THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

General concepts in the Ph. Eur.: theory and rationale

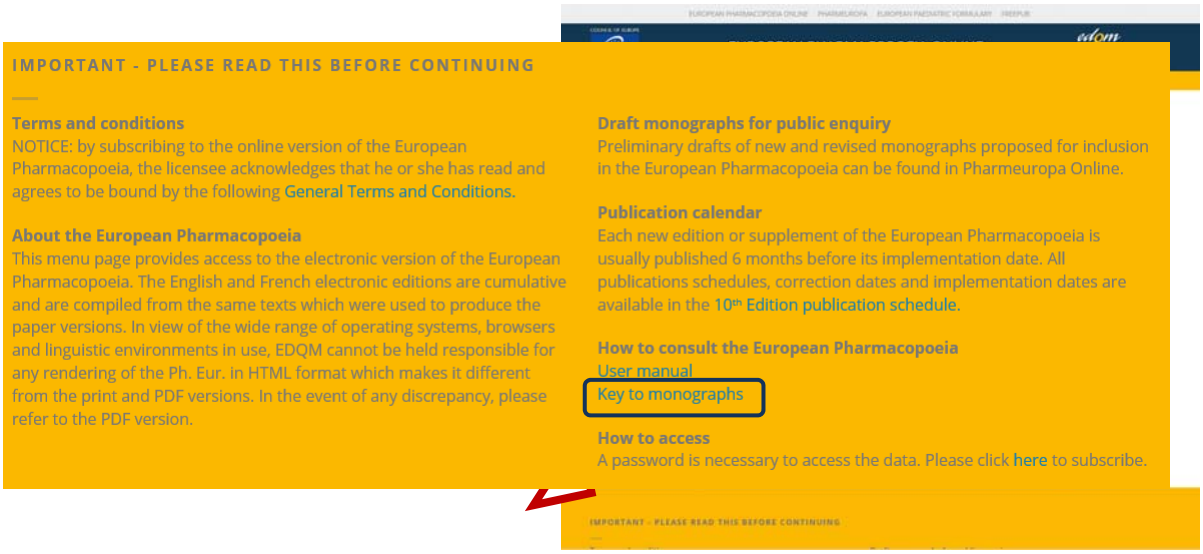
2019 Training Session
"The European Pharmacopoeia"
Mrs Cathie Vielle
EDQM, Head of European Pharmacopoeia Department

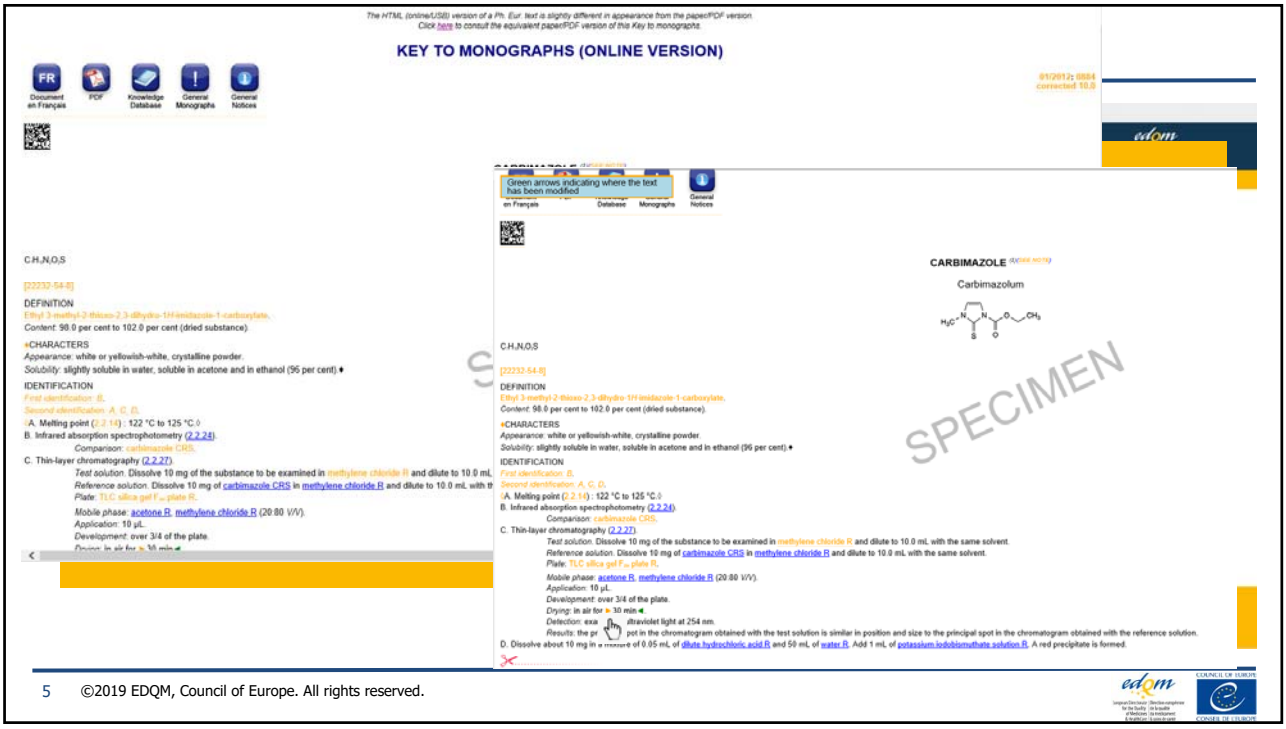
10 – 11 September 2019, Iselin, New Jersey, USA

Where do you start … … when using the Ph. Eur.?

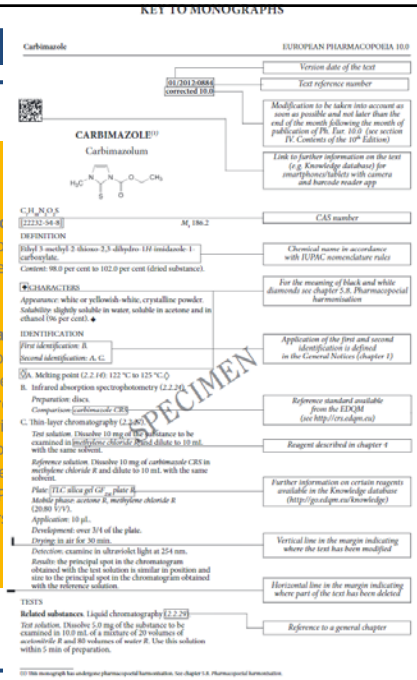
Sample of e.g. Omeprazole to be tested

Where do you start … … when using the Ph. Eur.?





Where d en using the Ph. Eur.?



IMPORTANT - P

Terms and conditi
NOTICE: by subscrib
Pharmacopoeia, the
agrees to be bound

About the Europea
This menu page pro
Pharmacopoeia. The
and are compiled fr
paper versions. In vi
and linguistic enviro
any rendering of the
from the print and F
refer to the PDF ver

Draft monographs for public enquiry
Preliminary drafts of new and revised monographs proposed for inclusion in the European Pharmacopoeia can be found in Pharmeuropa Online.

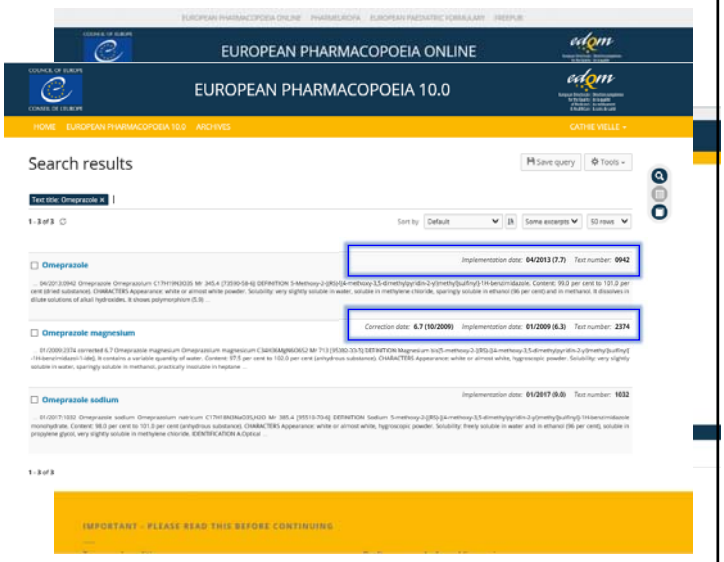
Publication calendar
Each new edition or supplement of the European Pharmacopoeia is usually published 6 months before its implementation date. All publications schedules, correction dates and implementation dates are available in the 10th Edition publication schedule.

How to consult the European Pharmacopoeia
User manual
Key to monographs

How to access
A password is necessary to access the data. Please click here to subscribe.

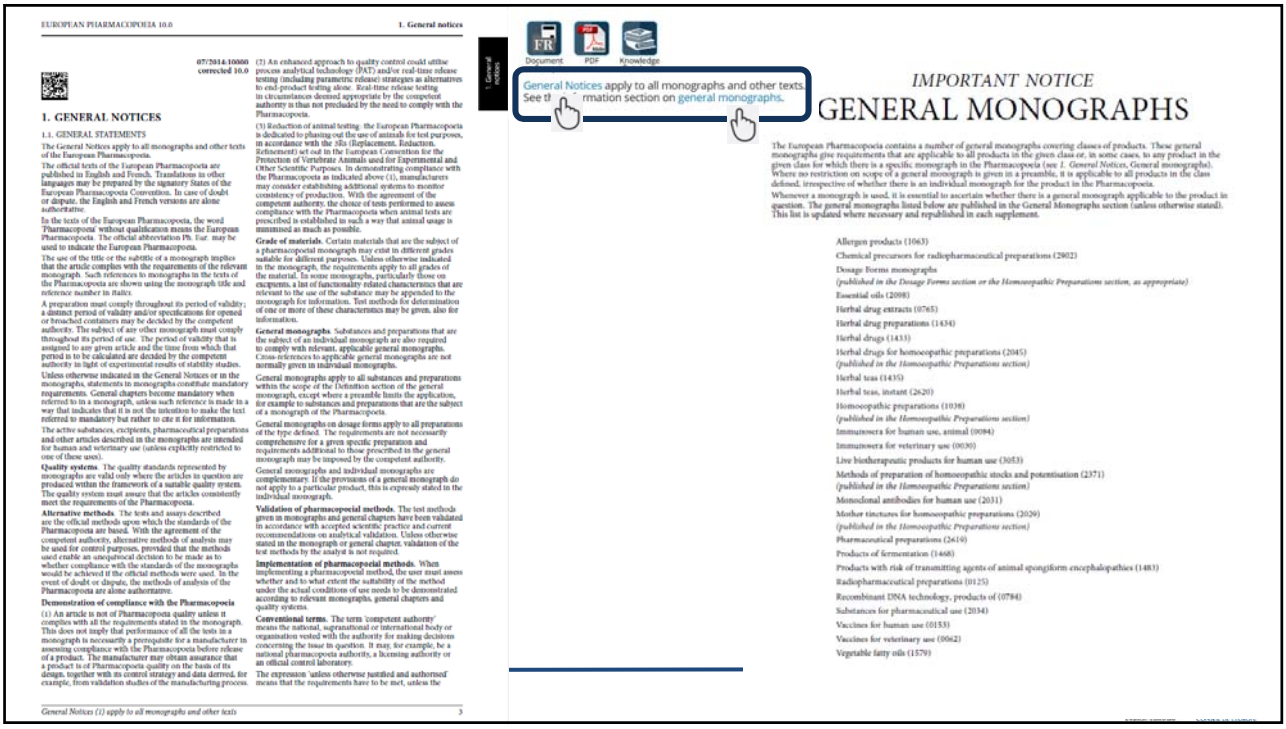
Where do you start … … when using the Ph. Eur.?

Sample of e.g. Omeprazole to be tested



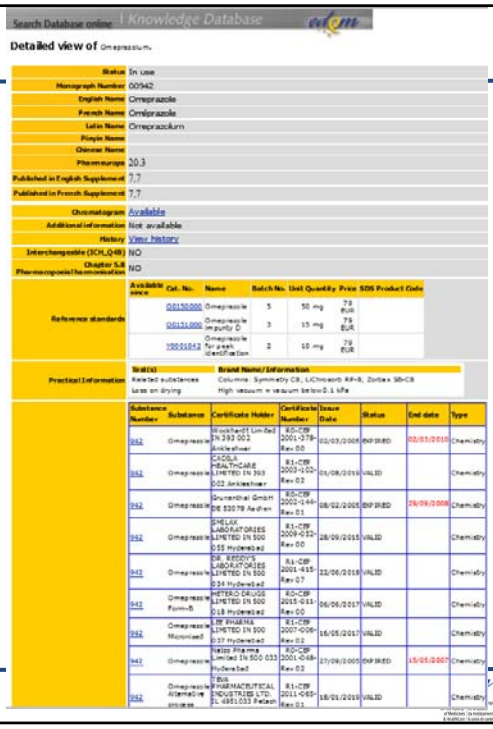
Where do you start … … when using the Ph. Eur.?

Sample of e.g. Omeprazole to be tested

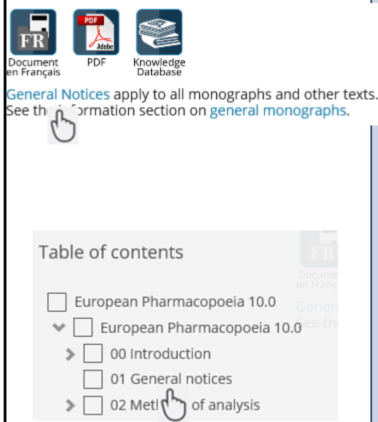


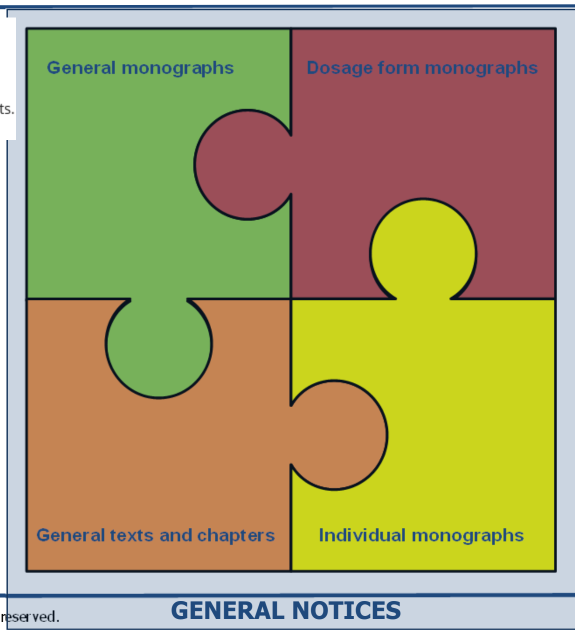
Knowledge database

General Notices apply to all monographs and other texts.
See the information section on general monographs.



The structure of the Ph. Eur.





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

And many more

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…

Flexibility in the Ph. Eur. **Alternative methods**

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!

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?

Ref: Ph. Eur. / General notices

- **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.

- **# 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.

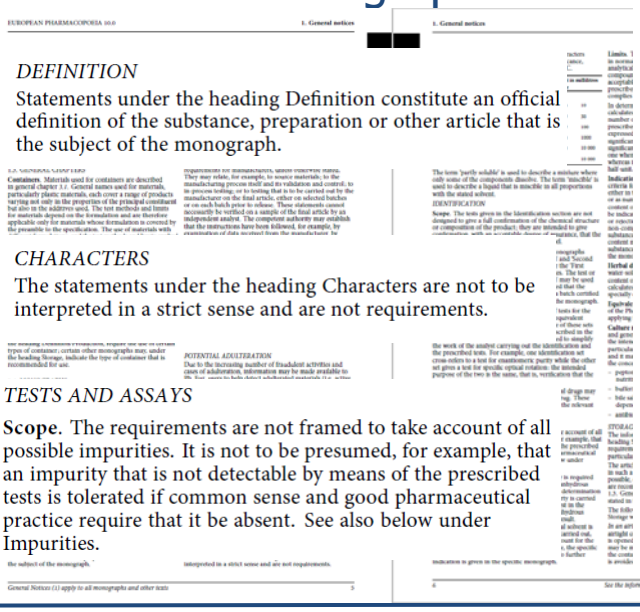
Reference to regulatory documents

- *"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."*

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*

Section 1.4 Monographs



DEFINITION

Statements under the heading Definition constitute an official definition of the substance, preparation or other article that is the subject of the monograph.

CHARACTERS

The statements under the heading Characters are not to be interpreted in a strict sense and are not requirements.

TESTS AND ASSAYS

Scope. The requirements are not framed to take account of all possible impurities. It is not to be presumed, for example, that an impurity that is not detectable by means of the prescribed tests is tolerated if common sense and good pharmaceutical practice require that it be absent. See also below under Impurities.

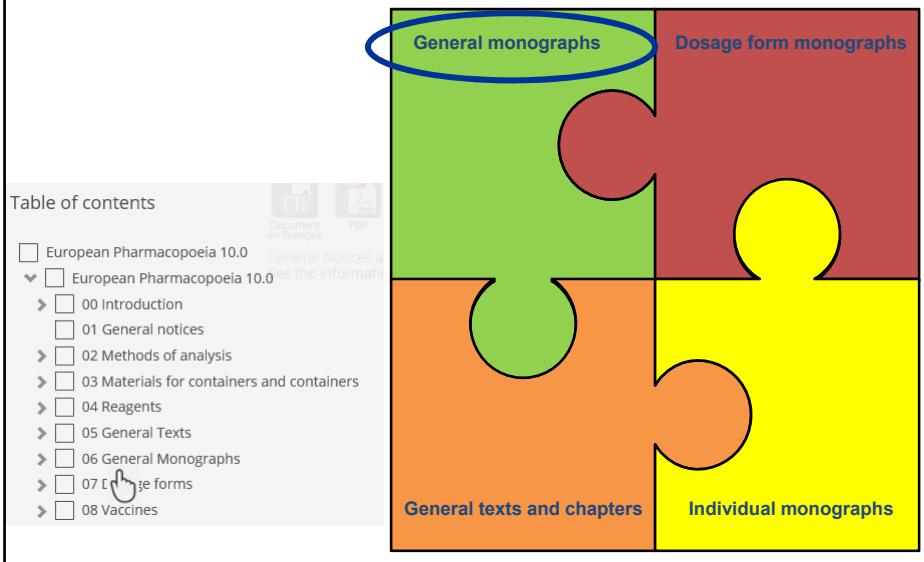
IDENTIFICATION

Scope. The tests given in the Identification section are not designed to give a full confirmation of the chemical structure or composition of the product; they are intended to give confirmation, with an acceptable degree of assurance, that the article conforms to the description on the label.

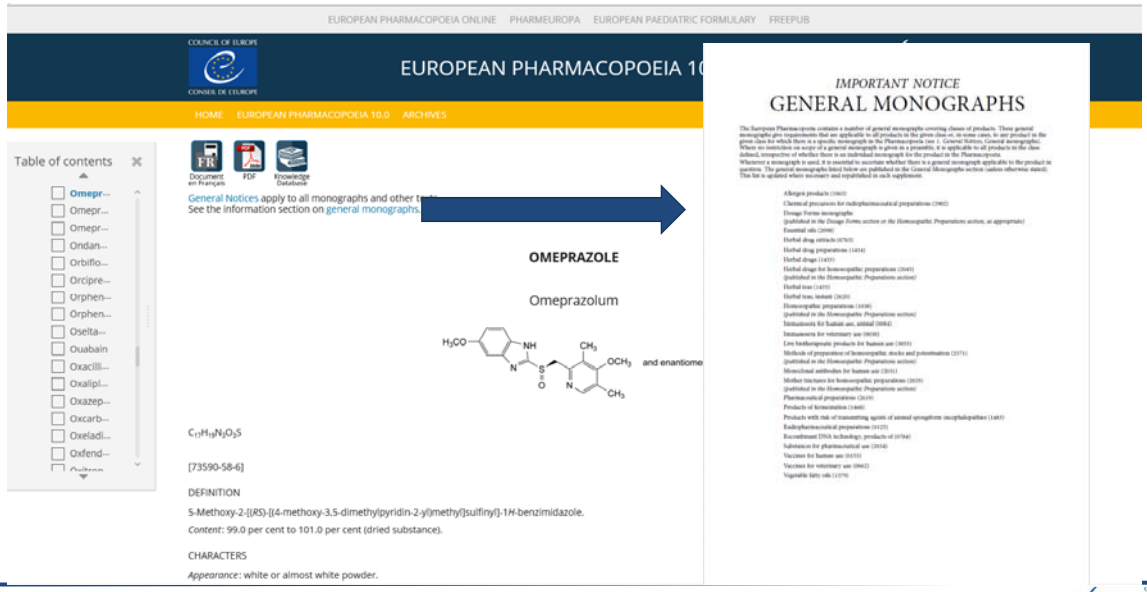
First and second identifications. Certain monographs have subdivisions entitled 'First identification' and 'Second identification'. The test or tests that constitute the 'First identification' may be used in all circumstances. The test or tests that constitute the 'Second identification' may be used 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.

Certain monographs give two or more sets of tests for the purpose of the first identification, which are equivalent and may be used independently. One or more of these sets usually contain a cross-reference to a test prescribed in the Tests section of the monograph. It may be used to simplify the work of the analyst carrying out the identification and the prescribed tests. For example, one identification set cross-refers to a test for enantiomeric purity while the other set gives a test for specific optical rotation: the intended purpose of the two is the same, that is, verification that the correct enantiomer is present.

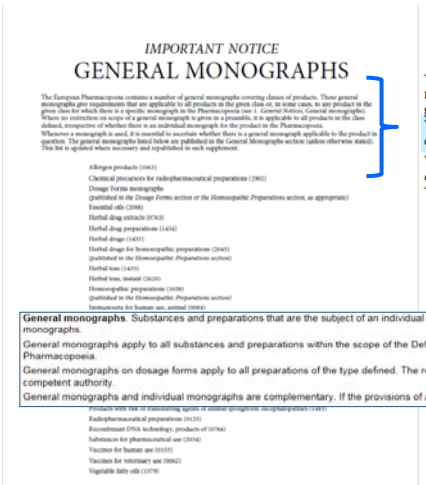
The structure of the Ph. Eur.



Important notice: General monographs



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.

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.

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

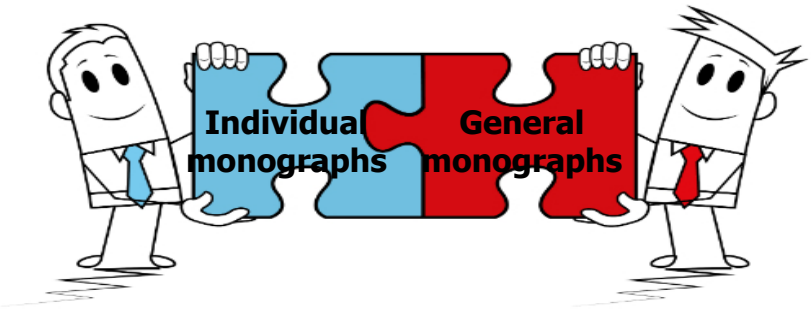
- Deal with aspects that cannot be treated in each individual monograph
- "*General monographs apply to all substances and preparations within the scope of the Definition section of the general monograph, except where a preamble limits the application, for example to substances and preparations that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

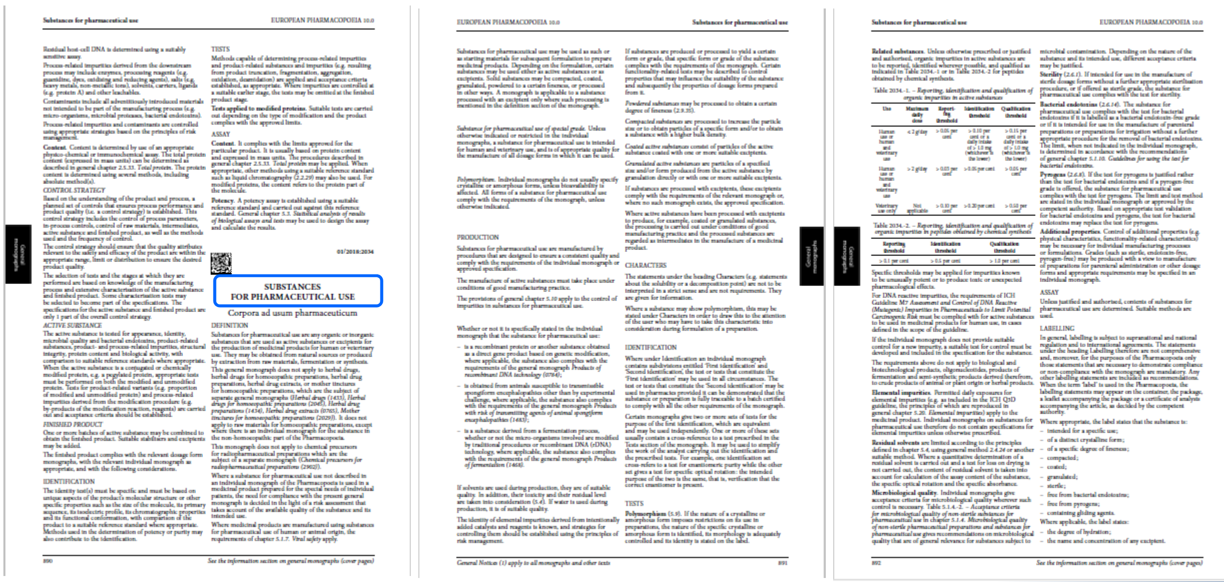
CHECK WHICH GENERAL MONOGRAPH APPLIES!

General vs. individual monographs

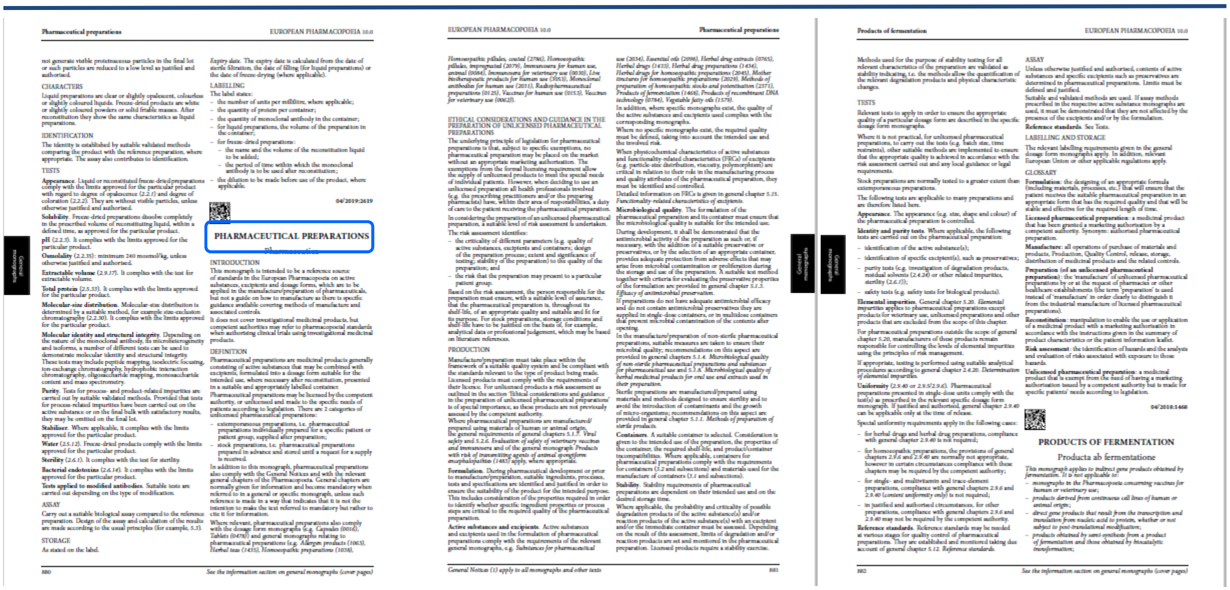


- Complementary
- One not overruling the other
- Exceptions are clearly indicated either in the general monograph or in the individual one

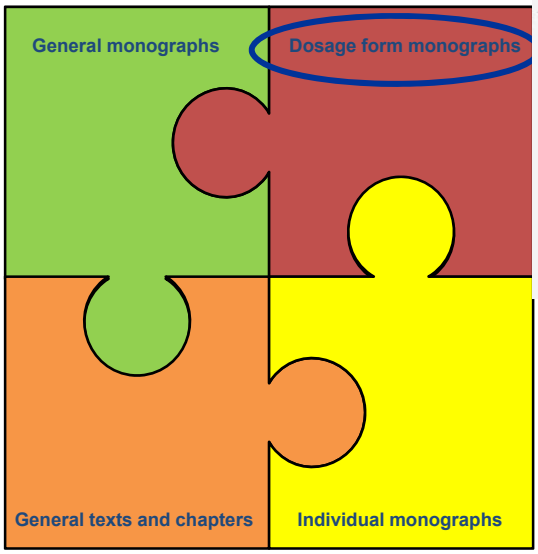
Two .. key .. examples

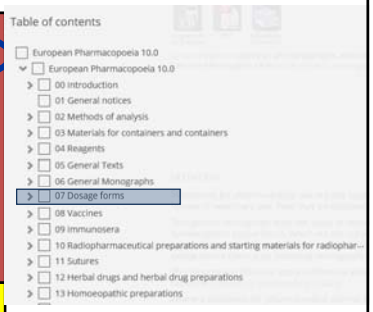


Two .. key .. examples



The structure of the Ph. Eur.





Section 7 Dosage forms

- 1st text published in there:

This glossary provides definitions and/or explanations of terms that may be found in, or used in association with, the general monographs on dosage forms and the corresponding chapters on Pharmaceutical technical procedures (2.9), but that are not defined within them. Where relevant, reference is made to other equivalent terms that may be found in other publications or contexts.

This glossary is published for information.

EUROPEAN PHARMACOPOEIA 10.0 — Glossary

07/2017:1502

GLOSSARY

Glossa

This glossary provides definitions and/or explanations of terms that may be found in, or used in association with, the general monographs on dosage forms and the corresponding chapters on Pharmaceutical technical procedures (2.9), but that are not defined within them. Where relevant, reference is made to other equivalent terms that may be found in other publications or contexts.

This glossary is published for information.

Active substance

Equivalent terms: active ingredient, drug substance, medicinal substance, active pharmaceutical ingredient.

Basis

Basis is an alternative term for 'vehicle' in a semi-solid or modified solid preparation. The basis may be single-phase or multiphase.

Conventional-release dosage form

A conventional-release dosage form is a preparation showing a release of the active substance(s) that is not deliberately modified by a special formulation design and/or manufacturing method. In the case of a solid dosage form, the dissolution profile of the active substance depends essentially on its intrinsic properties. Equivalent term: immediate-release dosage form.

Delayed-release dosage form

A delayed-release dosage form is a modified-release dosage form, usually administered orally, where the onset of release of the active substance(s) is adjusted to take place after a specific time or at a specific location in the gastrointestinal tract. Delayed release is achieved by a special formulation design and/or manufacturing method. Delayed-release dosage forms include gastro-resistant preparations as defined in the general monographs on solid oral dosage forms.

Dispersion

From a Ph. Eur. perspective, a dispersion is a system consisting of 2 or more phases.

– *Colloidal dispersion*

A colloidal dispersion is a system in which particles of colloidal size (a nominal diameter between approximately 1 nm and 1 µm) of any nature (solid, liquid or gas, including liposomes and nanosystems) are dispersed in a continuous phase of a different composition and/or state. The use of nominal diameter is intended to convey that not all particles are spherical. Dispersions of particles below 1 µm are considered less likely to undergo sedimentation because of the effect of Brownian motion.

– *Suspension*

A suspension is a dispersed system comprising solid particles of a nominal diameter greater than approximately 1 µm, dispersed in a liquid or semi-solid continuous phase. If the solid particles are of a nominal diameter lower than approximately 1 µm, the system is a colloidal suspension.

– *Emulsion*

An emulsion is a dispersed system consisting of a mixture of at least 2 liquids that are not miscible with each other. One of the liquids is dispersed in the other as droplets of a diameter greater than approximately 1 µm. If the droplets are of a nominal diameter lower than approximately 1 µm, the system is a colloidal emulsion.

Large-volume parenteral

A large volume parenteral is an infusion or injection supplied in a container with a nominal content of more than 100 mL.

Modified-release dosage form

A modified-release dosage form is a preparation where the onset, rate and/or place of release of the active substance(s) is different from that of a conventional-release dosage form administered by the same route. This deliberate modification is achieved by a special formulation design and/or manufacturing method. Modified release dosage forms include prolonged-release, delayed-release and pulsatile release dosage forms.

Prolonged-release dosage form

A prolonged-release dosage form is a modified-release dosage form showing a slower release of the active substance(s) than that of a conventional release dosage form administered by the same route. Prolonged release is achieved by a special formulation design and/or manufacturing method. Equivalent term: extended-release dosage form.

Pulsatile-release dosage form

A pulsatile release dosage form is a modified release dosage form showing a sequential, intermittent release of the active substance(s). Pulsatile release is achieved by a special formulation design and/or manufacturing method.

Small-volume parenteral

A small-volume parenteral is an infusion or injection supplied in a container with a nominal content of 100 mL or less.

Solution

A solution is a homogeneous mixture forming a single phase containing one or more dissolved substances, i.e. substances in a molecular or ionic state dispersed in a solvent or in miscible solvents. The dissolved substances can be solids, liquids or gases.

Spheroids

Spheroids are considered to be spherical or approximately spherical granules with a usually increased mechanical resistance compared to conventional *Granules (0499)*. They possess a smooth, uniform surface, with a typical size range of 200 µm to 2.8 mm. Spheroids may be prepared by any suitable method.

Standard Term

Standard Terms are approved terms for describing certain aspects of a medicinal product, namely the dosage form and route or method of administration, and certain important packaging items such as the container, closure and administration device. They are established by the European Pharmacopoeia Commission, which started working on the lists of Standard Terms in response to a request made by the EU Commission for use in the marketing authorisation application (MAA), summary of product characteristics (SmPC), labelling, and electronic communications. Standard Terms have the double purpose of bringing information to the patient/user/prescriber and distinguishing medicinal products having the same trade name, and are published in a specific Standard Terms database.

Vehicle

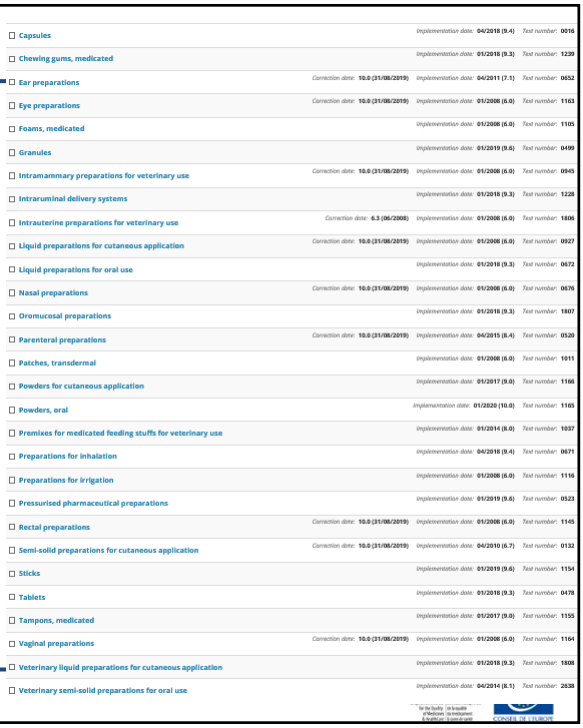
A vehicle is the carrier, composed of one or more excipients, in which the active substance(s) are contained, usually when referring to a liquid or semi-solid preparation.

General Notices (1) apply to all monographs and other texts 905

Dosage forms

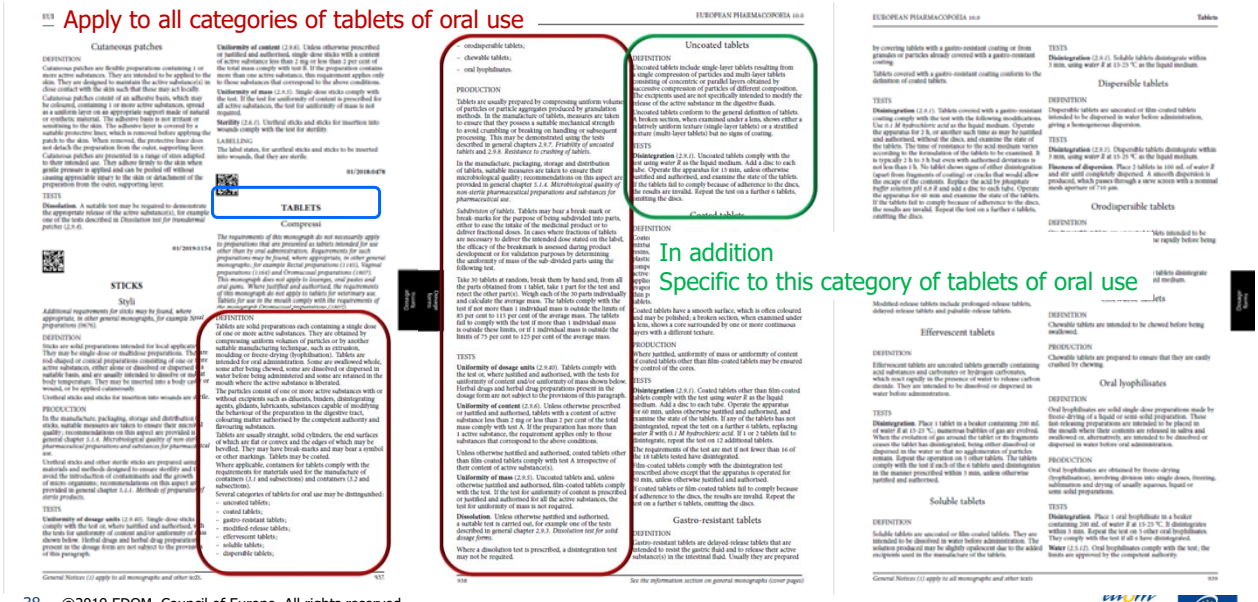
Section 7 Dosage forms

- 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



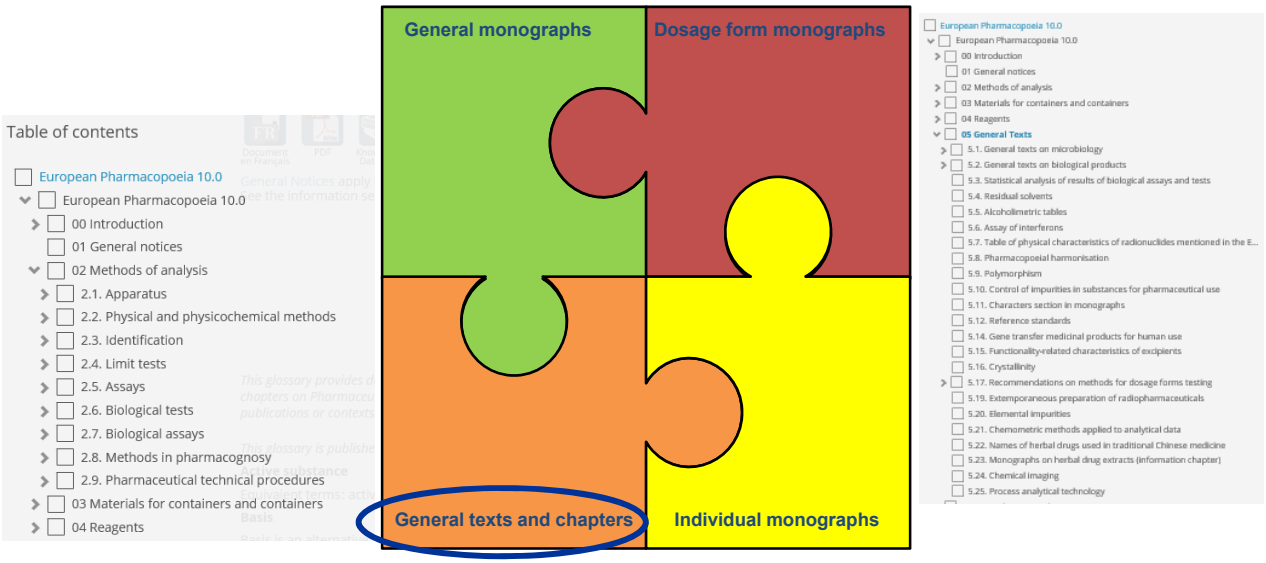
One example: Tablets

Apply to all categories of tablets of oral use



In addition
Specific to this category of tablets of oral 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 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 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.)

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.

PRODUCTION

Substances for pharmaceutical use are manufactured by procedures that are designed to ensure a consistent quality and comply with the requirements of the individual monograph or approved specification.

The manufacture of active substances must take place under conditions of good manufacturing practice.

The provisions of general chapter *5.10* apply to the control of impurities in substances for pharmaceutical use.

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*

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.

Residual solvents are limited according to the principles defined in chapter *5.4*, using general method *2.4.24* or another suitable method. Where a quantitative determination of a residual solvent is carried out and a test for loss on drying is not carried out, the content of residual solvent is taken into account for calculation of the assay content of the substance, the specific optical rotation and the specific absorbance.

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 monographs *2619 Pharmaceutical preparations* and *2034 Substances for pharmaceutical use* for ex.

Elemental impurities. General chapter *5.20. Elemental impurities* applies to pharmaceutical preparations except products for veterinary use, unlicensed preparations and other products that are excluded from the scope of this chapter.

For pharmaceutical preparations outside the scope of general chapter *5.20*, manufacturers of these products remain responsible for controlling the levels of elemental impurities using the principles of risk management.

If appropriate, testing is performed using suitable analytical procedures according to general chapter *2.4.20. Determination of elemental impurities*. **2619**

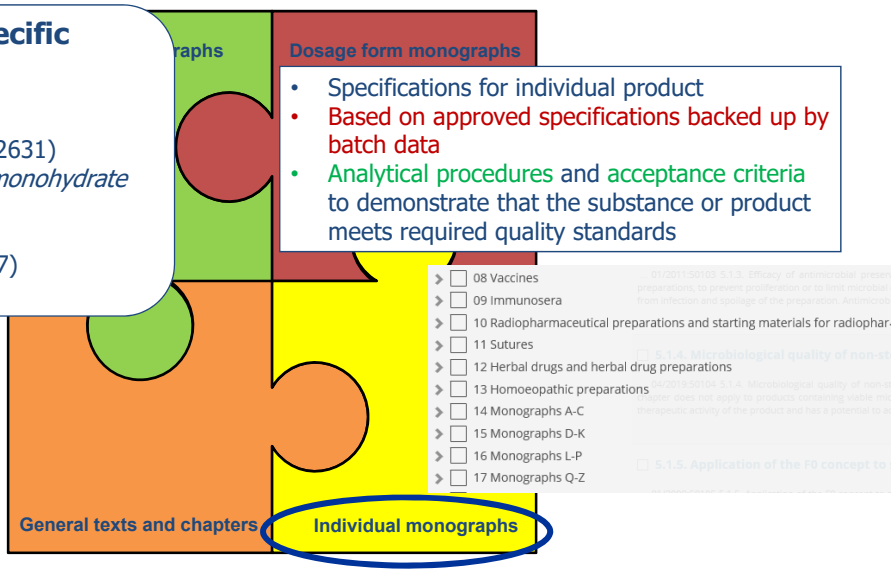
Elemental impurities. Permitted daily exposures for elemental impurities (e.g. as included in the ICH Q3D guideline, the principles of which are reproduced in general chapter *5.20. Elemental impurities*) apply to the medicinal product. Individual monographs on substances for pharmaceutical use therefore do not contain specifications for elemental impurities unless otherwise prescribed. **2034**

The structure of the Ph. Eur.

Product specific

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

Finished products:
- *Sitagliptin tablets* (2927)



- 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

Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: **https://go.edqm.eu/Newsletter**
LinkedIn: **https://www.linkedin.com/company/edqm/**
Twitter: **@edqm_news**
Facebook: **@EDQMCouncilofEurope**