

General concepts in the Ph. Eur.:

theory and rationale

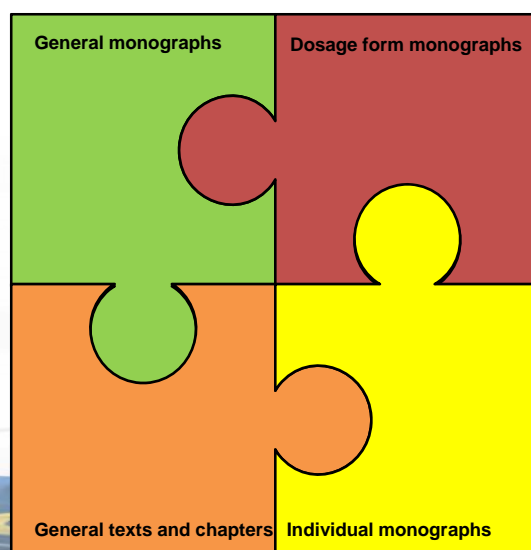
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The structure of the Ph. Eur.



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FR Document en Français PDF Knowledge Database General Monographs General Notices

General notices => apply to all !!!!

General monographs	Dosage form monographs
General texts and chapters	Individual monographs

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General Notices

At the very beginning of the Ph. Eur. (page 3)

- address general issues
- aim at providing basic information to the user
- apply to **all** texts
- include rules to understand texts, conventional expressions

Essential reading before starting to use monographs and chapters

General Notices – answer to a lot of questions!

Such as:

- What about alternative method?
- What about waiving of tests?
- What does compliance means?
- What is mandatory?
- What to do when implementing a method?
- Why two identification tests ... sometimes?
- Human and/or veterinary use?

And many more

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Conventional terms: meanings

'competent authority': the national, supranational or international body / organisation vested with the authority for making decisions concerning the issue in question. May be a national pharmacopoeia authority, a licensing authority or an official control laboratory.

'unless otherwise justified and authorised' means that the requirements have to be met, unless the competent authority authorises a modification or an exemption where justified in a particular case.

Etc...

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Flexibility in the Ph. Eur. Alternative methods



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Alternative methods

- Ph. Eur. tests = reference methods, alone authoritative in cases of doubt or dispute.
- Compliance required, but alternative methods may be used: **same pass/fail decision**
- Users' responsibility to demonstrate their suitability. Approval of *competent authority* needed in any case

The EDQM does not decide if acceptable or not!

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Alternative methods

Example:

- You may replace an existing HPLC method (impurities or assay) by an alternative one, provided the alternative method is cross-validated against the official one and leads to the same pass/fail decision.
- ✗ Not possible to replace a selective HPLC assay by a volumetric titration [since the same pass/fail cannot be obtained].

Flexibility in the Ph. Eur. Waiving of tests

Compliance ≠ **Performance**

↓
prerequisite

↓
not prerequisite



- 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 e.g. boron in salbutamol

Waiving of tests

"(1) An article is not of Pharmacopoeia quality unless it complies with all the requirements stated in the monograph. *This does not imply that performance of all the tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality on the basis of its design, together with its control strategy and data derived, for example, from validation studies of the manufacturing process.*"

Flexibility in the Ph. Eur. PAT

"(2) An enhanced approach to quality control could utilise *process analytical technology (PAT) and/or real-time release testing (including parametric release) strategies as alternatives to end-product testing alone. Real-time release testing in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia.*"

What does compliance mean?

- All **mandatory** parts of a **monograph**
(*"Unless otherwise indicated in the General Notices or in the monographs, statements in monographs constitute mandatory requirements."* Characters section, second identification test and storage section – not mandatory)
- Compliance **throughout period of validity** for preparations.
- A distinct period of validity and/or specifications for opened or broached containers may be decided by licensing authority for each preparation
- Compliance **until end of shelf-life** for all other items: API, excipients, ...

What to do when implementing a method?

- **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.
- **Implementation of pharmacopoeial methods.** When implementing a pharmacopoeial method, the user must assess whether and to what extent the suitability of the method under the actual conditions of use needs to be demonstrated according to relevant monographs, general chapters and quality systems.
Ref: Ph. Eur. / General notices
- **# Demonstration of suitability:** Each MAA still to provide to the competent authority demonstration that **tests in the monograph are appropriate** for the quality control of their product.

Reference to regulatory documents

“These references are provided for information for users for the Pharmacopoeia. Inclusion of such a reference does not modify the status of the documents referred to, which may be mandatory or for guidance.”

Identification

First and second identifications. Certain monographs have subdivisions entitled 'First identification' and 'Second identification'.

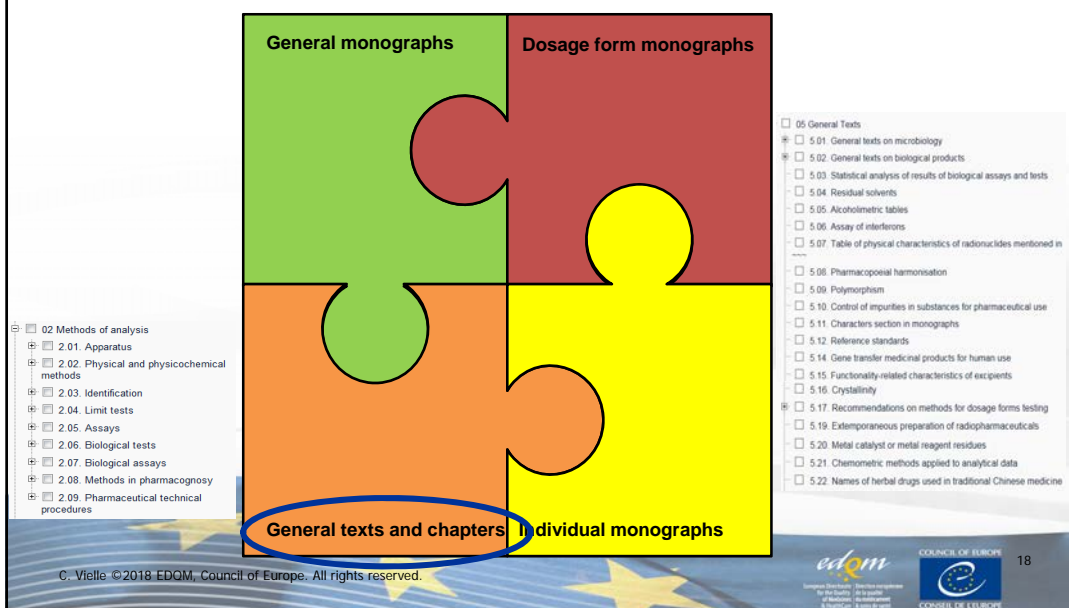
The test or tests that constitute the 'First identification' may be used in all circumstances.

The test or tests that constitute the 'Second identification' may be used in pharmacies provided it can be demonstrated that the substance or preparation is fully traceable to a batch certified to comply with all the other requirements of the monograph.

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 e.g. *Levamisole for veterinary use*

The structure of the Ph. Eur.



Why general chapters?

Analytical methods:

- Editorial convenience: avoid repeating standard methods in each monograph
- Provide standard methods that can be used when there is no monograph
- Give general requirements for equipment, equipment qualification or calibration

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 (2.4.30 EG and DEG in ethoxylated substances): useful guidance, can be referred to in applications

General Methods - Modernisation programme

- **Recently revised chapters:**
 - Melting point - capillary method 2.2.14 => Suppl. 9.1
 - Volumetric solutions 4.2.2 => Suppl. 9.2
 - Clarity and degree of opalescence 2.2.1=> Suppl. 9.2
 - X-Ray fluorescence spectrometry 2.2.37 => Suppl. 9.3
 - Water: micro determination 2.5.32 => Suppl. 9.4
 - **Infrared absorption spectrophotometry (2.2.24) – adopted March 2018 => Suppl. 9.7**
- **Underway - some examples:**
 - **Chromatographic separation techniques 2.2.46 (PDG)** (pharmeuropa 29.3 – deadline: 30/09/2017)
 - **Elemental impurities 2.4.20 (PDG)** not yet in pharmeuropa
 - **Conductivity 2.2.38 (PDG)** (pharmeuropa 27.4 – deadline: 31/12/2015) - FINALISED
 - **UV-VIS spectrophotometry 2.2.25** (pharmeuropa 29.4 – deadline: 31/12/2017)
 - **Degree of coloration of liquids 2.2.2 (PDG)** (pharmeuropa 28.1 – deadline: 31/03/2016) – TO COME SOON
 - **Loss on Drying, 2.2.32** – TO COME SOON

More to come!

General texts

- Are often published for information and guidance.
- Aspects that cannot be treated in each individual monograph ≠ standard methods
- **Become mandatory** when referred to in a g^{al} monograph

Examples

5.10. Control of impurities in substances for pharmaceutical use referred to in general monograph *Substances for pharmaceutical use (2034)* → chapter 5.10 applies to all APIs (whether or not an individual monograph exists in the Ph. Eur.)

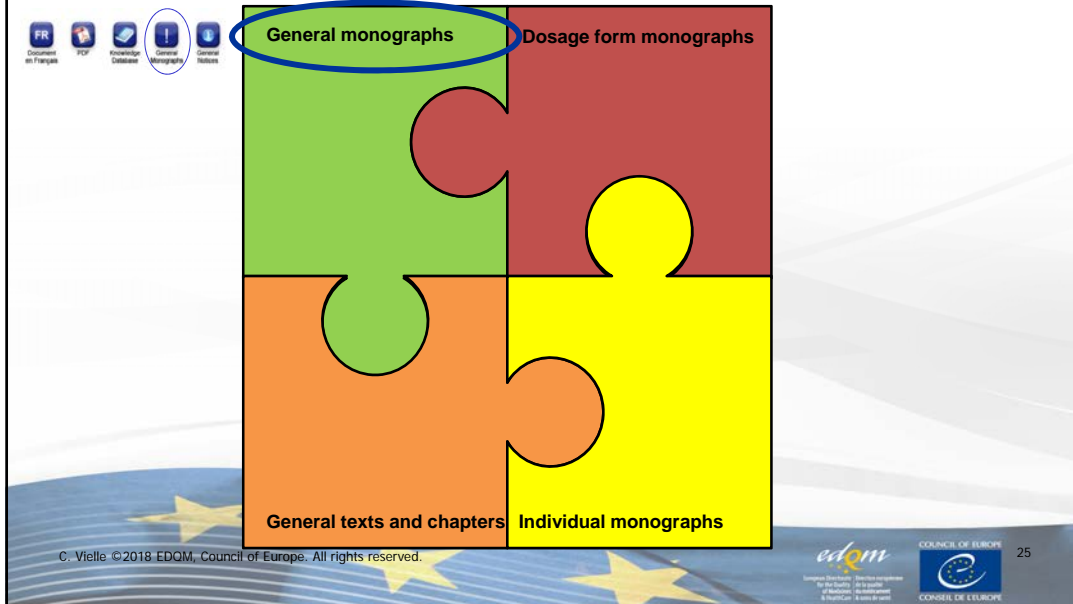
5.4 Residual solvents referred to in general monograph *2034* → chapter 5.4 applies to APIs and excipients covered by *2034*

5.20 Elemental impurities reproduces the essentials of ICH Q3D guideline, is referred to in general monograph *2619 Pharmaceutical preparations* - mandatory as of 1st January 2018

Some more examples...

- 5.12 Reference standards => revised when appr. to keep pace with ISO Guides 30 and 34 and EDQM's policies
- 5.21 Chemometric methods applied to analytical data – published Suppl. 8.7
- 5.24 Chemical imaging – published Suppl. 9.3
- 5.25 Process analytical technology - **Pharmeuropa 30.1 [deadline: 31/03/2018]**
- 5.8 Pharmacopoeial harmonisation
 - provides **information on the degree of harmonisation** of various general chapters and monographs between Ph. Eur., USP and JP
 - included for **guidance** of users
 - non-harmonised attributes and local requirements clearly indicated
 - work carried out by Pharmacopoeial Discussion Group (PDG), an informal structure composed of JP, Ph. Eur., USP members (+ WHO observer)

The structure of the Ph. Eur.



General monographs

IMPORTANT NOTICE
GENERAL MONOGRAPHS

The European Pharmacopoeia contains a number of general monographs covering classes of products. These general monographs give requirements that are applicable to all products in the given class or, in some cases, to any product in the given class for which there is a specific monograph in the Pharmacopoeia (see 1. General Notices, General monographs). Where no restriction on scope of a general monograph is given in a preamble, it is applicable to all products in the class defined, irrespective of whether there is an individual monograph for the product in the Pharmacopoeia. Whenever a monograph is used, it is essential to ascertain whether there is a general monograph applicable to the product in question. The general monographs listed below are published in the General Monographs section (unless otherwise stated). This list is updated where necessary and republished in each supplement.

The European Pharmacopoeia contains a number of general monographs covering classes of products. These general monographs give requirements that are applicable to all products in the given class or, in some cases, to any product in the given class for which there is a specific monograph in the Pharmacopoeia (see 1. General Notices, General monographs). Where no restriction on scope of a general monograph is given in a preamble, it is applicable to all products in the class defined, irrespective of whether there is an individual monograph for the product in the Pharmacopoeia. Whenever a monograph is used, it is essential to ascertain whether there is a general monograph applicable to the product in question. The general monographs listed below are published in the General Monographs section (unless otherwise stated). This list is updated where necessary and republished in each supplement.

General monographs. Substances and preparations that are the subject of an individual monograph are also required to comply with relevant, applicable general monographs. Cross-references to applicable general monographs are not normally given in individual monographs.

General monographs apply to all substances and preparations within the scope of the Definition section of the general monograph, except where a preamble limits the application, for example to substances and preparations that are the subject of a monograph of the Pharmacopoeia.

General monographs on dosage forms apply to all preparations of the type defined. The requirements are not necessarily comprehensive for a given specific preparation and requirements additional to those prescribed in the general monograph may be imposed by the competent authority.

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.

- Allergen products (1063)
- Chemical precursors for radiopharmaceutical preparations (2902)
- Dosage Forms monographs (published in the Dosage Forms section or the Homeopathic Preparations section)
- Essential oils (0298)
- Herbal drug extracts (0765)
- Herbal drug preparations (1434)
- Herbal drugs (1433)
- Herbal drugs for homeopathic preparations (2045) (published in the Homeopathic Preparations section)
- Herbal teas (1435)
- Herbal teas, infusions (2620)
- Mother tinctures for homeopathic preparations (2029) (published in the Homeopathic Preparations section)
- Pharmaceutical preparations (2619)
- Products of fermentation (1468)
- Products with risk of transmitting agents of animal spongiform encephalopathies (1483)
- Radiopharmaceutical preparations (0125)
- Recombinant DNA technology, products of (0784)
- Substances for pharmaceutical use (2034)
- Vaccines for human use (0153)
- Vaccines for veterinary use (0062)
- Vegetable fatty oils (1579)

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General monographs

Two types:

- General monographs on **classes of substances**

e.g. Products of fermentation, Allergen products, Herbal drugs, Essential oils, Monoclonal antibodies for human use, etc.

- General monographs on **dosage forms**

e.g. capsules, tablets, parenteral preparations, eye preparations, etc.

General monographs

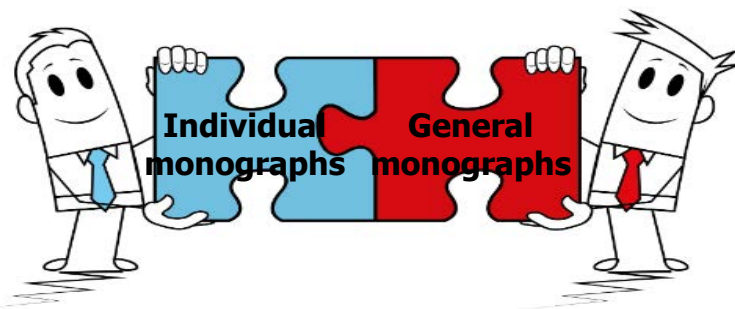
- Deal with aspects that cannot be treated in each individual monograph
- "*General monographs apply to all substances and preparations within the scope of the Definition section of the general monograph, except where a preamble limits the application, for example to substances and preparations that are the subject of a monograph of the pharmacopoeia.*"

General monographs

- No cross-reference in individual monographs:
"Whenever a monograph is used, it is essential to ascertain whether there is a general monograph applicable to the product in question."

CHECK WHICH GENERAL MONOGRAPH APPLIES!

General vs. individual monographs



- Complementary
- One not overruling the other
- Exceptions are clearly indicated either in the general monograph or in the individual one

Two .. key .. examples



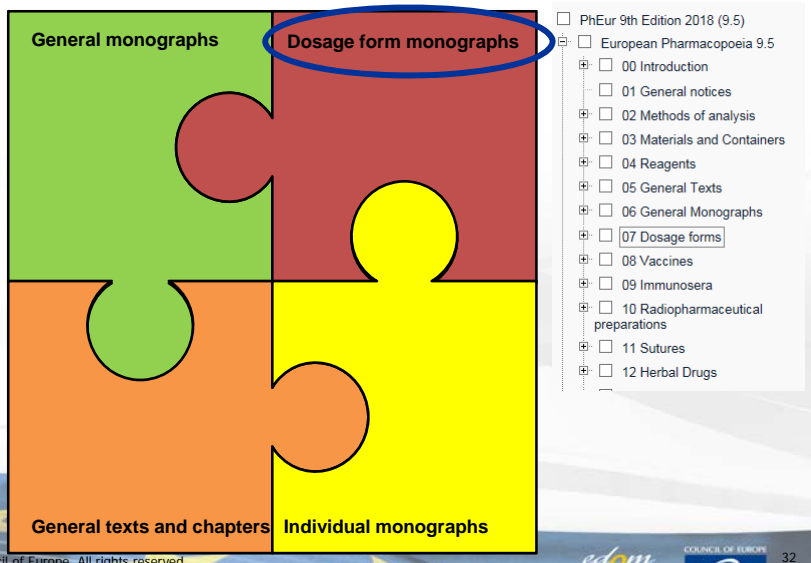
Substances for pharmaceutical use
Corpora ad usum pharmaceuticum

DEFINITION
Substance for pharmaceutical use is any active or inactive substance that is used as an active substance or excipient for the manufacture of medicinal products for human or veterinary use.

Where a substance for pharmaceutical use not described in an individual monograph of the Pharmacopoeia is used in a medicinal product prepared for the special needs of individual patients, the need for compliance with the present general monograph is decided in the light of a risk assessment that takes account of the available quality of the substance and its intended use.

Intended use
An Intended use is a specific use of a substance for pharmaceutical use in a medicinal product prepared for the special needs of individual patients, the need for compliance with the present general monograph is decided in the light of a risk assessment that takes account of the available quality of the substance and its intended use.

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General monographs on dosage forms

- Contain requirements **common to all dosage forms** of the type defined e.g. sterility, uniformity of dosage units, dissolution ...
- Classified by **pharmaceutical form/route of administration** e.g. Tablets, Preparations for inhalation ...
- Applied during **licensing**
- **Framework** specification: extra tests and acceptance criteria are proposed by manufacturer and approved by competent authority

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Product specific

Active substances:

- *Paracetamol* (0049)
- *Rosuvastatin calcium* (2631)
- *Sitagliptin phosphate monohydrate* (2778)

Finished products:

- *Sitagliptin tablets* (2927)

Dosage form monographs

- Specifications for individual product
- **Based on approved specifications backed up by batch data**
- **Analytical procedures and acceptance criteria** to demonstrate that the substance or product meets required quality standards

General texts and chapters

Individual monographs

- 08 Vaccines
- 09 Immunosera
- 10 Radiopharmaceutical preparations
- 11 Sutures
- 12 Herbal Drugs
- 13 Homoeopathic preparations
- 14 Monographs A-C
- 15 Monographs D-K
- 16 Monographs L-P
- 17 Monographs Q-Z

**Thank you for
your
attention!**



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