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

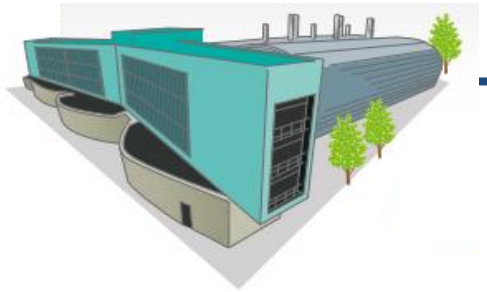
Module 1: General Methods, General Chapters & General Monographs

Mr Bruno Spieldenner

European Pharmacopoeia Department, EDQM

(Live Webinar)
Date: 2 December 2024

Who’s talking ?



Mr Bruno SPIELDENNER

Great team of 10 scientific programme managers and 4 administrative support assistants

French
Strasbourg

Studied Phys-Chem
MSc in Analytical Chemistry
Strasbourg/Marseille

7 years in Pharmaceutical industry in Switzerland
Specialised in Mass spectrometry

Joined EDQM in 2013
European Pharmacopoeia Department

Work on transversal projects:
General methods chapters, implementation ICH Q3D

Since 2022:
Head of Division A
(Chemicals, herbals and general methods)

Outline

- The EDQM and the European Pharmacopoeia
- Structure of the Ph. Eur. & general principles
  - General Notices
  - General monographs
  - General chapters
- General chapters work programme update
  - Recently published
  - Major items in the work programme
  - Public consultation items
  - New entries in the work programme
- Update on Ph. Eur. strategy
- Working procedures of the Ph. Eur.

The EDQM and the Ph. Eur.

Our Mission

"To contribute to public health protection, by engaging with an international community of experts and stakeholders."

The EDQM, a Directorate of the COUNCIL OF EUROPE

COUNCIL OF EUROPE

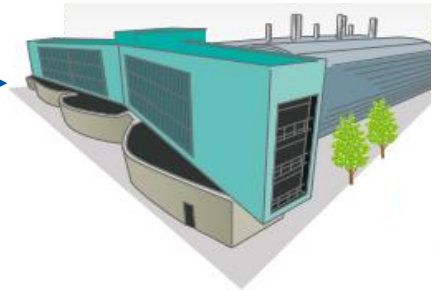
CONSEIL DE L'EUROPE

COMMITTEE OF MINISTERS | PARLIAMENTARY ASSEMBLY | CONGRESS OF LOCAL AND REGIONAL AUTHORITIES | EUROPEAN COURT OF HUMAN RIGHTS | COMMISSIONER OF HUMAN RIGHTS | CONFERENCE OF INGOS

- Founded in **1949**
- **Intergovernmental** organisation, Strasbourg
- **46** Member States
- More than **700 Million** of Citizens

Council of Europe is not the European Union!

The **European Directorate for the Quality of Medicines and 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

- Founded in 1964
- Work in the framework of a **Partial Agreement, 39 Members & the EU**
- Contribute to **Public Health and access to good quality medicines and healthcare in Europe**
- Oversee the **European Pharmacopoeia**

EDQM 60 1964 - 2024 | COUNCIL OF EUROPE 75 1949 - 2024 CONSEIL DE L'EUROPE

The EDQM, key figures

9 **Administrative entities**

4 **Areas of work**

- Medicinal products
- Substances of human origin
- Pharmaceutical care
- Consumer health

More than 400 staff members

27 nationalities and dozens of different professions

Working with a global network of almost 2 000 experts from a wide variety of scientific disciplines

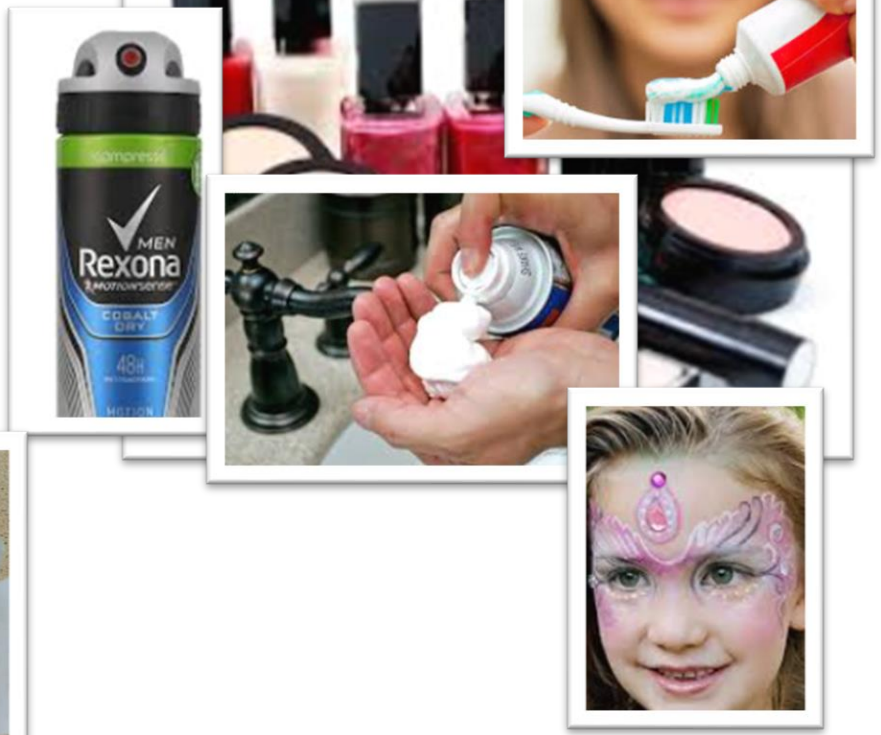
2 **Sites**

- **5** intergovernmental committees
- **1** treaty-based body (The Ph. Eur. Commission)
- **2** steering committees (BSP, CEP)
- **3** networks
- More than **100** expert groups

1 **Vision**

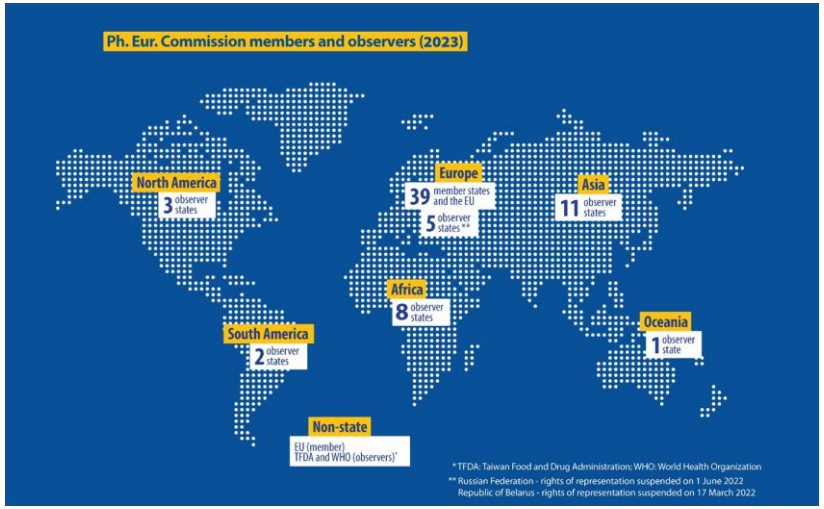
Together for better health, for all

The edqm is relevant to you in many ways...



European Pharmacopoeia: Reference Standards & Methods

Binding in the **39** signatory states of the Ph. Eur. Convention and used as a reference worldwide; **33** observers from all continents



- More than **2 800 documentary standards** for the quality control of medicines
  - Cover the whole manufacturing process (e.g. excipients, medicinal products)
  - All stages of the life cycle of a medicine from development through to production and market surveillance
  - Methods verified & standardised
- **About 3000 reference standards shipped to 132 countries**

European Pharmacopeia Commission - treaty-based body - and its expert groups

Biological Standardisation Steering Committee

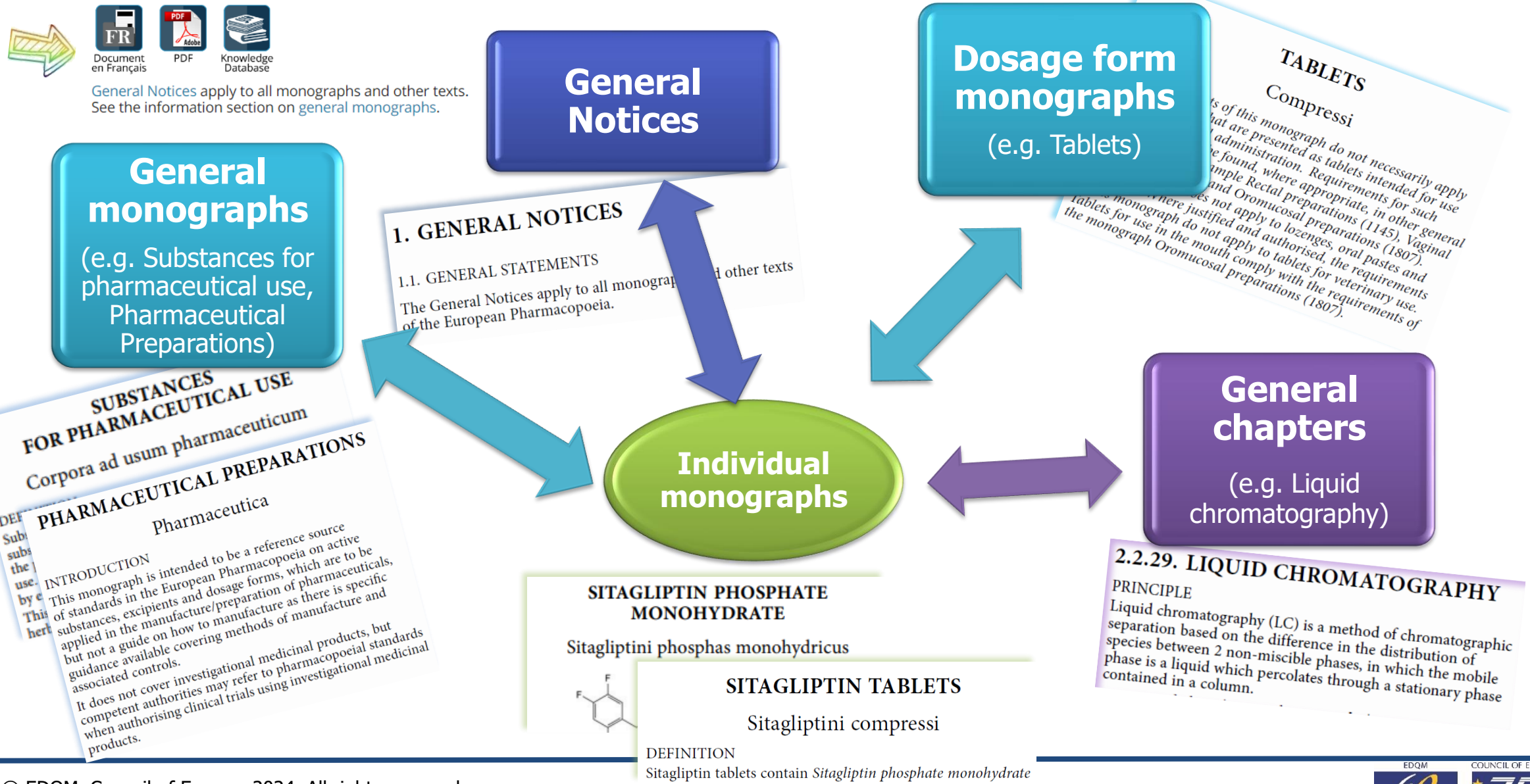
Laboratory, production, storage and distribution

PUBLIC HEALTH IMPACT

- **Ensure equivalent quality and safety of medicinal products throughout Europe and facilitate their free movement in Europe and beyond for all citizens**

The structure of the Ph. Eur.

General principles and structure



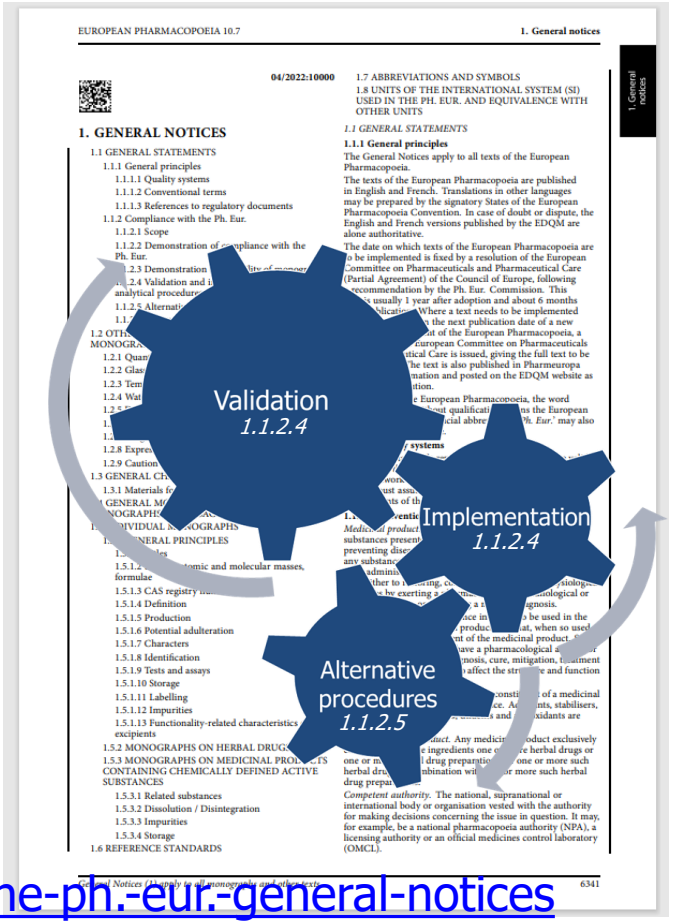
General Notices

Revised in 11th Edition

At the very beginning of the Ph. Eur.

- apply to all texts including general chapters and texts
- aim at providing basic information to the user
- address **general topics**
- describes **general principles**, including *flexibility*
- include rules to understand texts, conventional expressions

Essential reading before starting to use monographs and other texts

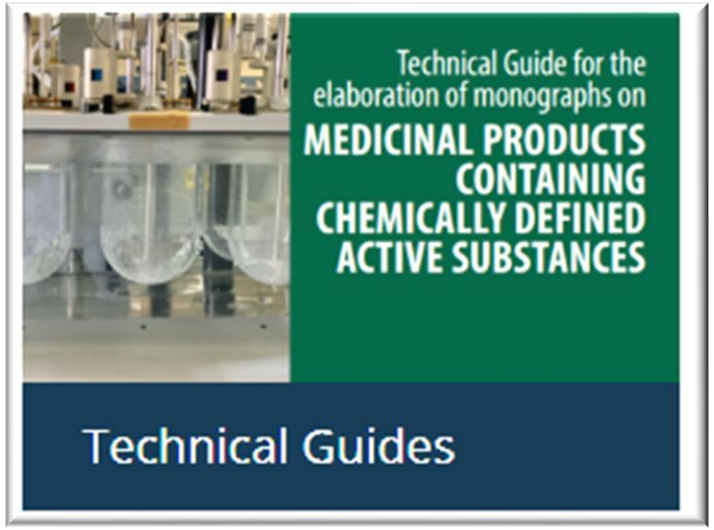


Ph. Eur. concepts related to analytical procedures

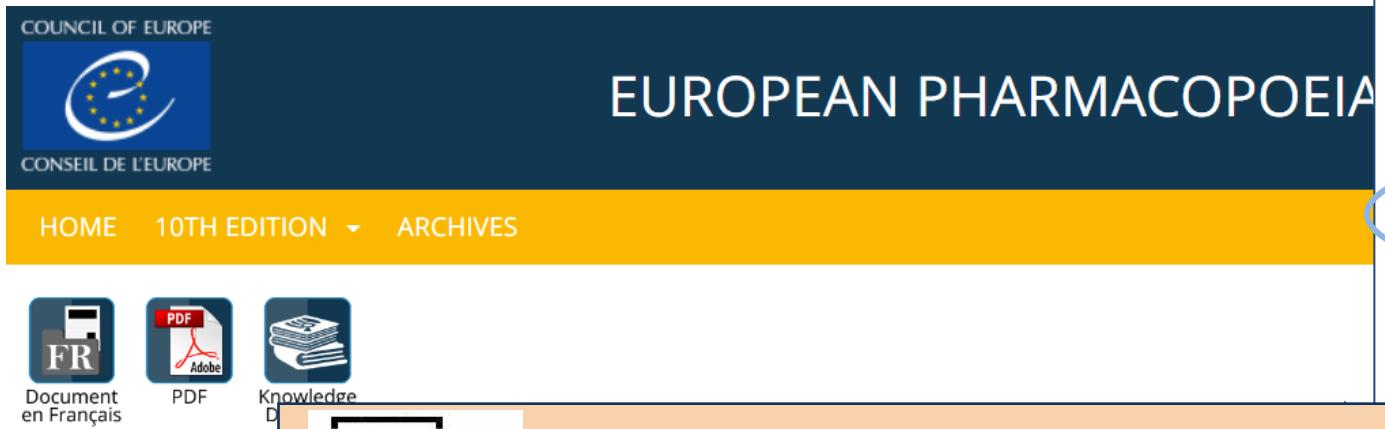
On demand webinar is available for learning more on the recent changes
https://www.edqm.eu/en/-/getting-the-big-picture-what-has-changed-in-the-ph.-eur.-general-notices

Ph. Eur. Monograph Elaboration: General Principles

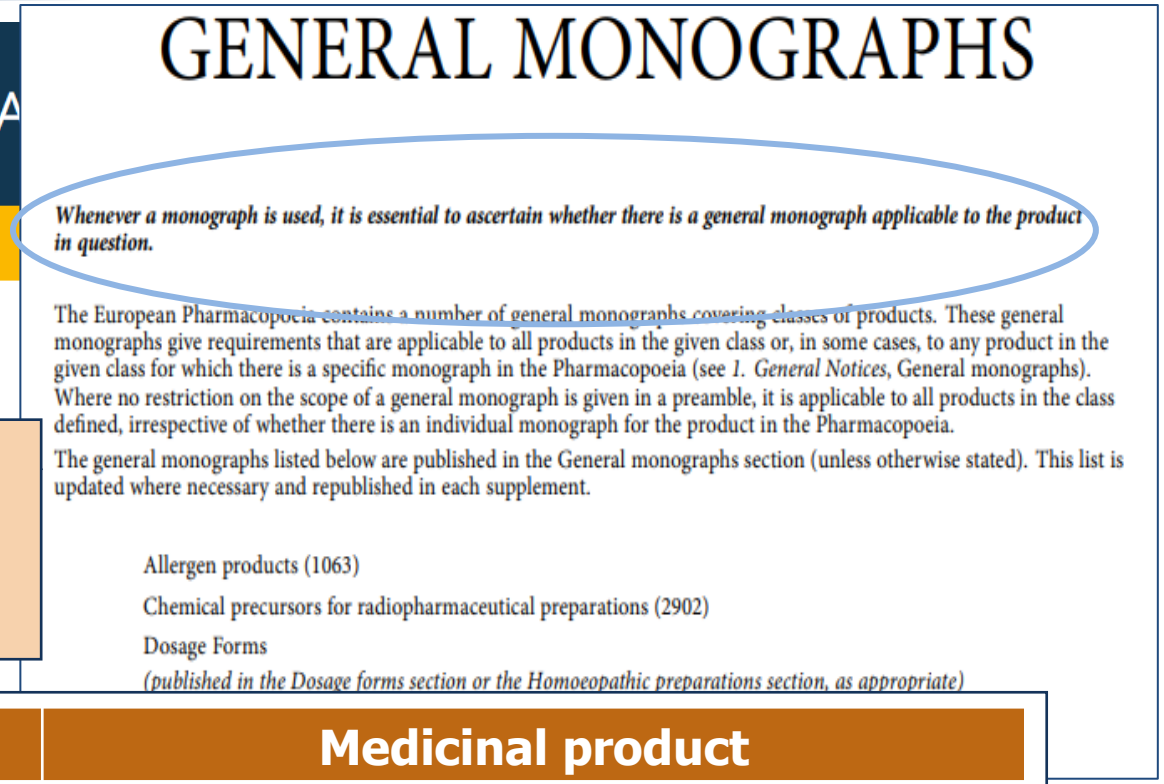
- **Monograph specifications** are based on those of medicinal products currently approved by member states unless otherwise agreed by the EPC (e.g. in the case of unlicensed medicinal products)
- Approved specification(s) are the main basis for monograph elaboration, backed up by batch data
- **Analytical procedures** included in monographs are validated according to current guidelines
- All individual monographs are verified experimentally
- Draft monographs are **reviewed by stakeholders/users** including regulatory authorities, at Pharmeuropa stage
- Policy for monograph development is given in **technical guides** (available on the EDQM website)



General monographs



Check which general monograph(s) applies!



GENERAL MONOGRAPHS

Whenever a monograph is used, it is essential to ascertain whether there is a general monograph applicable to the product in question.

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 the 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.

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.

Allergen products (1063)

Chemical precursors for radiopharmaceutical preparations (2902)

Dosage Forms

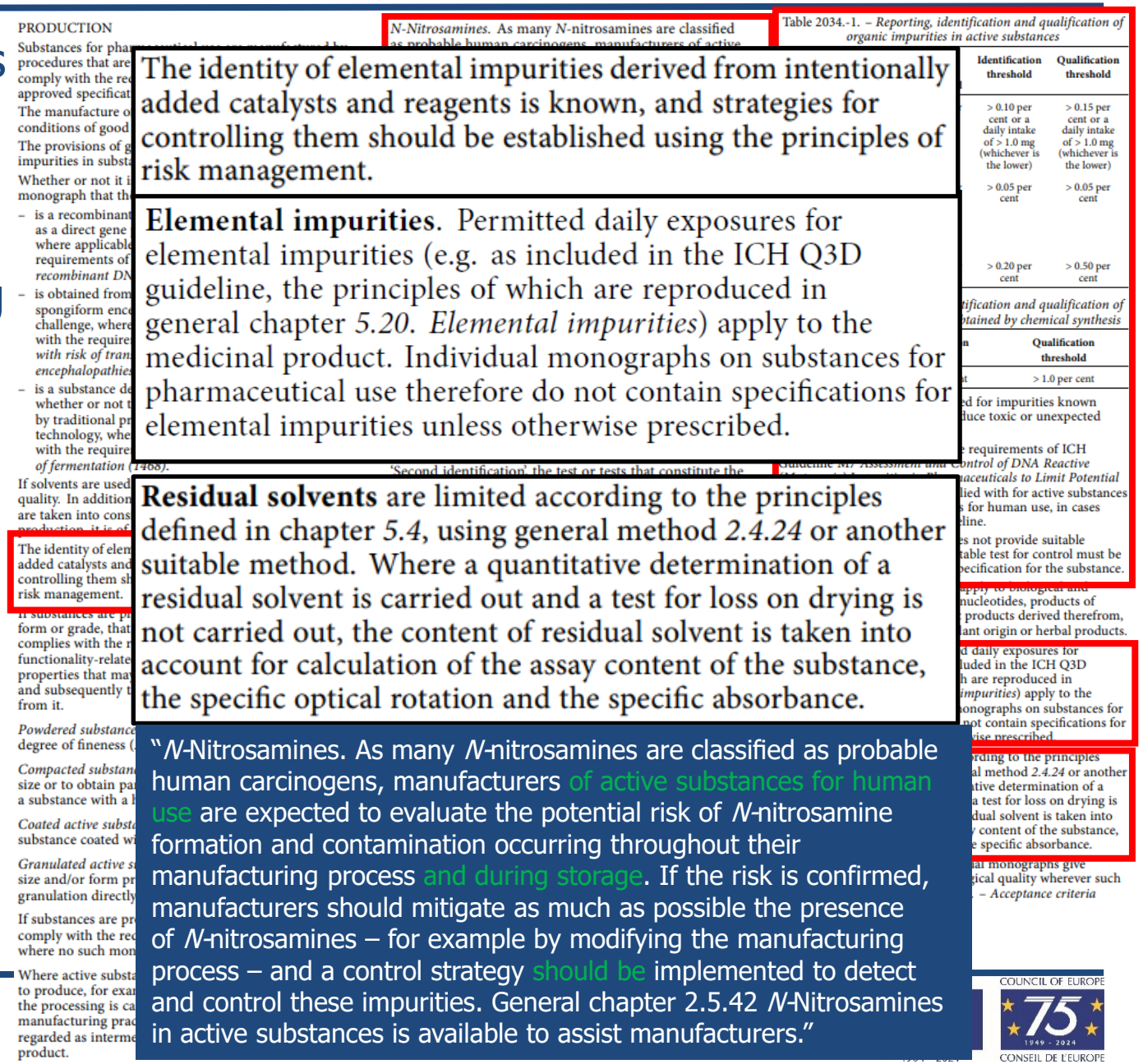
(published in the Dosage forms section or the Homoeopathic preparations section, as appropriate)

EXAMPLES

	API	Medicinal product
Ibuprofen (0721)	Substances for pharmaceutical use (2034)	Pharmaceutical preparations (2619) *Capsules (0016)*
Azithromycin (1649)	Substances for pharmaceutical use (2034) + Products of fermentation (1468)	Pharmaceutical preparations (2619) *Tablets (0478)*

Example: General monograph 2034

- Related substances: defining thresholds and refering to 5.10. Control of impurities in substances for pharmaceutical use (ICH Q3A)
- Elemental impurities: considered during production with risk management. 5.20 Elemental impurities (= principles of ICH Q3D guideline) applies for medicinal products
- Residual solvents: refers to 5.4 Residual solvents (=ICH Q3C); the chapter applies to APIs and excipients in scope of *2034*
  ➔*often no specific test in monograph*
- **NEW**: *N*-Nitrosamines



SUBSTANCES FOR PHARMACEUTICAL USE

The identity of elemental impurities derived from intentionally added catalysts and reagents is known, and strategies for controlling them should be established using the principles of risk management.

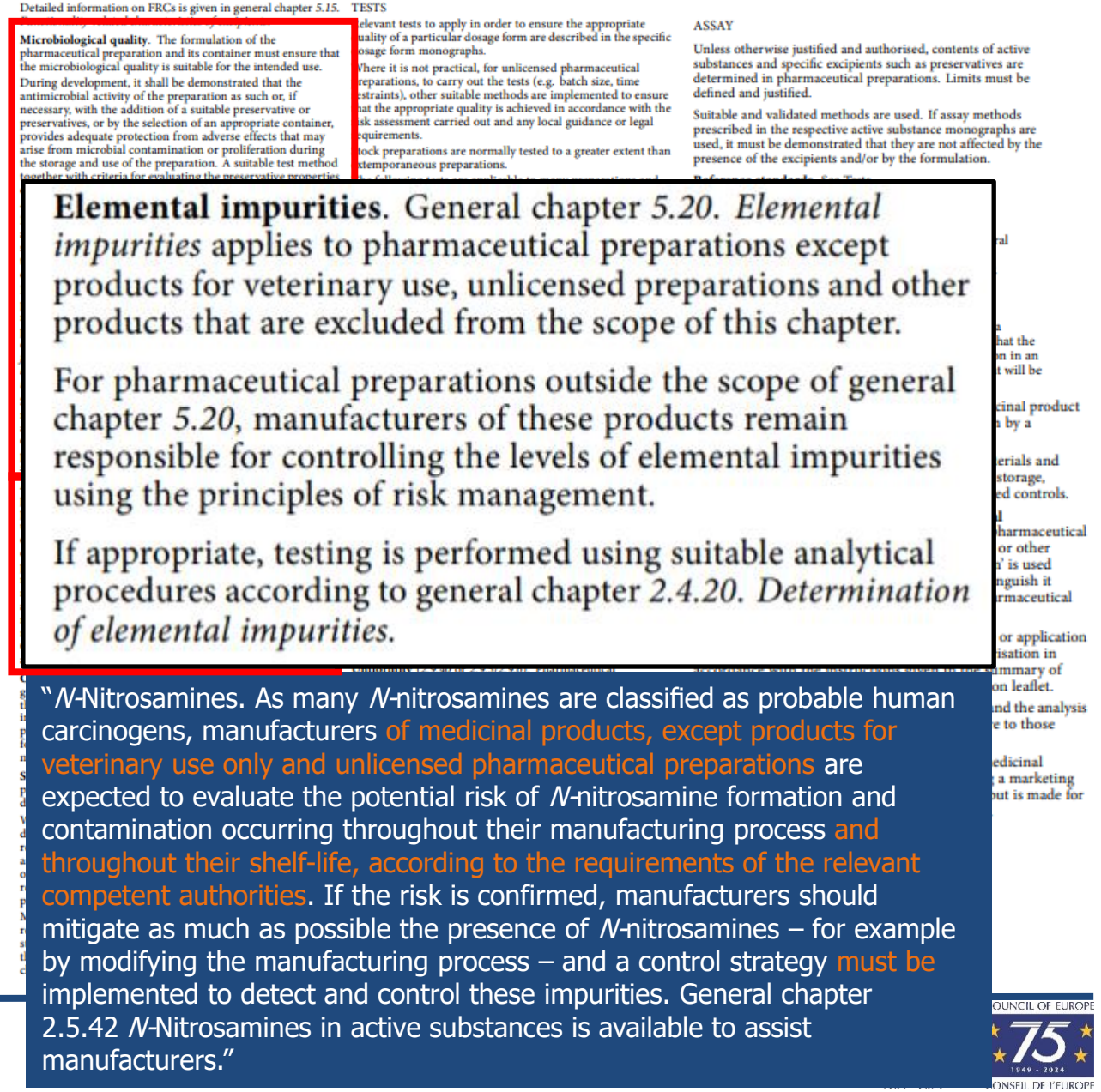
Elemental impurities. Permitted daily exposures for elemental impurities (e.g. as included in the ICH Q3D guideline, the principles of which are reproduced in general chapter *5.20. Elemental impurities*) apply to the medicinal product. Individual monographs on substances for pharmaceutical use therefore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

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.

"*N*-Nitrosamines. As many *N*-nitrosamines are classified as probable human carcinogens, manufacturers of active substances for human use are expected to evaluate the potential risk of *N*-nitrosamine formation and contamination occurring throughout their manufacturing process and during storage. If the risk is confirmed, manufacturers should mitigate as much as possible the presence of *N*-nitrosamines – for example by modifying the manufacturing process – and a control strategy should be implemented to detect and control these impurities. General chapter 2.5.42 *N*-Nitrosamines in active substances is available to assist manufacturers."

Example: General monograph 2619

- reference source of standards in the European Pharmacopoeia on active substances, excipients and dosage forms, which are to be applied in the manufacture/preparation of pharmaceuticals
- Microbiological quality: links given to the relevant general texts (5.1.1, 5.1.3, 5.1.4, 5.1.8)
- Elemental impurities: refers to general text 5.20 (= principles of ICH Q3D guideline) rendered mandatory according to its scope. For products outside scope, EI are a risk that needs to be managed
- **NEW**: *N*-Nitrosamines



Detailed information on FRCs is given in general chapter *5.15*.

Microbiological quality. The formulation of the pharmaceutical preparation and its container must ensure that the microbiological quality is suitable for the intended use. During development, it shall be demonstrated that the antimicrobial activity of the preparation as such or, if necessary, with the addition of a suitable preservative or preservatives, or by the selection of an appropriate container, provides adequate protection from adverse effects that may arise from microbial contamination or proliferation during the storage and use of the preparation. A suitable test method together with criteria for evaluating the preservative properties

TESTS

elevant tests to apply in order to ensure the appropriate uality of a particular dosage form are described in the specific osage form monographs.

Where it is not practical, for unlicensed pharmaceutical reparations, to carry out the tests (e.g. batch size, time estraints), other suitable methods are implemented to ensure hat the appropriate quality is achieved in accordance with the isk assessment carried out and any local guidance or legal equirements.

tock preparations are normally tested to a greater extent than xtemporaneous preparations.

ASSAY

Unless otherwise justified and authorised, contents of active substances and specific excipients such as preservatives are determined in pharmaceutical preparations. Limits must be defined and justified.

Suitable and validated methods are used. If assay methods prescribed in the respective active substance monographs are used, it must be demonstrated that they are not affected by the presence of the excipients and/or by the formulation.

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.*

"*N*-Nitrosamines. As many *N*-nitrosamines are classified as probable human carcinogens, manufacturers of medicinal products, except products for veterinary use only and unlicensed pharmaceutical preparations are expected to evaluate the potential risk of *N*-nitrosamine formation and contamination occurring throughout their manufacturing process and throughout their shelf-life, according to the requirements of the relevant competent authorities. If the risk is confirmed, manufacturers should mitigate as much as possible the presence of *N*-nitrosamines – for example by modifying the manufacturing process – and a control strategy must be implemented to detect and control these impurities. General chapter 2.5.42 *N*-Nitrosamines in active substances is available to assist manufacturers."

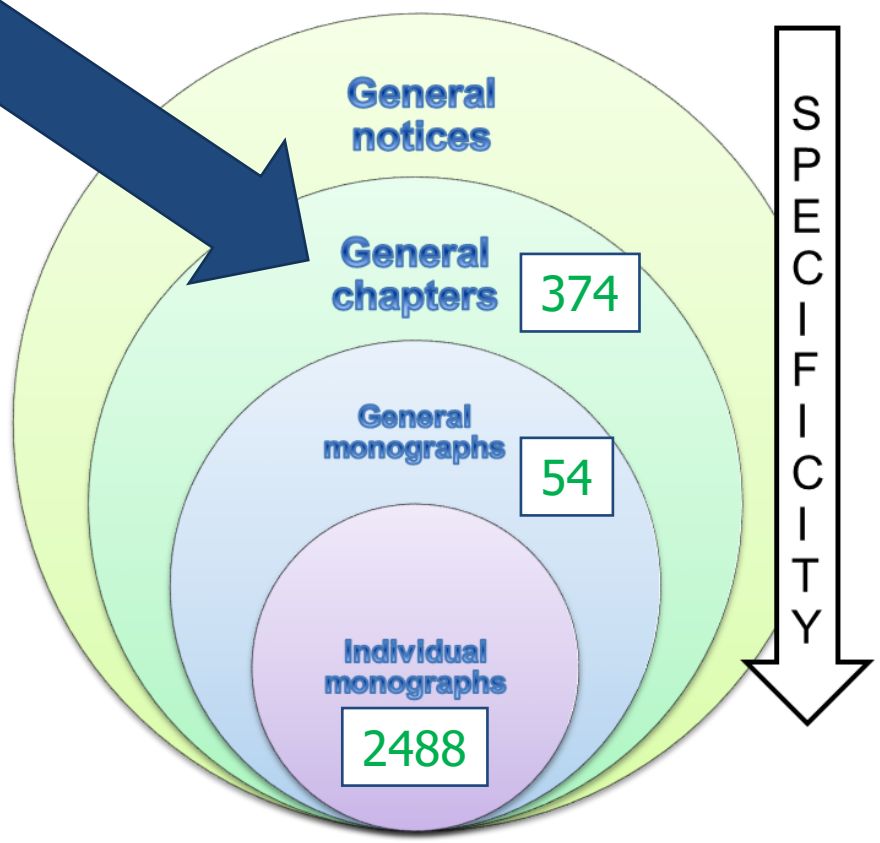
General chapters

Table of contents

- European Pharmacopoeia 10.0
  - European Pharmacopoeia 10.0
    - 00 Introduction
    - 01 General notices
    - 02 Methods of analysis
      - 2.1. Apparatus
      - 2.2. Physical and physicochemical methods
      - 2.3. Identification
      - 2.4. Limit tests
      - 2.5. Assays
      - 2.6. Biological tests
      - 2.7. Biological assays
      - 2.8. Methods in pharmacognosy
      - 2.9. Pharmaceutical technical procedures
    - 03 Materials for containers and containers
    - 04 Reagents

- 05 General Texts
  - 5.1. General texts on microbiology
  - 5.2. General texts on biological products
  - 5.3. Statistical analysis of results of biological assays and tests
  - 5.4. Residual solvents
  - 5.5. Alcoholimetric tables
  - 5.6. Assay of interferons
  - 5.7. Table of physical characteristics of radionuclides mentioned in
  - 5.8. Pharmacopoeial harmonisation
  - 5.9. Polymorphism
  - 5.10. Control of impurities in substances for pharmaceutical use
  - 5.11. Characters section in monographs
  - 5.12. Reference standards
  - 5.14. Gene transfer medicinal products for human use
  - 5.15. Functionality-related characteristics of excipients
  - 5.16. Crystallinity
  - 5.17. Recommendations on methods for dosage forms testing
  - 5.18. Methods of pretreatment for preparing traditional Chinese d
  - 5.19. Extemporaneous preparation of radiopharmaceuticals
  - 5.20. Elemental impurities
  - 5.21. Chemometric methods applied to analytical data
  - 5.22. Names of herbal drugs used in traditional Chinese medicine
  - 5.23. Monographs on herbal drug extracts (information chapter)
  - 5.24. Chemical imaging
  - 5.25. Process analytical technology
  - 5.28. Multivariate statistical process control

(number of texts from Suppl. 11.7)



General chapters

Section 2: Methods of analysis

- Give general requirements for equipment and procedures
- Editorial convenience: avoid repetition in each monograph
- Provide standard procedures that can be used where there is no monograph (with product specific validation)

Section 5: General texts

- Informative texts
- Specific to certain topics (e.g. microbiology, chemometrics)
- In some cases, reproduces the principles of regulatory guidelines

➔ Not mandatory on their own

➔ When referred to in a (general or individual) monograph, they become part of the standard

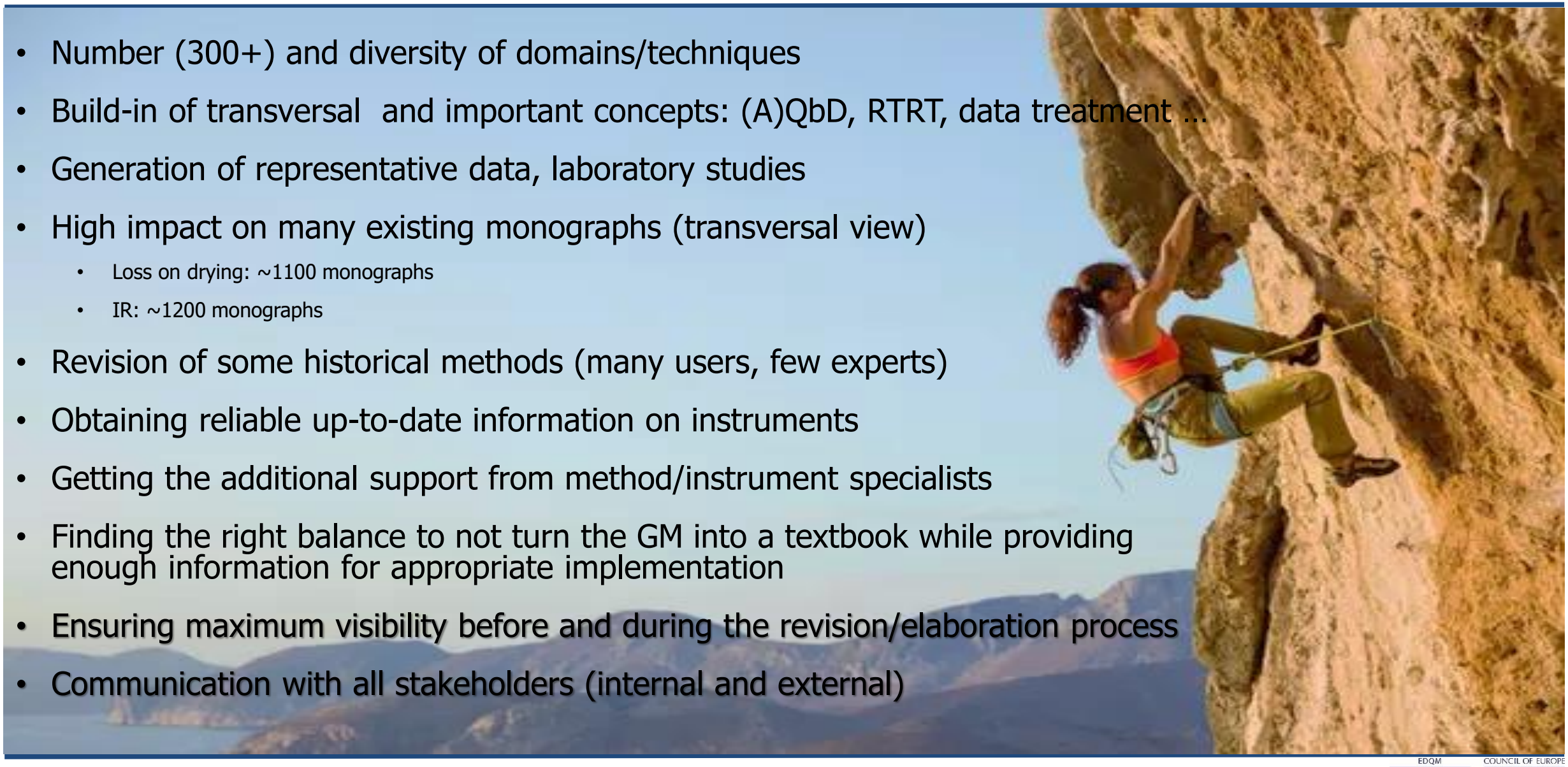
✓ *2.2.24 IR spectrophotometry,* referred in many ID tests ⟹ Mandatory application

✓ *2.2.48 Raman spectroscopy,* no monograph reference ⟹ For guidance
can be mentioned in applications but has no mandatory character

➔ Some chapters are only informative or provide examples ➔ This is clearly indicated

GENERAL CHAPTERS IN THE Ph. Eur. WORK PROGRAMME UPDATE

Challenges for general chapters



- Number (300+) and diversity of domains/techniques
- Build-in of transversal and important concepts: (A)QbD, RTRT, data treatment …
- Generation of representative data, laboratory studies
- High impact on many existing monographs (transversal view)
  - Loss on drying: ~1100 monographs
  - IR: ~1200 monographs
- Revision of some historical methods (many users, few experts)
- Obtaining reliable up-to-date information on instruments
- Getting the additional support from method/instrument specialists
- Finding the right balance to not turn the GM into a textbook while providing enough information for appropriate implementation
- Ensuring maximum visibility before and during the revision/elaboration process
- Communication with all stakeholders (internal and external)

Recent achievements : revised/new texts

(Not exhaustive)

- Balances for analytical purposes, 2.1.7
- Chromatographic separation techniques, 2.2.46
- Extractable elements in plastic materials for pharmaceutical use, 2.4.35
- Monocyte-activation test (2.6.30) and MAT for vaccines containing inherently pyrogenic components, 2.6.40
- General chapters on procedures for powder characterisation:
  - ★ *Particle size analysis by dynamic light scattering (2.9.50)*
  - ★ *Bulk density of powders (2.9.34)*
  - ★ *Powder flow (2.9.36)*
  - *Density of solids (2.2.42)*
  - *Particle size and shape determination by image analysis (2.9.48)*

★ International harmonisation

Balances for analytical purposes, 2.1.7

- Applicable for all weighings described in Ph. Eur. texts
- Fitting in the international regulatory landscape (aligned with USP <41> & <1251>)
- Giving recommendations for installation and location
- Including lifecycle management of balances:
  - Qualification;
  - Performance checks, i.e. routine tests for evaluating its error (sensitivity and repeatability tests);
  - internal adjustments.
- Introducing the concepts of smallest net weight (user) and minimum weight (instrument)

Further reading available: https://pbiosn.edqm.eu/app/pbiosn/content/default/2022-1_Weighing_according_to_the_European_Pharmacopoeia.pdf

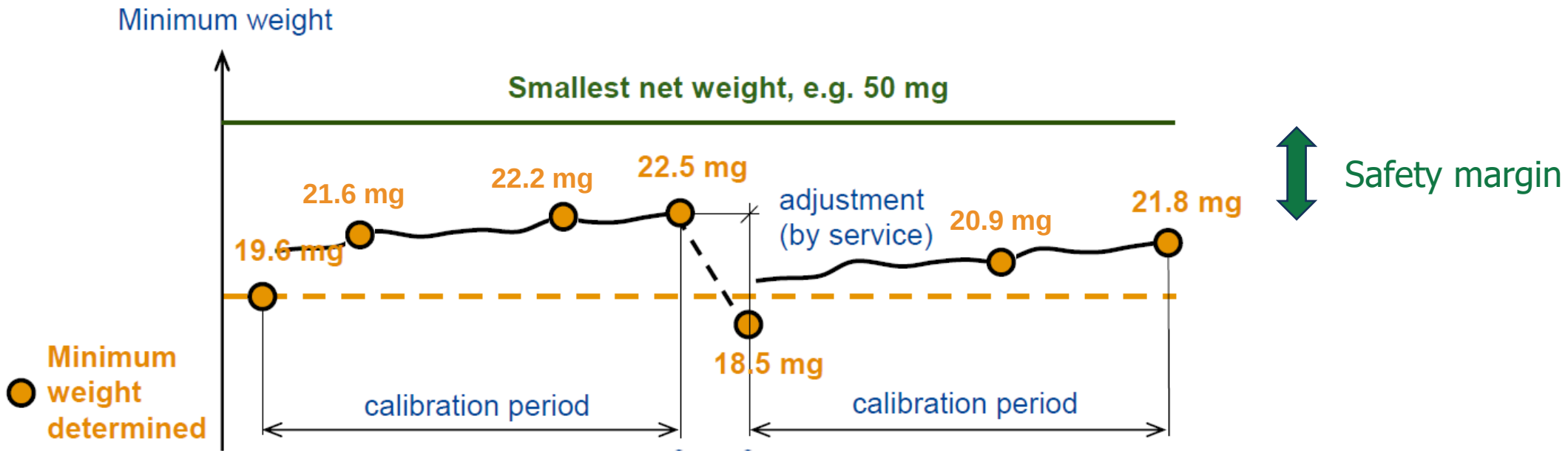
Balances for analytical purposes, 2.1.7: Minimum weight

- Instrument parameter; linked to repeatability performance (st. dev.)

➔Varies with time and external factors

➔m_{snw} must be superior to m_{min} (at least equal=high risk)

In an ideal case: $m_{min} = 2000 \times s = 820 \times d$ (readability)



Chromatographic separation techniques (2.2.46)

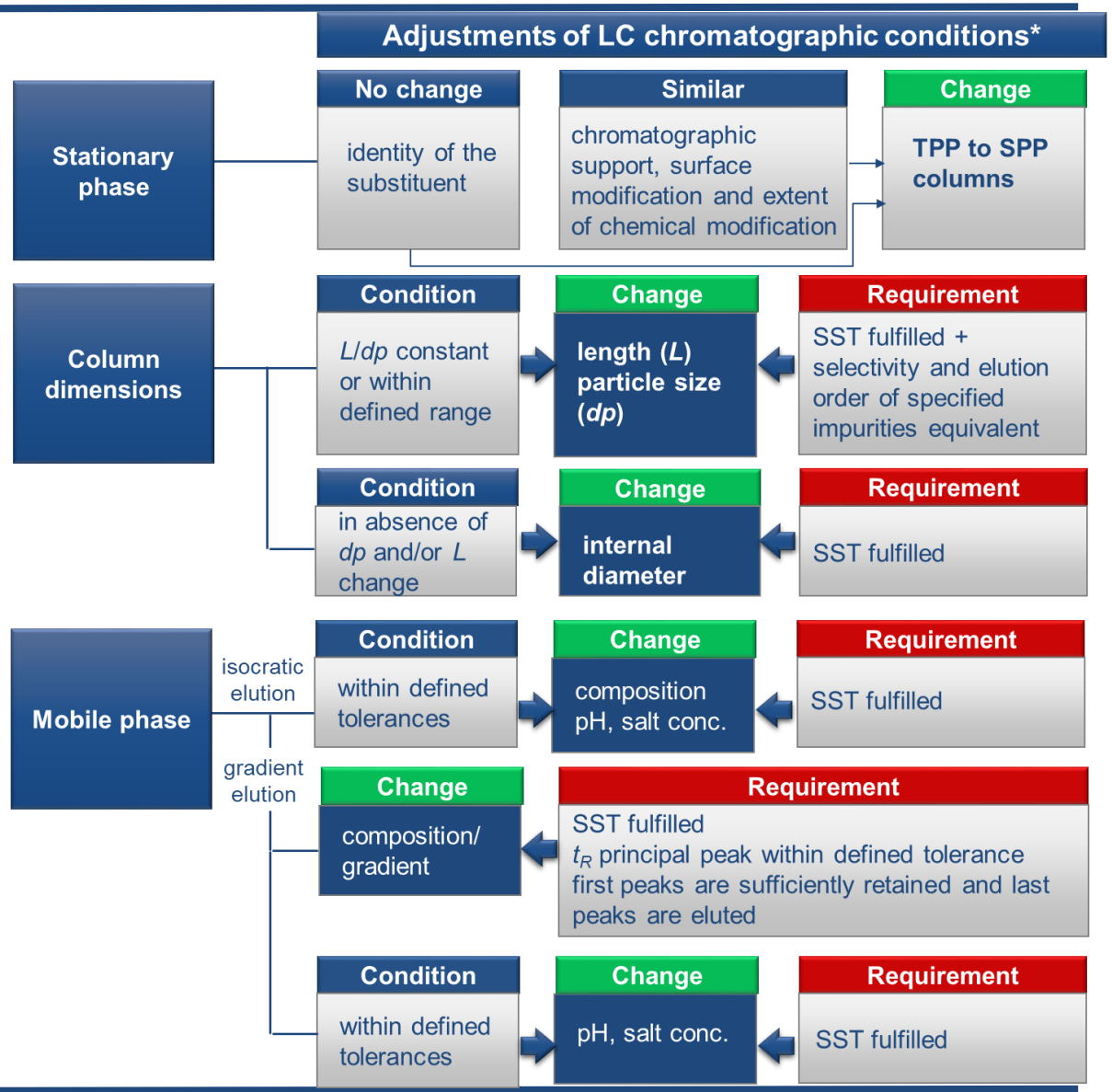
Widely applicable across chromatography chapters

- Definitions and calculation methods for common parameters (peak, retention time, resolution, etc.)
- System suitability requirements for LC and GC procedures:
  - system repeatability (assay)
  - system sensitivity (tests)
  - peak symmetry [≠ normalisation] (tests and assays)

  complementing those given in the individual monographs.
- **Describes framework for adjustments of chromatographic conditions**

SUSTAINABILITY ENABLER

Revised chapter (harmonised with USP and JP), Ph. Eur. 11th Edition, July 2022



*list not exhaustive (further adjustments: flow rate, injection volume)

Adjustments and requirements-compromise at PDG

Chapter 2.2.46 provides the framework for adjustments that can be performed without revalidation

NEW concept

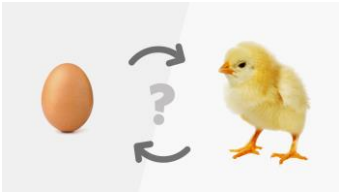
- *Column dimensions, permitted modifications* (11.0)
  - For TPP: L/dp within -25 % to +50 % of the prescribed L/dp ratio

  (change from HPLC to UHPLC possible)
  - For SPP: other L/dp provided *N* within – 25 % to + 50 % of the original *N*
- *Stationary phase of column*
  - no change to identity of substituent e.g. no replacement C18 ↔ C8 (older text)
  - similar physico-chemical characteristics + similar surface modification and extent of modification (11.0)

NEW

Requirements

- **Former text:** SST requirements must be fulfilled when chromatographic conditions are adjusted and adjustments possible to comply with SST



- **Revised text (11.0):**

SST compliant :
- symmetry (A_s) of peak used for quantitation OK (general SST)
- sensitivity (S/N) at reporting threshold OK (general SST)

+ ADDITIONAL REQUIREMENTS:
- selectivity of specified impurities equivalent
- elution order

➢Valid for isocratic and gradient systems

More flexibility but more safeguards

Key principle of the Ph. Eur.: no successive changes

Ph. Eur. procedure = Reference procedure

- "In the event of doubt or dispute, the analytical procedures of the Pharmacopoeia are alone authoritative."

Adjusted procedure

- Adjustments based on chapter 2.2.46

Adjusted procedure no. 2

- New procedure ➔requires validation

Q&A (1/2)

IMPLEMENTATION OF GENERAL CHAPTER 2.2.46 FOR EXISTING MONOGRAPHS

Revised chapter *(i.e. 2.2.46)* applies to all individual monographs since 1.01.2023.

(Via cross references in the instrumental chapters on LC (2.2.29), GC (2.2.30), etc.)

As mentioned in the *General Notices*, 'General chapters become mandatory when referred to in a monograph, unless the wording clearly indicates that it is not the intention to make the text referred to mandatory but rather to cite it for information.'

[…]

Reference procedure = Ph. Eur. procedure

Q&A (2/2)

IMPLEMENTATION OF GENERAL CHAPTER 2.2.46 FOR IN-HOUSE PROCEDURES

When using an in-house analytical procedure, i.e. a non-pharmacopoeial analytical procedure, general chapter *2.2.46* is not mandatory.

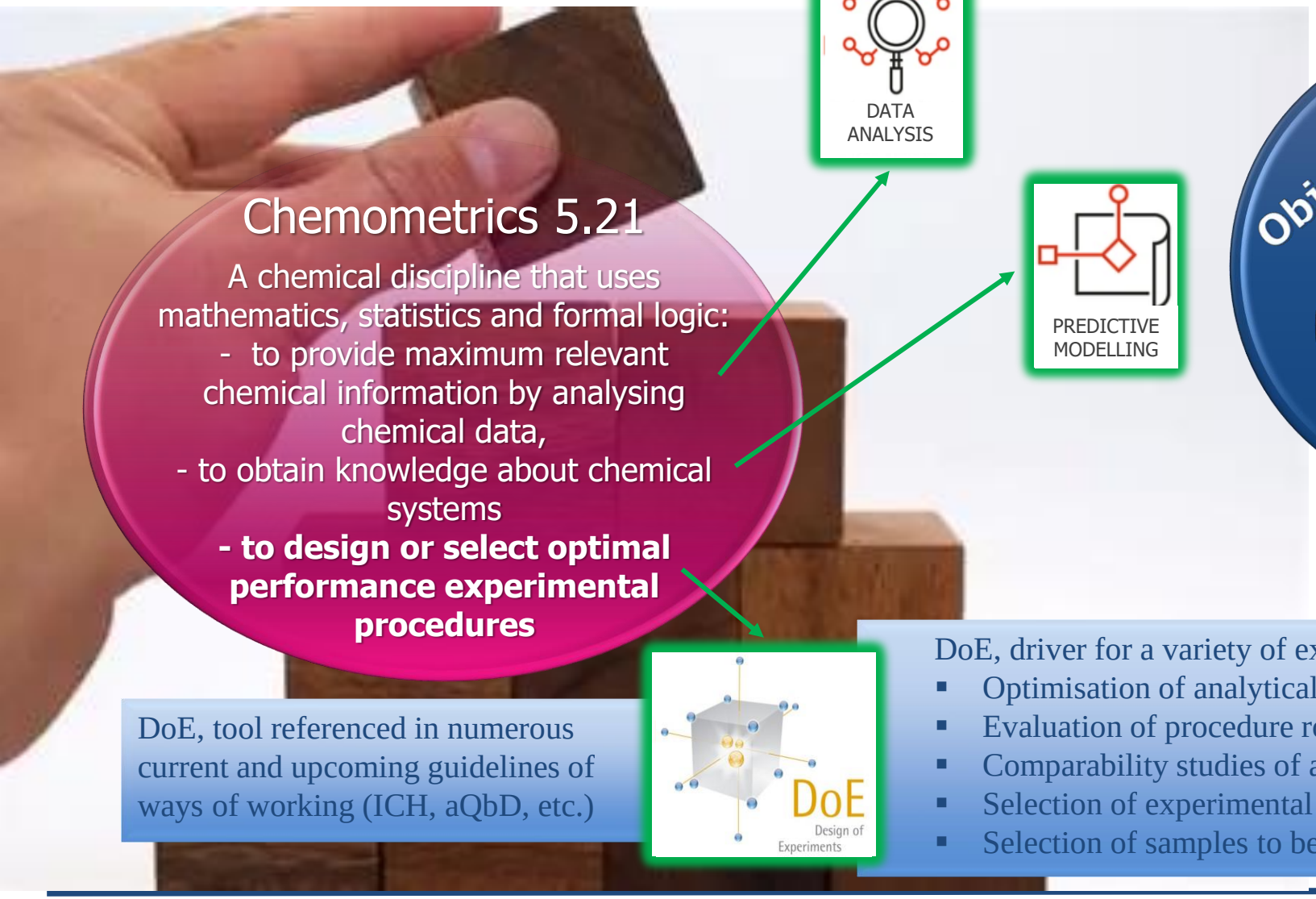
Any reference to and/or application of general chapter *2.2.46* for quality control of substances or medicinal products using chromatographic procedures not described in relevant Ph. Eur. monographs is subject to approval by the competent authority as part of the assessment of a marketing authorisation application.

New Q&A published by EMA: Quality of medicines questions and answers: Part 1 | European Medicines Agency (EMA)

General texts recently published/revised

- ✓Multivariate statistical process control, 5.28 (Supp. 10.4)
  - analyse data with potentially correlated variables and generation of control charts for control and improvement of manufacturing processes.
  - tool for continuous manufacturing (CM), real-time release testing (RTRT).
- ✓Chemometric methods applied to analytical data, 5.21 (Suppl. 11.1)
- ✓Design of experiments, 5.33 (Suppl. 11.7)
- ✓Implementation of pharmacopoeial procedures, 5.26 (Ed. 11.0)
- ✓Comparability of alternative analytical procedures, 5.27 (Suppl. 11.5)

General Chapter on Design of experiments (5.33)



Chemometrics 5.21

A chemical discipline that uses mathematics, statistics and formal logic:
- to provide maximum relevant chemical information by analysing chemical data,
- to obtain knowledge about chemical systems
- to design or select optimal performance experimental procedures

DATA ANALYSIS

PREDICTIVE MODELLING

DoE
Design of Experiments

DoE, tool referenced in numerous current and upcoming guidelines of ways of working (ICH, aQbD, etc.)

DoE, driver for a variety of experimental situations:
- Optimisation of analytical procedures
- Evaluation of procedure robustness
- Comparability studies of analytical procedures
- Selection of experimental and instrument settings
- Selection of samples to be prepared for calibration of NIR, Raman, etc.

Objectives 5.33

Introduction to the use of DoE
Provide guidance on good practice
Set out the regulatory framework and critical aspects that needs to be addressed

Important concepts: validation and implementation

VALIDATION

The **analytical procedures given in an individual monograph have been validated** in accordance with accepted scientific practice and recommendations on analytical validation. **Unless otherwise stated** in the individual monograph or in the corresponding general chapter, **validation of these procedures by the user is not required**.

IMPLEMENTATION

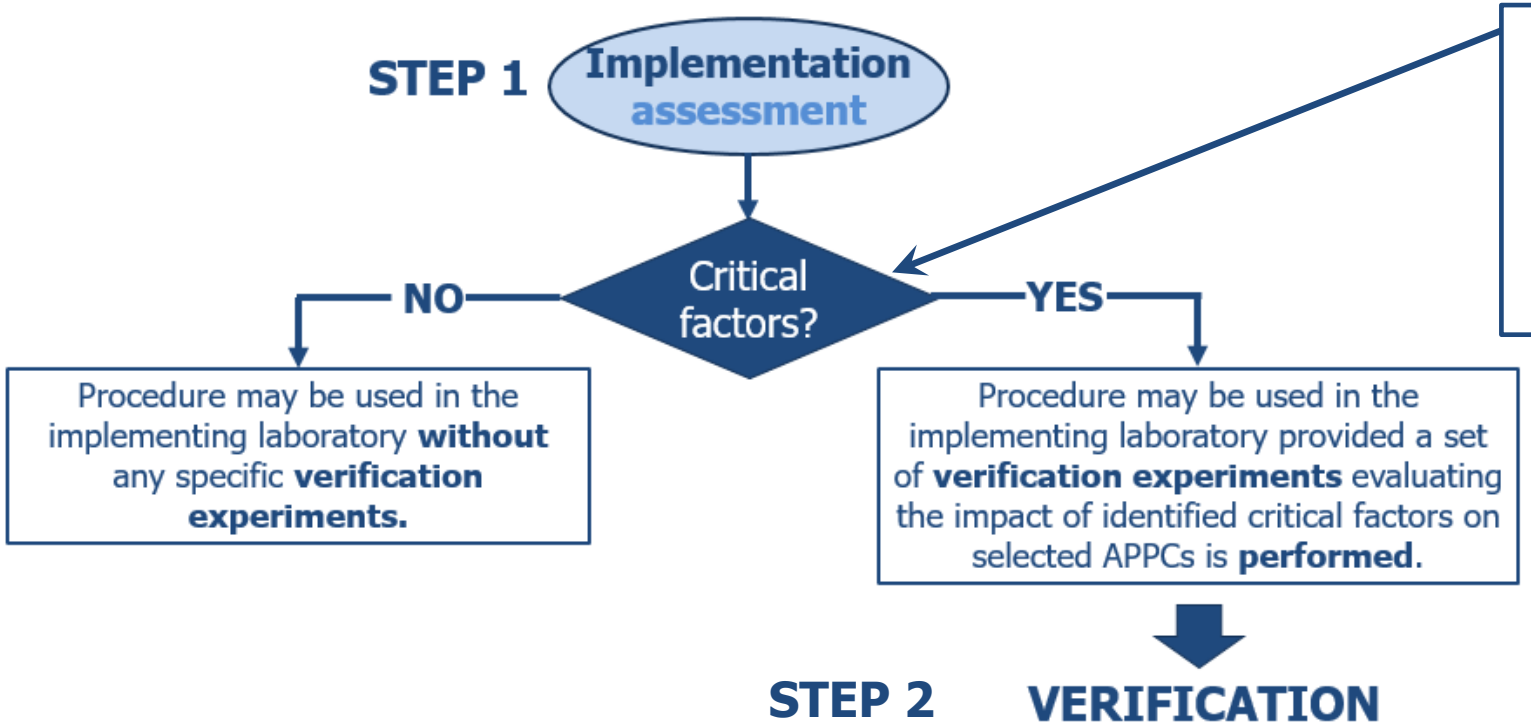
When implementing a Ph. Eur. analytical procedure, the **user must assess** whether and to what **extent** its **suitability under the actual conditions of use needs to be demonstrated** according to relevant monographs, general chapters and quality systems.

MORE DETAILED IN NEW CHAPTER 5.26 (PH. EUR. 11th EDITION)

Implementation of pharmacopoeial procedures, 5.26

- **Aim**: to provide guidance on setting up an approach for implementation
- « **For information** » chapter; other approaches may be appropriate

NEW 11th Ed., 01/2023



= experiments to verify **relevant APPCs** depending on **intended use** wrt defined **acceptance criteria**

- composition of the article under test ;
- complexity of the sample preparation ;
- reagents required to run the procedure ;
- laboratory equipment required to run the procedure ;
- laboratory environment.

Intended use / APPCs	Identification	Testing for impurities		Assay - content/potency - dissolution (measurement only)	Other quantitative tests
		limit	quant.		
Accuracy	○	○	○	◗	◗
Precision					
Repeatability	○	○	●	●	●
Interm. prec.	○	○	◗	◗	◗
Specificity/ Selectivity	◗	●	●	●	◗
Sensitivity	○	●	●	○	◗
Linearity	○	○	○	◗	◗
Range	○	○	○	◗	◗
Robustness	○	○	◗	◗	◗

5.26 IMPLEMENTATION EXAMPLES

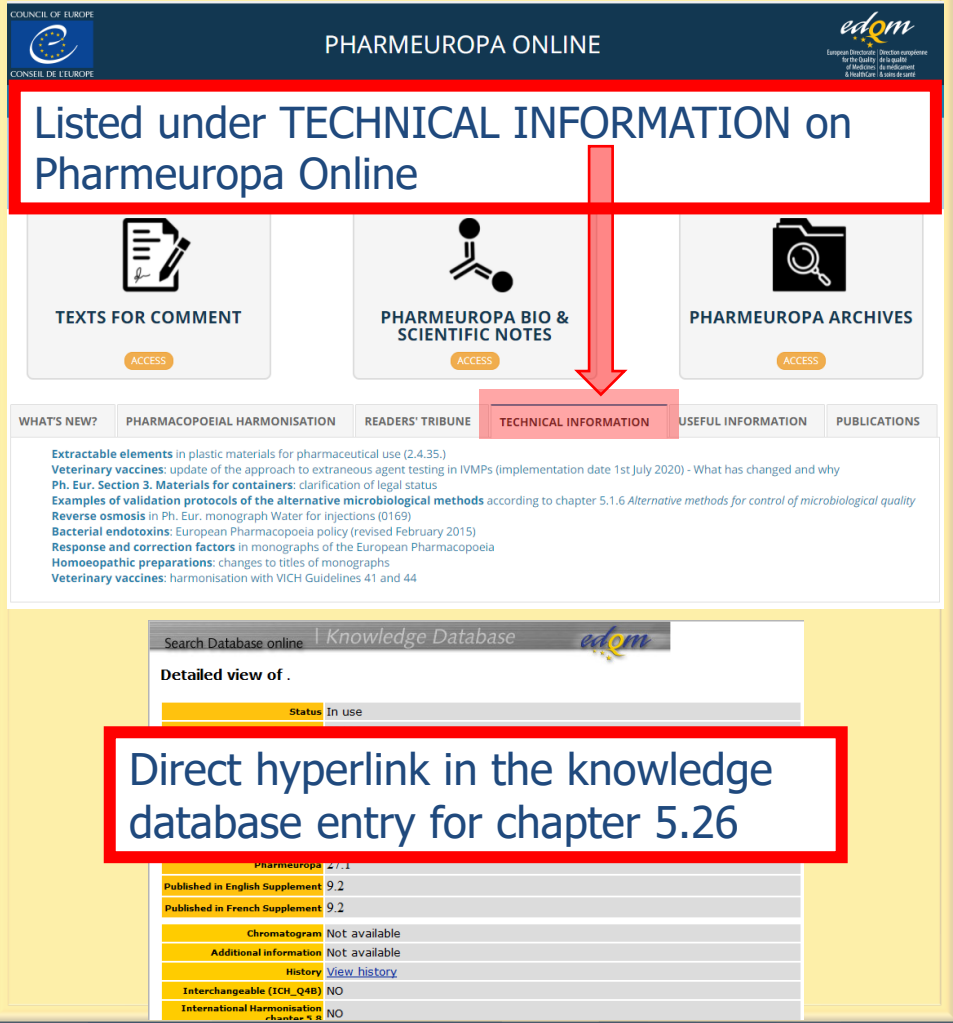
AVAILABLE ONLINE

WHY

WHAT

Assay for an active substance (by LC-UV)
Impurity test for a medicinal product (by LC)
Cell based assay
Identification by IR spectroscopy
Simple procedure : Sulfated Ash
Microbial enumeration tests

WHERE



Comparability of alternative analytical procedures, 5.27

✓Flexibility in the Ph. Eur., extract of the General Notices (1.1.2.5)

"The tests and assays described are the official analytical procedures upon which the standards of the Ph. Eur. are based. With the agreement of the competent authority, alternative analytical procedures may be used for control purposes, provided that they enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official procedures were used. In the event of doubt or dispute, the analytical procedures of the Ph. Eur. are alone authoritative."

✓Users' responsibility to demonstrate comparability to the satisfaction of the *competent authority*

✓Compliance required, but alternative procedures may be used: same pass/fail decision

✓The pharmacopoeial procedure is the reference procedure

Principle

- Published for information
- Guidance on some possible approaches
- Thin line between sufficient guidance and restrictive requirements

Scope

- **Cases where a pharmacopoeial (official) analytical procedure, as referenced in an individual monograph, would be replaced by an alternative ("in-house") analytical procedure**

Not in scope

- Development of new analytical procedures
- Application of pharmacopoeial analytical procedures to articles not covered by Ph. Eur.

Key Aspects of General Chapter 5.27

Framework

- Published for information
- Guidance on possible approaches
- No new requirements introduced
- 'Comparability' ≠ 'equality'

Scope

- Cases where a pharmacopoeial (official) analytical procedure, as referenced in an individual monograph, would be replaced by an alternative ("in-house") analytical procedure
- Applies to qualitative and quantitative analytical procedures

Not in scope

- Development of new analytical procedures
- Application of pharmacopoeial analytical procedures to articles not covered by Ph. Eur.

5.27. COMPARABILITY OF ALTERNATIVE ANALYTICAL PROCEDURES

This general chapter is published for information. It
an alternative analytical procedure to a pharmacop
demonstrated. Other approaches to demonstrating c
The use of an alternative procedure is subject to autho
The final responsibility for the demonstration of compara
the successful outcome of the process needs to be demonstrated and documented to the satisfaction of the competent authority. Comparability must be maintained over the lifecycle of both the pharmacopoeial and alternative

Process for comparability, 5.27

Comparison of data obtained in the implementation of the phar.AP and validation of the alt.AP in terms of APPCs

Validation of the alternative procedure

Prerequisites

Implementation of the pharrmacopoeial procedure

Step 1: Comparability assessment

Study design

Step 2: Comparability study

Head-to-head testing, with the aim of reaching the same analytical decision
→ particularities: same experiments, same samples

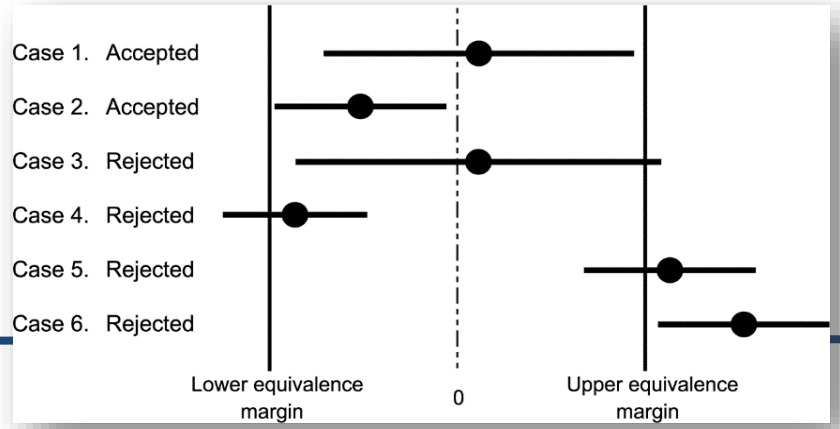
Study report

summarises the results and conclusion of the study, as well as other relevant information (e.g. deviations from study protocol, newly obtained information on the procedure(s) and or tested samples)

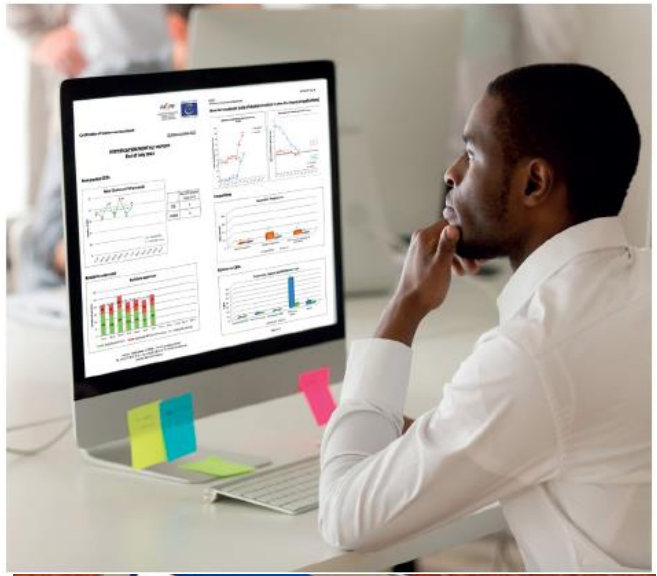
Study protocol

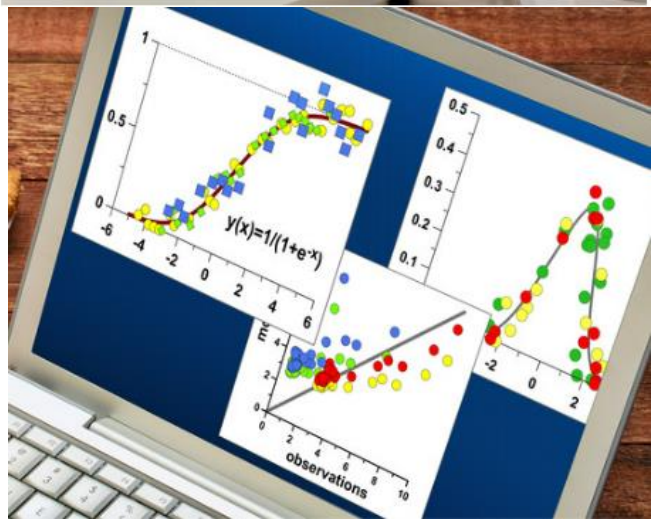
Covers selection of samples and sample size, APPCs to be included and method for statistical evaluation of data
Includes definition of comparability through setting of **equivalence margin(s)** and **acceptance criteria**

Typical outcomes of a comparability study

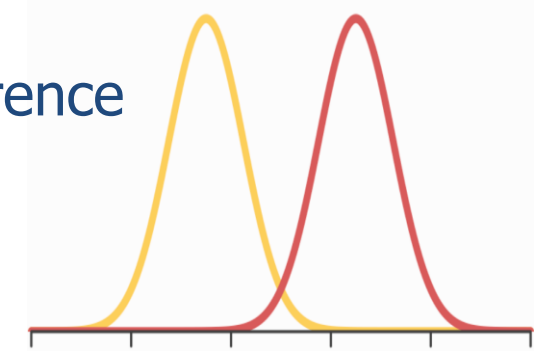


Acceptance Criteria for Comparability





- Defined in the study design phase and stated in the study protocol
- **Equivalence margin:** the acceptable difference between the means of results from two procedures, which includes an acceptable confidence level
- Determined by a combination of scientific knowledge and statistical expertise
- For quantitative results: example (most commonly used approach) - comparison of two group means: TOST method
- **Pass/Fail criterion is key**



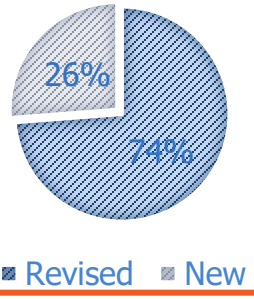
Online training

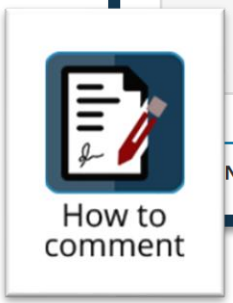
Webinar on new general chapter Comparability of alternative analytical procedures (5.27)

EUROPEAN PHARMACOPOEIA | 17/01/2024 | ON-DEMAND WEBINAR

New texts in public consultation

https://pharmeuropa.edqm.eu/home





Pharmeuropa 36.4:

- Quality aspects for data analysis, (5.38)
- High-performance thin-layer chromatography of herbal products (2.8.25)

Some updates in the pipeline

★ International harmonisation

- *N*-Nitrosamines in active substances **& medicinal products**, 2.5.42 (recently adopted)
- ★ Determination of elemental impurities, 2.4.20 (recently adopted)
- Evaporative light scattering detection, 2.2.62 (prepared for Pharmeuropa)
- Alternative methods for control of microbiological quality, 5.1.6 (prepared for Pharmeuropa)
- HTS for the detection of viral extraneous agents, 2.6.41 (after Pharmeuropa)
- Total organic carbon in water for pharmaceutical use , 2.2.44 (after Pharmeuropa)
- ★ Capillary electrophoresis (after Pharmeuropa)
- ★ Disintegration of tablets and capsules, 2.9.1 (after Pharmeuropa)

5.1.6. Alternative methods for control of microbiological quality

General principles of alternative microbiological methods

3 categories
Basic principles of methods

- Growth-based methods
- Direct measurement
- Cell component analysis

- No recommendation of one method over another
- Not an exclusive or exhaustive list
- Other methods may be applicable

As alternative methods often associated with commercial equipment, they are only described at a high level in 5.1.6

No specific methods, no specific equipment described

Objective: Facilitate the implementation and use of alternative microbiological methods where this can lead to cost-effective microbiological control and improved assurance for the quality of pharmaceutical products

Revision on-going
General update of the chapter

- Already lots of flexibility
- Inclusion of information on automated methods
- Reflect the techniques currently in use
- Clarify supplier and user responsibilities
- Clarify guidance and complement the information on implementation

Recent major additions on the work program

NON EXHAUSTIVE

- Mass spectrometry, 2.2.43
- Chapters on elemental analysis by absorption/ emission and ICP (2.2.22, 2.2.23, 2.2.57 & 2.2.58)
- Optical rotation, 2.2.7
- Water: micro-determination, 2.5.32
- Heavy metals, 2.4.8
- Charged aerosol detection, 2.2.69
- Identification and control of residual solvents, 2.4.24
  - *Alignment with ICH Q3C(R8) and general revision*
- Water activity determination of liquids, 2.9.57
- Liposomal preparations (5.45)

Update on strategy

EUROPEAN PHARMACOPOEIA COMMISSION PRIORITIES 2023-2025

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

Read more: European Pharmacopoeia Commission Priorities for 2023-2025

European Pharmacopoeia future programme/directions

▶ Ph.Eur. Priorities for 2023-2025: document

1. Non-technical priorities

1.1. Rules of procedures and guides

1.2. Modernisation of ways of working

1.3. Stakeholder engagement

1.4. Harmonisation and international collaboration

2. Technical priorities

2.1. Modernisation of analytical procedures and integration of new technologies

2.2. Biologicals

2.3. Alternatives to animal testing

2.4. Impurities

2.5. Herbal drugs and herbal drug preparations

2.6. Excipients

2.7. Nanomedicines

2.8. Medicinal product monographs for chemically defined APIs

2.9. European Paediatric Formulary

International Collaboration

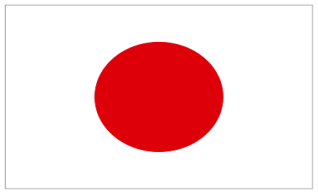
- Ph. Eur.: **successful model of work-sharing and harmonisation between** currently **39 countries**, but based on strong political will and legal commitment
- Ph. Eur., United States Pharmacopoeia and Japanese Pharmacopoeia, with WHO as an observer, are partners in the **Pharmacopoeial Discussion Group** (PDG) that has recently been further expanded to include the Indian Pharmacopoeia Commission (as a pilot for global expansion)
- **Bilateral Agreements** / MoUs with pharmacopoeia authorities on collaboration and exchanges; involvement of observers in the elaboration of texts.
- **Prospective harmonisation:** joining forces on new monograph elaboration with other pharmacopoeias (individually with USP, and more recently with JP and WHO)
- **Global harmonisation (Good Pharmacopoeial Practices)**: EDQM key player in International Meeting of World Pharmacopoeias
- **International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)**: EDQM is an observer of the ICH Association and contributes to the development of relevant ICH guidelines, e.g. related to the control of impurities, the development and validation of analytical methods and on continuous manufacturing

The Pharmacopeial Discussion Group (PDG)

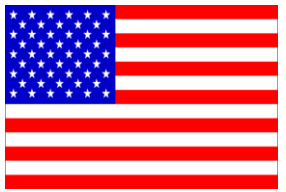
- Began as an informal group in 1989; participants include USP, EP, IPC, and JP
  - IPC joined as member in 2023
  - WHO joined as observer in 2001
- Focuses on selected official, broad-impact General Chapters and excipient monographs
- Eliminates/minimizes need to perform multiple tests and procedures and to comply with multiple acceptance criteria for the same article
- Detailed process, with specific stages and terminology
- One face-to-face meeting a year, with a video conference in the interim

EP (EDQM)

IPC



JP (MHLW/PMDA)



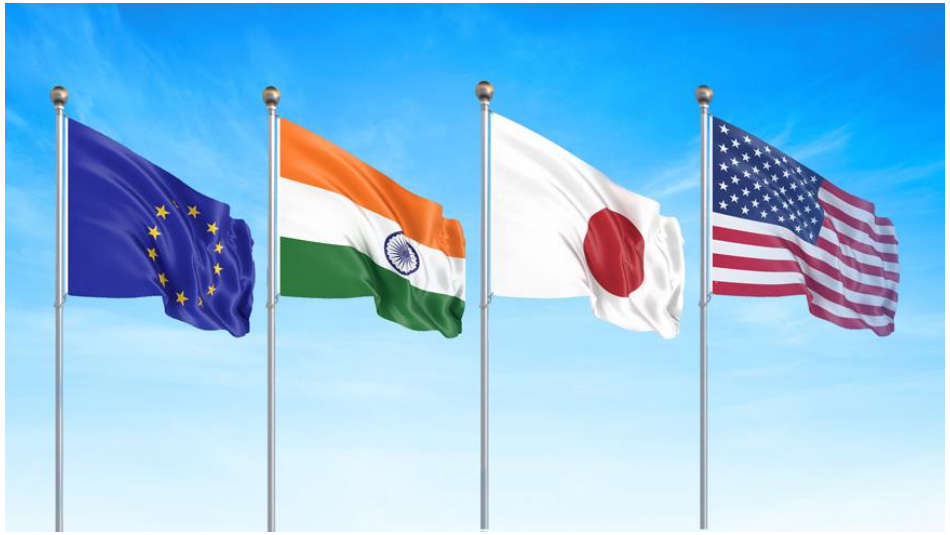
USP

PDG Mission

To harmonize pharmacopeial standards while maintaining a constant level of science with the shared goal of protecting public health.

PDG expansion

After more than 34 years, PDG's founding pharmacopoeias are pleased to welcome a 4th member



- 2021 decision to launch expansion pilot
- 2022-2023 IPC became a **regular participant** in all PDG activities **for one year**
- October 2023: **IPC new 4th member**
- **2nd half 2024 new call for further expansion of the PDG**
- **New members will implement all finalised harmonised texts (31 general chapter and 48 excipient monographs)**

PDG Work Program: General Chapters

General Methods Relevant to Q6A:

Q-01 Dissolution*3
Q-02 Disintegration*3
Q-03/04 Uniformity of Content/Mass
Q-05a Tests for Specified Microorganism
Q-05b Microbial Enumeration
Q-05c Limits for Non-sterile Products
Q-06 Bacterial Endotoxin
Q-07 Color (Instrumental Method)
Q-08 Extractable Volume*3
Q-09 Particulate Contamination*3
Q-10 Residue on Ignition
Q-11 Sterility Test

General Chapters:

G-01 Analytical Sieving*3
G-02 Bulk Density and Tapped Density
G-03 Conductivity
G-04 Gas Pycnometric Density of Solids
G-05 Powder Flow
G-06 Tablet Friability
G-07 Elemental Impurities*2
G-09 Optical Microscopy*3
G-10 Powder Fineness
G-11 Specific Surface Area
G-13 Laser Diffraction Measurement of Particle Size*3

General Chapters:

G-14 X-Ray Powder Diffraction
G-15 Water-solid Interaction
G-16 Thermal Analysis*3
G-20 Chromatography*1
G-21 Dynamic Light Scattering*1

Methods for Biotechnology Products:

B-01 Amino Acid Determination
B-02 Capillary Electrophoresis*3
B-03 Isoelectric Focusing
B-05 Peptide Mapping
B-06 Polyacrylamide Gel Electrophoresis

*1 : Signed-Off in 2021-2023
*2 : Recent Sign Off in 2024!
*3 : Under revision

All 31 general chapters have now been harmonized!

PDG Work Program: Excipients

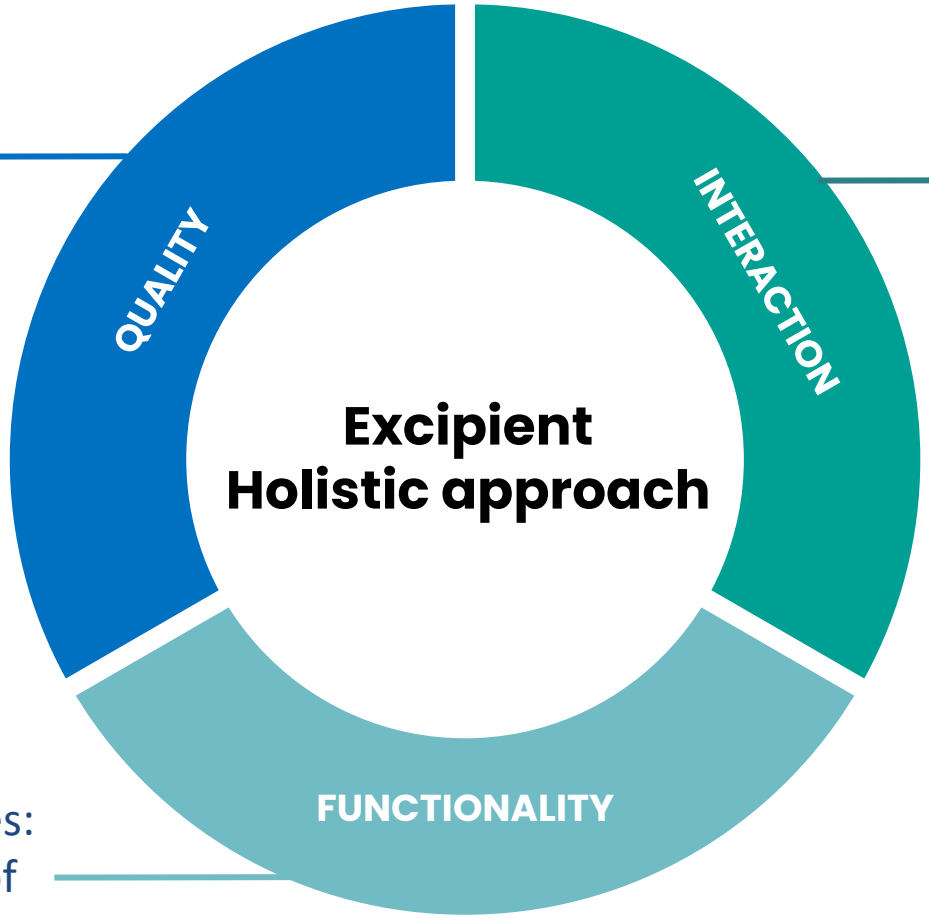
E-01 Alcohols
E-02 Dehydrated Alcohol
E-03 Benzyl Alcohol
E-04 Calcium Disodium Edetate*3
E-05 Calcium Phosphate Dibasic
E-06 Calcium Phosphate Dibasic Anhydrous
E-07 Carmellose Calcium
E-08 Carmellose Sodium*2
E-09 Croscarmellose Sodium*3
E-10 Microcrystalline Cellulose
E-11 Cellulose, Powdered
E-13 Cellulose Acetate Phthalate
E-14 Citric Acid, Anhydrous
E-15 Citric Acid, Monohydrate
E-16 Crospovidone
E-17 Ethylcellulose
E-18 Hydroxyethylcellulose*3
E-19 Hydroxypropylcellulose
E-20 Hydroxypropylcellulose, Low Substituted
E-21 Hypromellose
E-22 Hypromellose Phthalate
E-23 Lactose, Anhydrous*3
E-24 Lactose, Monohydrate*3
E-25 Magnesium Stearate
E-26 Methylcellulose
E-27 Methyl Paraben
E-28 Petrolatum*1
E-29 Petrolatum, White*1
E-30 Polyethylene Glycol*2
E-31 Polysorbate 80*3
E-32 Povidone*3
E-36 Silicon Dioxide*2
E-37 Silicon Dioxide, Colloidal*2
E-38 Sodium Chloride
E-39 Sodium Starch Glycolate
E-40 Starch, Corn*3
E-41 Starch, Potato
E-42 Starch, Rice
E-43 Starch, Wheat
E-44 Stearic Acid
E-45 Sucrose*3
E-46 Talc
E-48 Ethyl Paraben
E-49 Propyl Paraben
E-50 Butyl Paraben
E-51 Glycerin*2
E-52 Carmellose
E-54 Copovidone*3
E-55 Gelatin
E-56 Sucrose
E-58 Mannitol
E-59 Propylene Glycol*2
E-60 Sodium Laurylsulfate
E-61 Starch, Pregelatinized*2
E-62 Sterile Water for Injection*2
E-64 Isomalt
E-65 Isostearyl Alcohol*2
E-66 Myristyl Myristate*2
E-68 Polysorbate 65*2
E-69 Calcium Silicate*2
E-70 Polysorbate 20*2
E-71 Purified Water*2

*1 : Signed-Off in 2021-2023
*2 : Under discussion towards first harmonization
*3 : Under revision

48 of the 62 excipient monographs have now been harmonized

Ph. Eur. Strategy for excipients

Presence of mutagenic impurities, solvents, elemental impurities?



Role of excipients in formation of nitrosamines in drug products (e.g. residual nitrite)

Interdependencies: Different routes of administration

► Review the **current approach of the Ph. Eur.** when setting standards (fully fit for purpose)?

►2022: Decision of the Ph. Eur. Commission to **create a dedicated Working Party (EXS)**

►2024: first outcome expected

Stakeholders involvement needed !

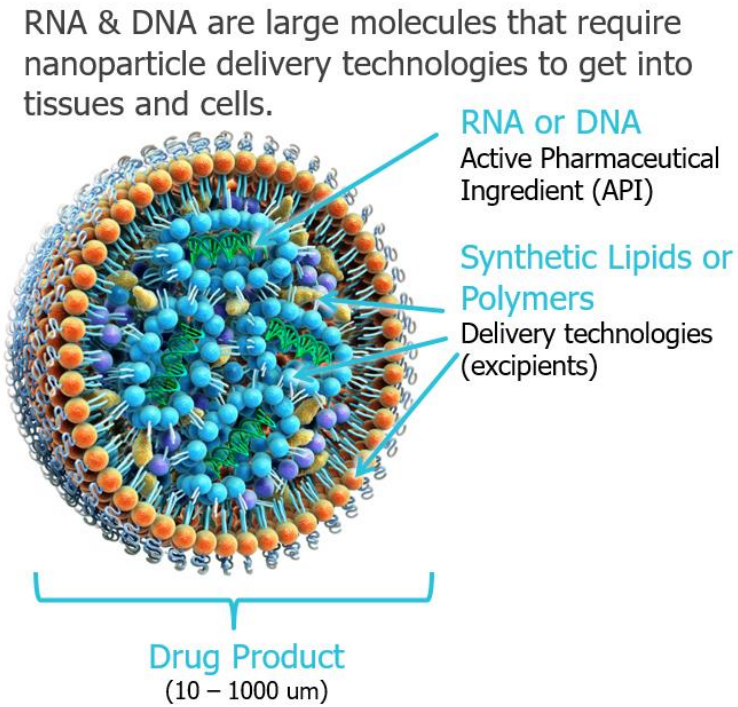
WATCH THE SPACE

Quality of mRNA vaccines and their components

JUST ADOPTED !!!

Recent adoption **3 new general texts** addressing aspects related to the production and control of mRNA vaccines and their components, namely:

- *mRNA Vaccines for human use (5.36)*, the mRNA packaged in lipid nanoparticles, i.e. mRNA-LNP medicinal product;
- *mRNA Substances for the production of mRNA vaccines for human use (5.39)*, the mRNA active substances in the manufacture of mRNA vaccines;
- *DNA Template for the preparation of mRNA transcript (5.40)*, the starting material for the preparation of the mRNA component.



Kickoff news: https://www.edqm.eu/en/-/ph.-eur.-commission-kicks-off-elaboration-of-three-general-texts-on-mrna-vaccines-and-components

➔ Updated communication coming soon ! Stay tuned…

Nanomedicines

Working party constituted with experts having the experience in:

- the development and/or quality control of nanomedicines, preferably but not limited to liposomal formulations,
- the development of analytical procedures for liposomal formulations, or
- the assessment of applications for marketing authorisation in the field (e.g. from licensing authorities, official medicines control laboratories or industry)

Aiming for the development of monographs and general text for liposomal formulations and beyond

Bacteriophages

One of Ph. Eur. Commission priorities for 2023-2025

https://www.edqm.eu/en/the-european-pharmacopoeia-commission

Phage therapy medicinal products (5.31)

- Renewed interest in phage therapy in the context of antimicrobial resistance
- **General chapter** adopted at 178th ECP Session (March 2024)
- Pre-published on the EDQM website due to exceptionally high interest pending its publication in Supplement 11.6
- Outlines framework of requirements for phage therapy active substances and medicinal products for human and veterinary use
- Includes paragraph on phage adaptation (training)

Bacteriophage potency determination (2.7.38)

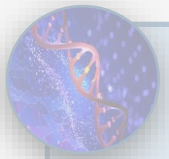
- **General chapter** added to the Work Programme at 176th EPC Session (June 2023)
- Aiming at standardisation of potency testing of single phage preparations and providing guidance for potency testing of multicomponent mixtures of phages

Gene therapy

New strategy

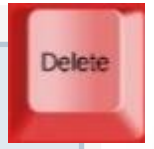
One of Ph. Eur. Commission priorities for 2023-2025

178th EPC Session March 2024



General chapter

Gene transfer medicinal products for human use (5.14)



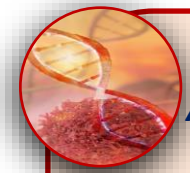
From Ph. Eur. Supplement 11.7

General monograph

Gene therapy medicinal products for human use (3186)

- Definition
- General requirements on:
  - the Production of GTMPs
  - *Recombinant vectors*
  - *Genetically modified cells*
- *Genetically modified autologous human cells modified by integrating retroviral or lentiviral vectors*
- *Adeno-associated-virus vectors for human use*
- *Oncolytic herpes simplex virus for human use*

Revised from 5.14
Newly elaborated



General chapter

Additional information on gene therapy medicinal products for human use (5.34)

- *Plasmid vectors for human use* together with *Bacterial cells used for the manufacture of plasmid vectors for human use*
- *Genetically modified bacterial cells for human use*
- *Adenovirus vectors for human use*
- *Poxvirus vectors for human use*
- *Retroviridae-derived vectors for human use*

EDQM contributions to address medicines shortages

Governance

- Certification Steering Commitee
- OMCL Network
- European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH)
- European Pharmacopoeia Commission (EPC)

Certification procedure

Measures in place

▶ **fast-tracking CEP** assessment for API

▶ Providing **information on reliable source** of API

Shortage related to API

OMCL Network

Ad hoc support from the OMCL network for **testing of medicines non authorised** in EU for potential importation

Similar medecines to the one affected by shortage

Methodological Guide

Guidance for identification and selection of medicines that can be in short supply under certain circumstances and can be prepared in pharmacies

European Drug Shortages Formulary

Monographs of **standardised** unlicensed pharmaceutical preparations

–> Proactive action

Technical recommendations and expert opinions

–> Reactive action

Shortage related to medicinal product - Support to prepare pharmacy preparations

European Pharmacopoeia

Assessment of the **Union list of critical medecines** and targeted additions of API monographs to the Ph. Eur. Work programme

Update on strategies

Removal of animal biological safety tests

Suppression of Rabbit Pyrogen Test: Major Milestone Achieved!

https://www.edqm.eu/en/-/ph.-eur.-bids-adieu-to-rabbit-pyrogen-test-in-its-monographs

At is Session in June 2024 the Ph. Eur. Commission **adopted 57 revised texts from which the RPT has been deleted** and a new chapter on *Pyrogenicity (5.1.13)*

→ As a result, the use of the RPT will no longer be required in any text of the Ph. Eur.

The revised texts and new chapter will be published in Supplement 11.8 of the Ph. Eur. with the implementation date of 1 July 2025

A major achievement for animal welfare and the advancement of modern *in vitro* approaches!

Deletion of animal biological safety tests

Present since Ph. Eur. 1st Edition

Pyrogens (2.6.8)

Histamine (2.6.10) **&** **Depressor substances (2.6.11)**

2017 — Start — **2021** — Start — **2023**

Abnormal toxicity (2.6.9)

Test deleted from 49 Ph. Eur. monographs; chapter suppressed in Suppl. 9.6

Replacement of RPT by suitable control strategies in 59 Ph. Eur. texts;
Elaboration of general chapter *Pyrogenicity (5.1.13)*;
Revision general monographs (2034 and 0520)

Ph. Eur. 11.8 (upcoming)

GOAL

Suppression of *(2.6.8)* in 2026

Removal of references to *(2.6.10)* and *(2.6.11)* and their vestiges (sentences referring to control of substances lowering blood pressure in Production section) from 14 Ph. Eur. monographs;

ISSUE 12.1 (upcoming)

GOAL

Suppression of *(2.6.10)* and *(2.6.11)* in 2026

Elaboration of general chapter *Histamine in active substances (2.5.47)*

Strategy for the replacement of chapter *2.6.8*

***2.6.8** in 60 texts of the Ph. Eur.*

***2.6.8** in 60 texts of the Ph. Eur.*

5.1.13
Pyrogenicity

New! Chapter *5.1.13.* Pyrogenicity

USER

Potential pyrogens other than endotoxins can be ruled out

Risk analysis, potential presence of non-endotoxin pyrogens Stage of manufacturing process

Exclusion of potential pyrogens other than endotoxins not possible

Chapters *2.6.14/ 2.6.32.* BET

or both

Chapter *2.6.30.* MAT

Decision on a testing strategy
Decision on the limits


BREAKING
NEWS
ALERT

2025 - European Pharmacopoeia in online-only format

LAUNCH June/July 2025

- More user-friendly platform with content organised in a more intuitive way
- Direct access to all versions of texts (including obsolete/archived) in one place
- Simplified publication process for earlier availability
- Simplified licensing model

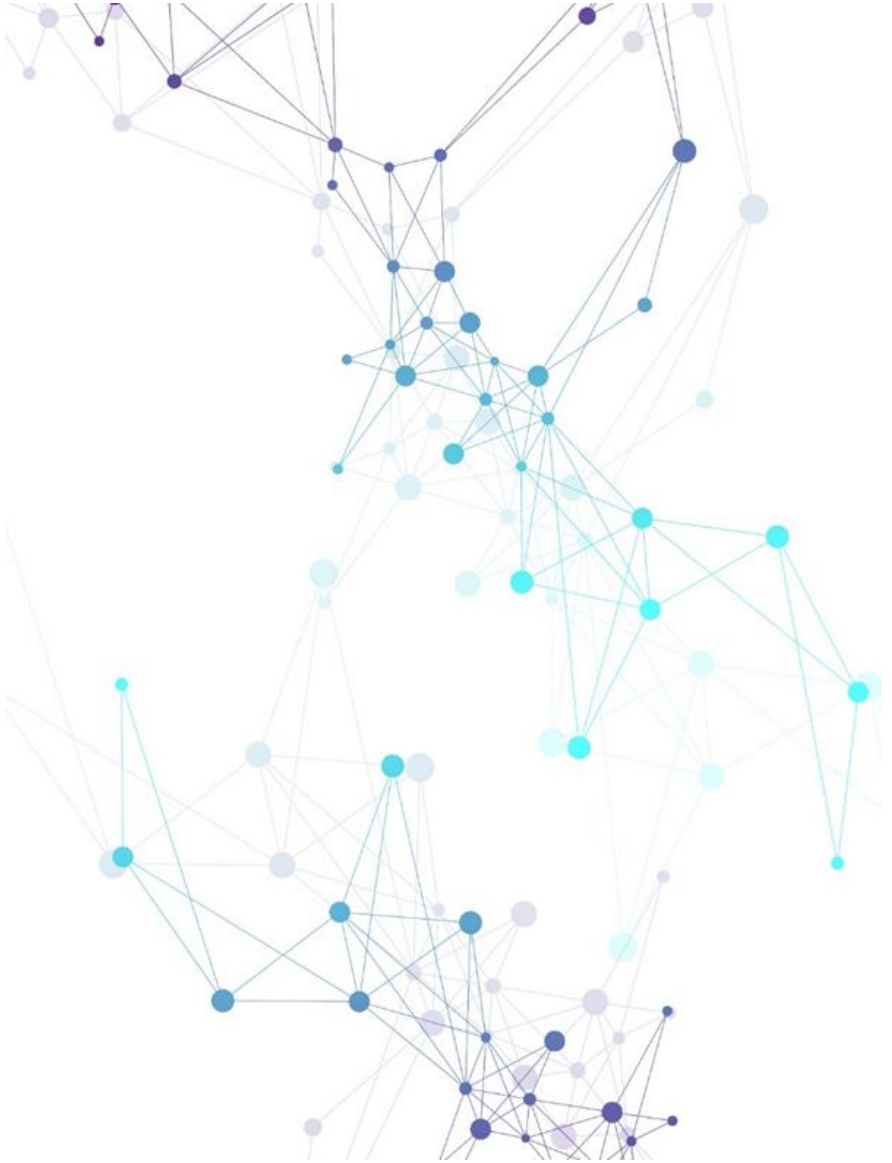
https://www.edqm.eu/en/-/a-new-era-for-the-european-pharmacopoeia-online-only-format-from-june-2025

Main changes

Before	After
1 edition and 8 supplements – 3 years e.g. 11.0, 11.1,…, 11.7, 11.8	1 edition composed of 3 issues per year e.g. 12.1, 12.2 and 12.3
Each online supplement/edition is provided as an updated cumulative version	Each issue contains new and updated texts only
Printed + Online version	Online version only No publication of paper version of the Ph. Eur. in its current format
Subscription : includes 3 supplements Maximum duration validity 18 months.	365 day licensing model: access to all the content for 1 year
Access to a supplement and then to the version of a specific text in this supplement	Easier access to text and all previous and future versions (each version is linked to an issue - starting from 11.0)
Archives : PDFs	Archives are available online (from 11.0) / and previous editions/supplements (as of 10.8 will remain accessible in PDFs)

Concluding remarks

Help us on this journey !



https://www.edqm.eu/en/european-pharmacopoeia

The European Pharmacopoeia

- Background & Mission
- Membership & Observership
- The Ph. Eur. Commission
- Groups of experts and working parties
- European Pharmacopoeia 11th Edition

Focus

- Biotherapeutics
- Alternatives to animal testing (3Rs)

How to participate in the work of the Ph. Eur.

- Join the Network!
- Submitting drafts and requests for revision
- Comment on drafts (Pharmeuropa)

The Ph. Eur. work programme

- Elaborations & Revisions
- Where to find: the Knowledge database
- The Ph. Eur. work programme

Pharmacopoeial Harmonisation

- International harmonisation
- Harmonisation status for Excipient monographs (PDG)
- Harmonisation status for General Texts (PDG)

Ph. Eur. reference standards

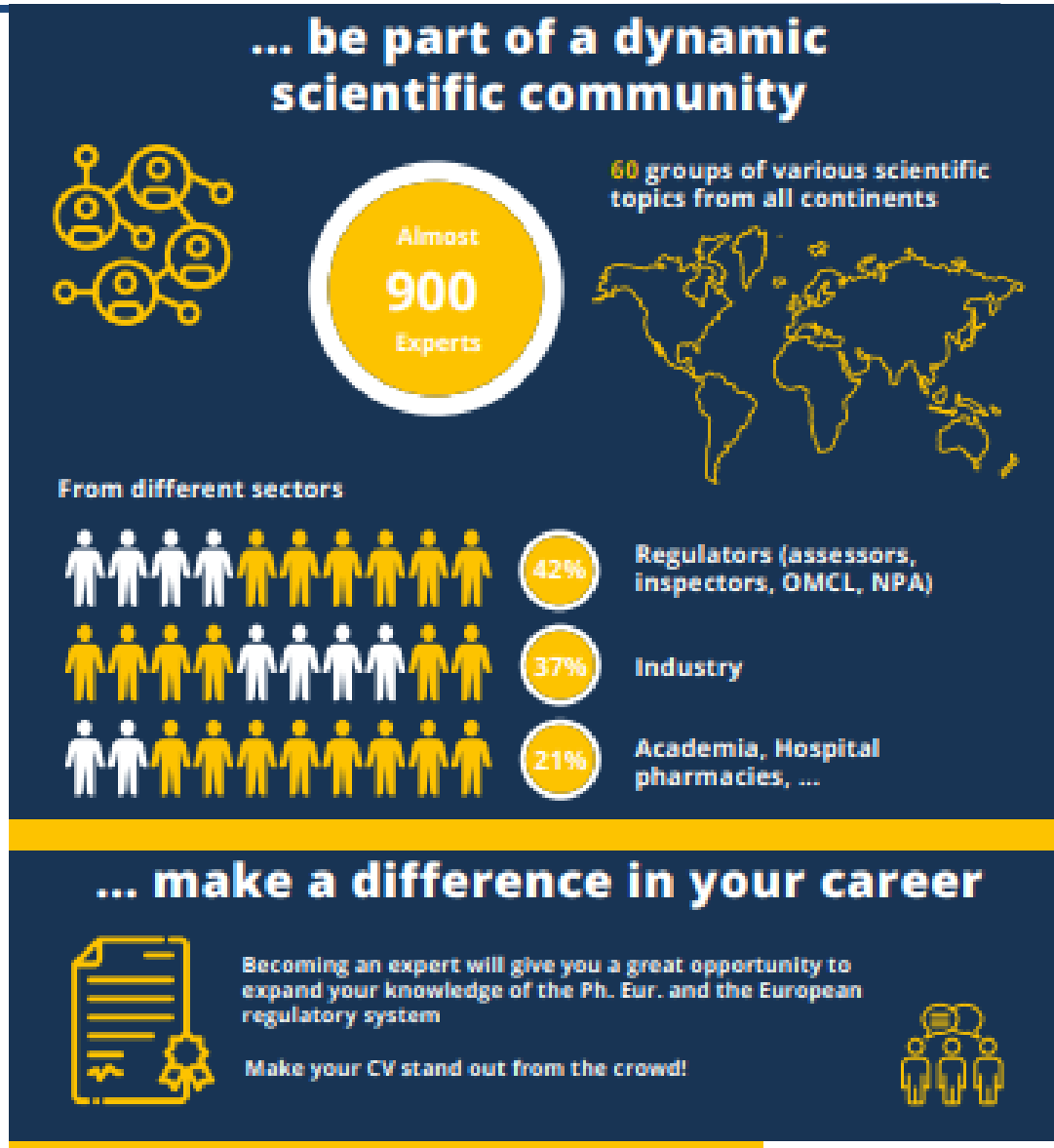
- Ph. Eur. reference standards
- Biological standardisation programme (BSP)

Find information on

- Standard terms Database

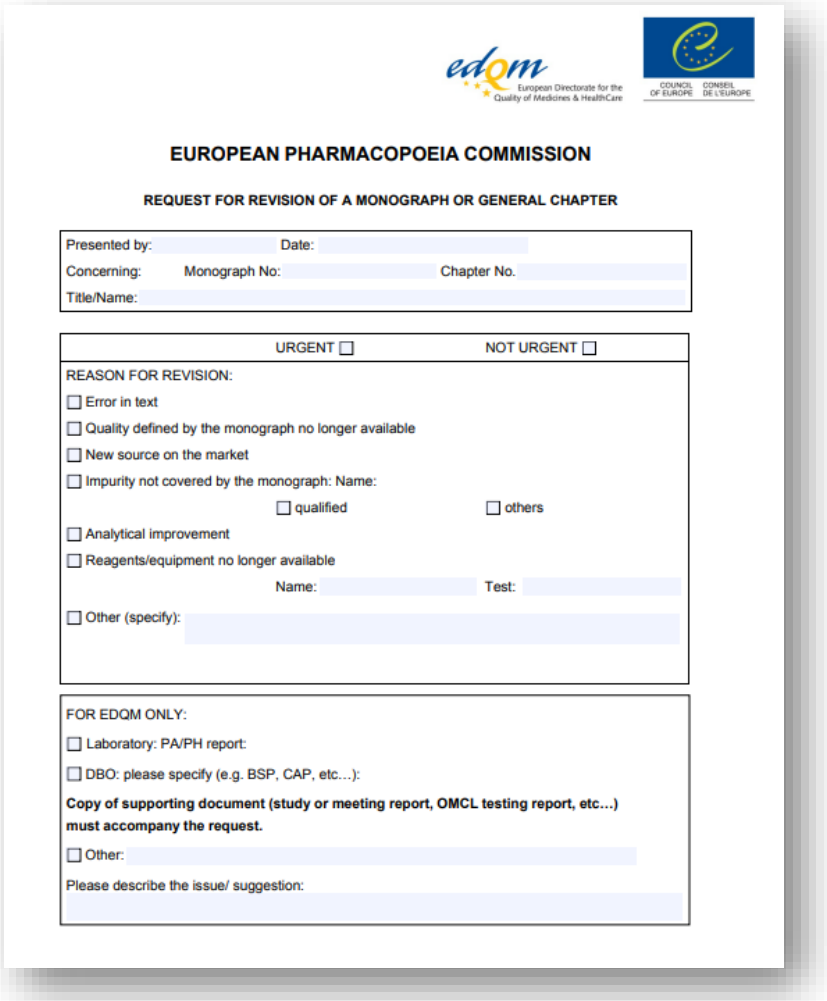
How to participate:

https://www.edqm.eu/en/join-the-network-



How to participate:

https://www.edqm.eu/en/submitting-drafts-and-requests-for-revision



EUROPEAN PHARMACOPOEIA COMMISSION

REQUEST FOR REVISION OF A MONOGRAPH OR GENERAL CHAPTER

Presented by: Date:

Concerning: Monograph No: Chapter No.

Title/Name:

URGENT ☐ NOT URGENT ☐

REASON FOR REVISION:

☐ Error in text

☐ Quality defined by the monograph no longer available

☐ New source on the market

☐ Impurity not covered by the monograph: Name:

☐ qualified ☐ others

☐ Analytical improvement

☐ Reagents/equipment no longer available

Name: Test:

☐ Other (specify):

FOR EDQM ONLY:

☐ Laboratory: PA/PH report:

☐ DBO: please specify (e.g. BSP, CAP, etc…):

Copy of supporting document (study or meeting report, OMCL testing report, etc…) must accompany the request.

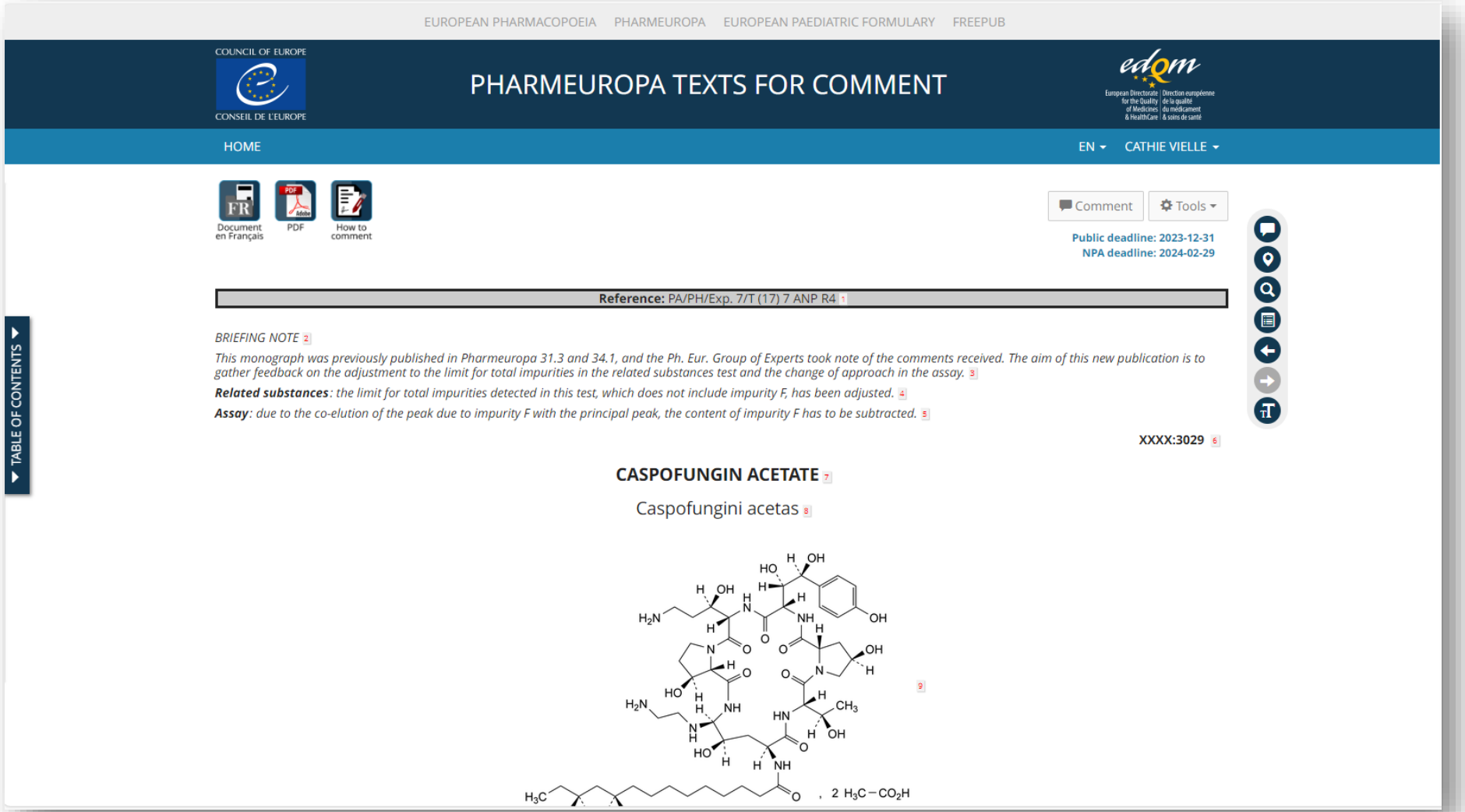
☐ Other:

Please describe the issue/ suggestion:

For manufacturers and other interested parties from Member States of the Ph. Eur. Convention: via the national pharmacopoeia authority.

For others (manufacturers and other interested parties from non-Member States of the Ph. Eur. Convention or multinational interested parties, for international organisations and for industry associations or other associations): via EDQM HelpDesk

How to participate …. last but not least ….



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