If impurity is not covered, supplementary tests will be given on certificate, monograph will probably need revision**