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

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

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# Module 1: General Methods, General Chapters & General Monographs

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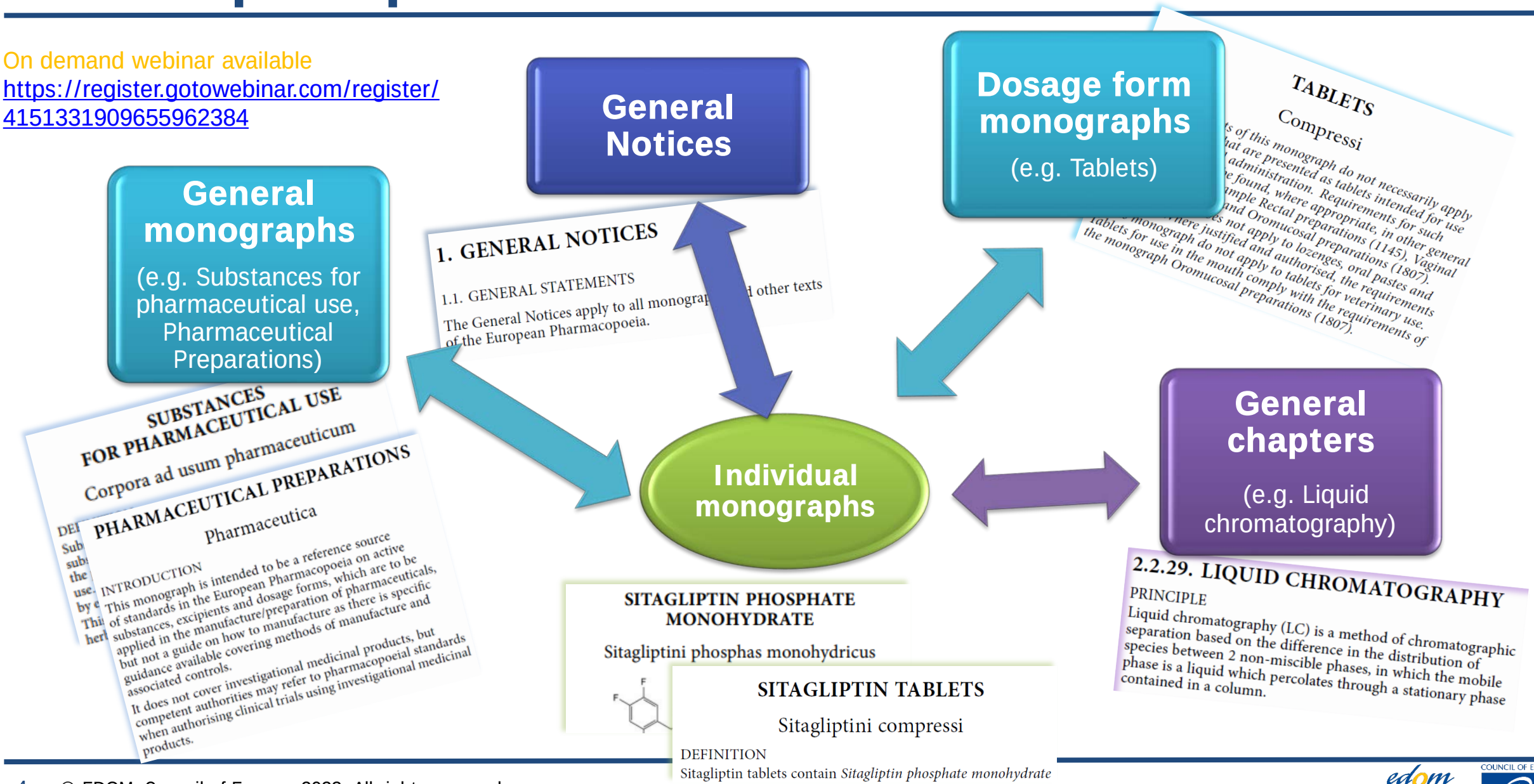
**(Live Webinar)**
**Date**: 26 June 2023

# Outline

- Structure of the Ph. Eur. & general principles
  - General Notices
  - General monographs
  - General chapters
- General chapters work programme update
- Update on Ph. Eur. strategy

# General principles and structure

On demand webinar available
https://register.gotowebinar.com/register/4151331909655962384



# Ph. Eur.: Content and structure

## Ph. Eur. Reference standards / preparations & reagents

## General chapters & general texts

- avoid repeating standard procedures or requirements in each monograph; aspects that cannot be treated in each monograph
- become mandatory when referred to in a monograph
- provide standard analytical procedures; guidance

## Individual monographs

- Specific but not a stand alone text
- Analytical procedures and acceptance criteria represent required quality standards
- Based on approved specifications backed up by batch data
- Reliance on manufacturers' feedback (public consultation)

## General notices

- Essential reading
- Apply to all texts
- Address general topics
- Provide basic information
- Include rules to understand texts, conventional expressions

## General monographs

## Dosage form monographs

- Classes of substances/medicinal products
- Mandatory for all substances/products within scope of their definition
- Aspects that cannot be included in each individual monograph
- Not cross-referenced in individual monographs (exceptions)

# General Notices – answers to a lot of questions!

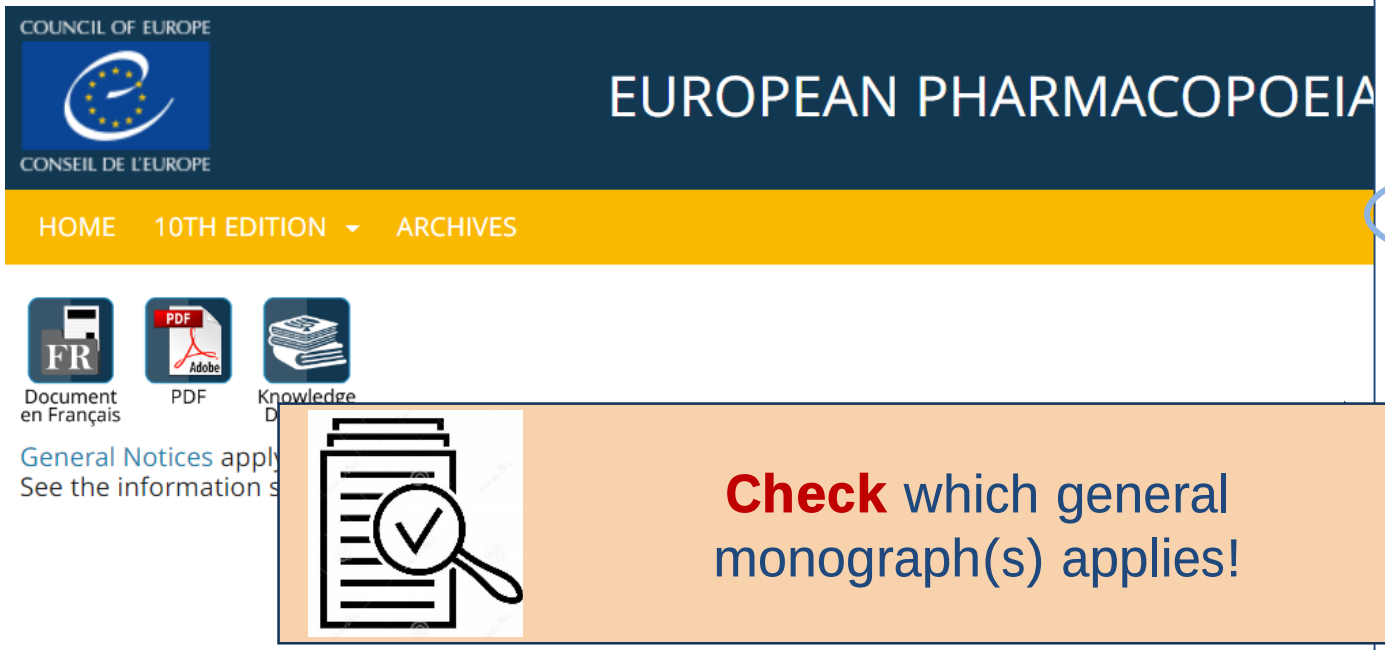
**Revised in supplement 10.7**

- Such as:
  - What does compliance mean?
  - What is mandatory?
  - What to do when implementing a pharmacopoeial procedure?
  - What about alternative analytical procedures?
  - What about waiving of tests?
  - Why two identification tests ... sometimes?
  - Human and/or veterinary use?

And many more...

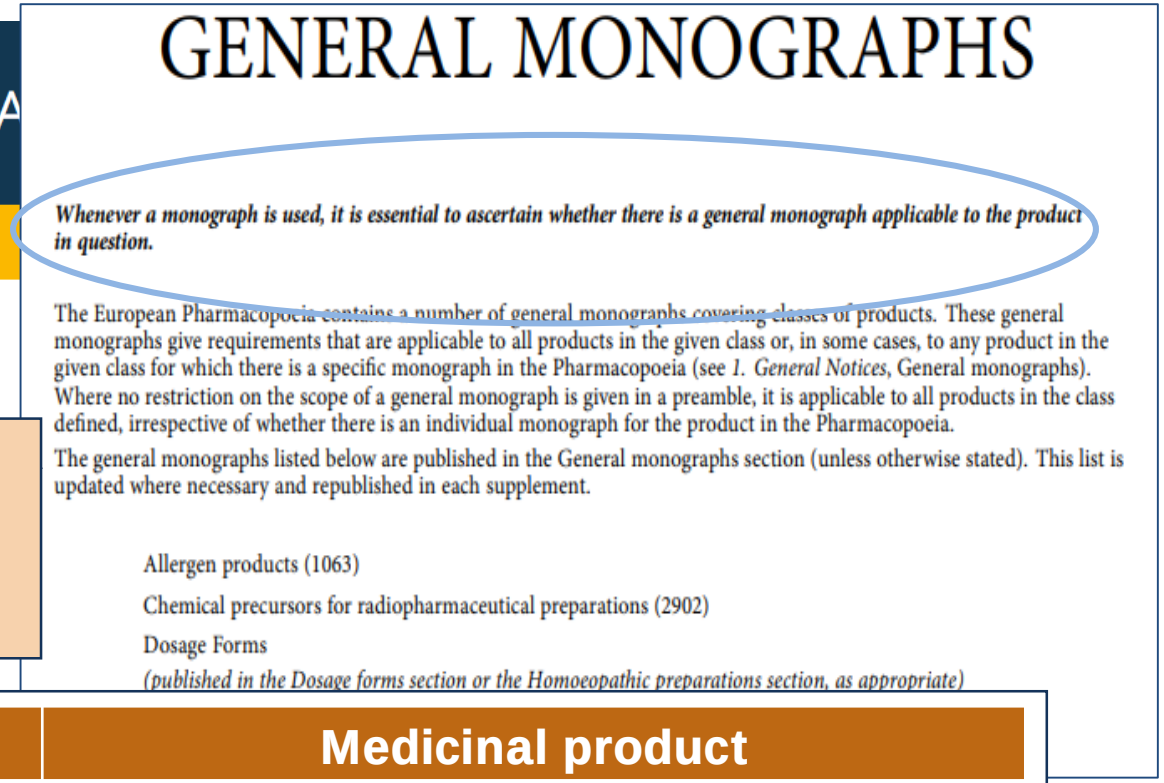
On demand webinar is available for learning more on the recent changes
https://www.edqm.eu/en/-/getting-the-big-picture-what-has-changed-in-the-ph.-eur.-general-notices

# 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.

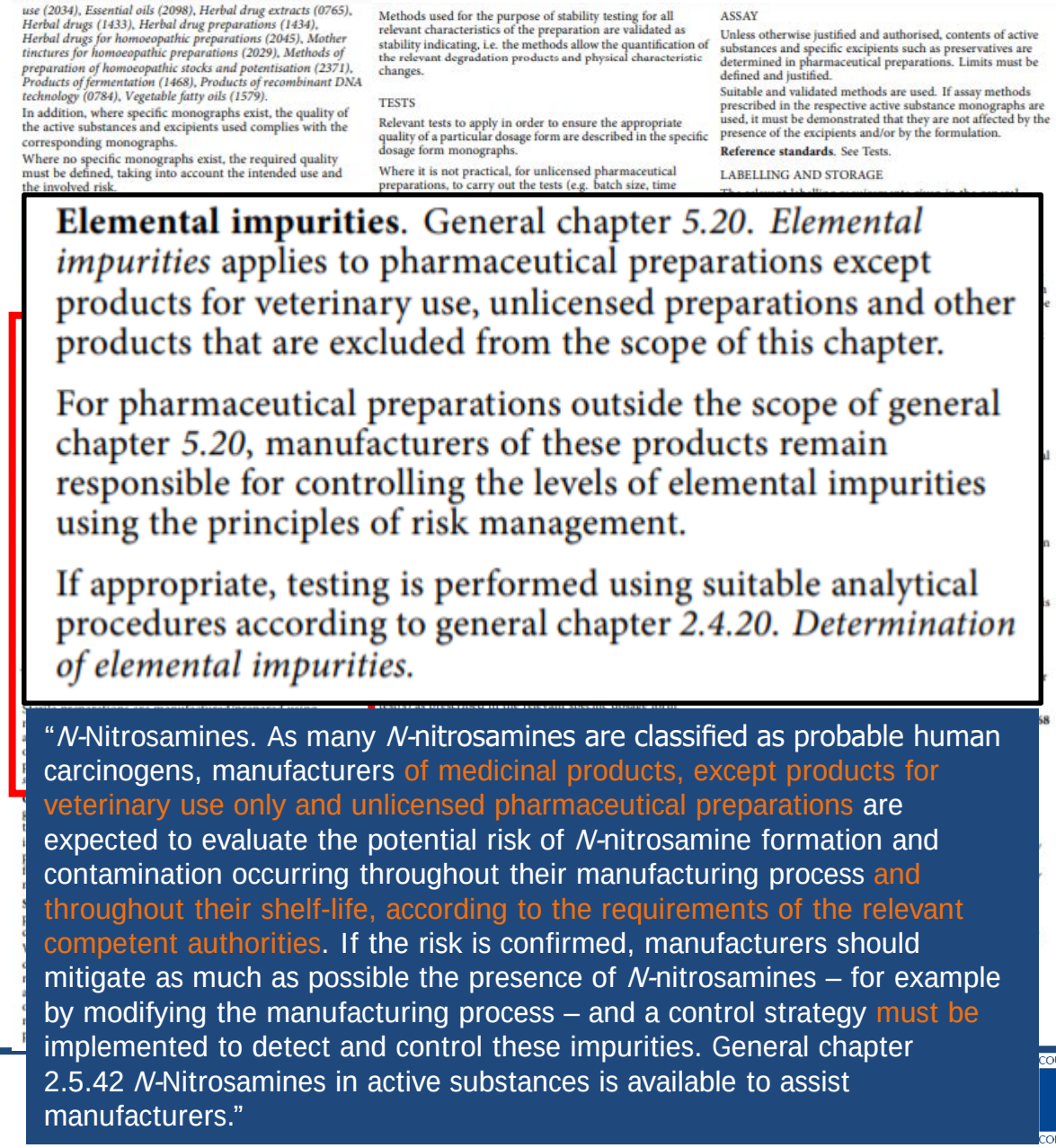
**Residual solvents** are limited according to the principles defined in chapter *5.4*, using general method *2.4.24* or another suitable method. Where a quantitative determination of a residual solvent is carried out and a test for loss on drying is not carried out, the content of residual solvent is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



*use (2034), Essential oils (2098), Herbal drug extracts (0765), Herbal drugs (1433), Herbal drug preparations (1434), Herbal drugs for homoeopathic preparations (2045), Mother tinctures for homoeopathic preparations (2029), Methods of preparation of homoeopathic stocks and potentisation (2371), Products of fermentation (1468), Products of recombinant DNA technology (0784), Vegetable fatty oils (1579).*

In addition, where specific monographs exist, the quality of the active substances and excipients used complies with the corresponding monographs.

Where no specific monographs exist, the required quality must be defined, taking into account the intended use and the involved risk.

Methods used for the purpose of stability testing for all relevant characteristics of the preparation are validated as stability indicating, i.e. the methods allow the quantification of the relevant degradation products and physical characteristic changes.

TESTS

Relevant tests to apply in order to ensure the appropriate quality of a particular dosage form are described in the specific dosage form monographs.

Where it is not practical, for unlicensed pharmaceutical preparations, to carry out the tests (e.g. batch size, time

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.

**Reference standards**. See Tests.

LABELLING AND STORAGE

**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."

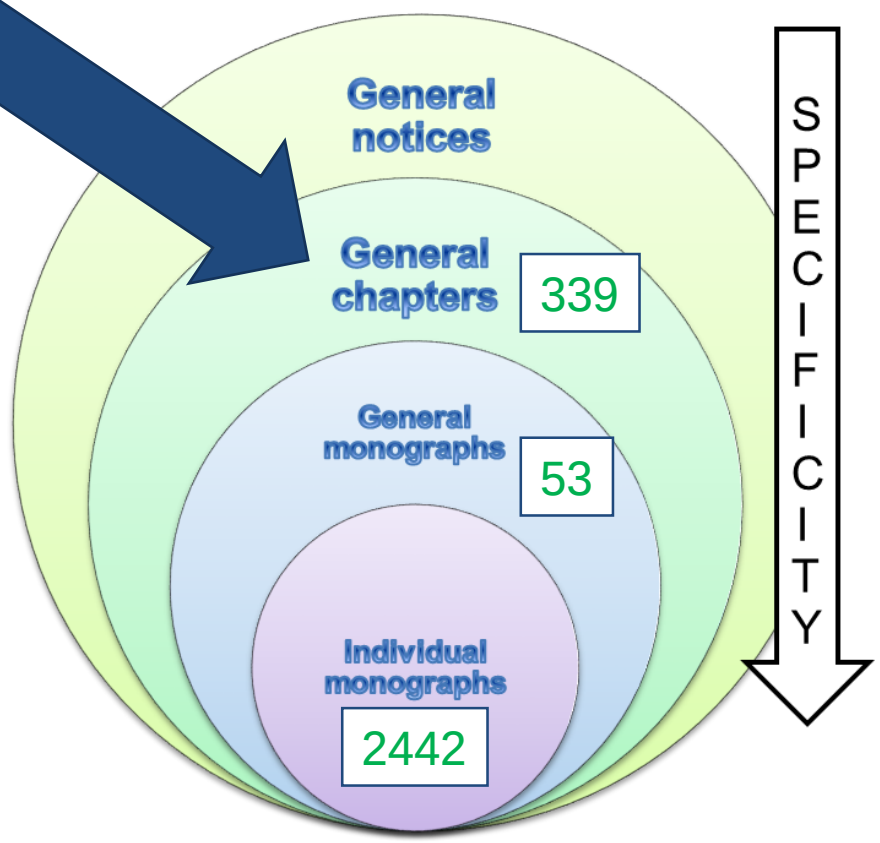
# General chapters

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. 11.2)



# 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

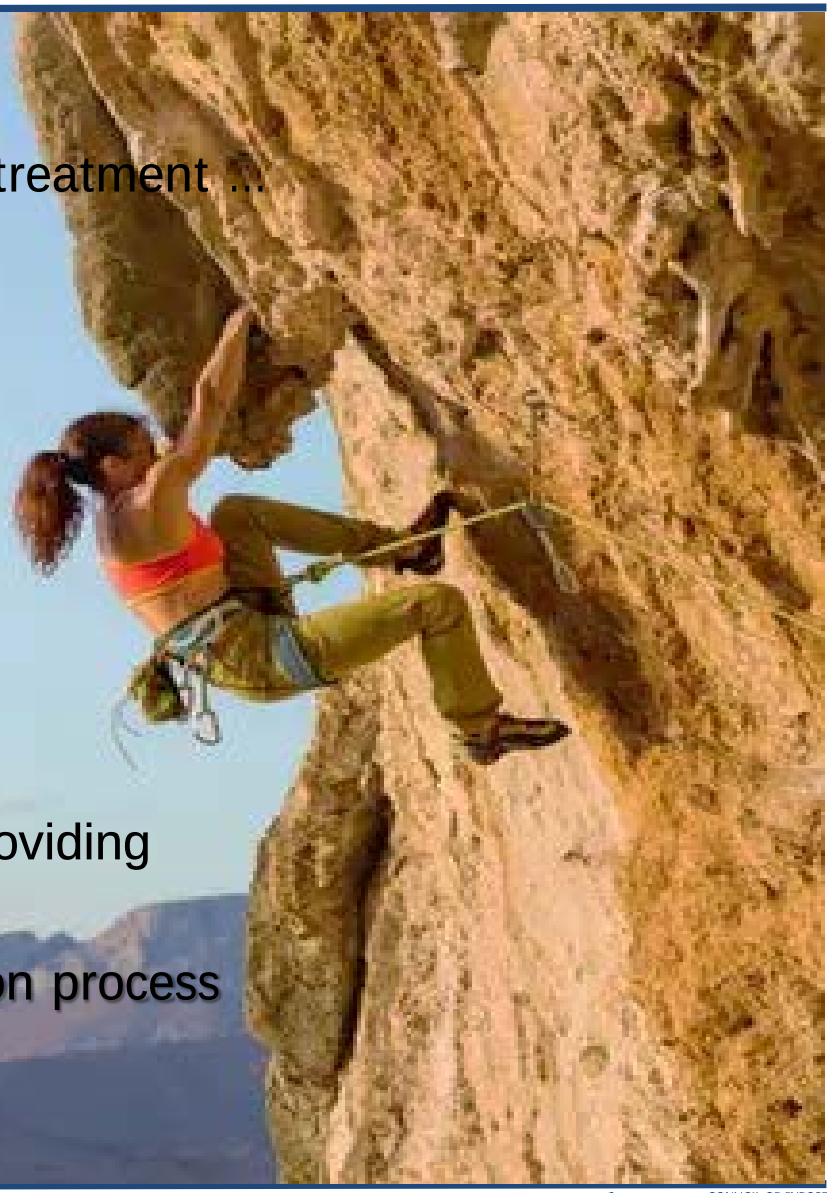
✓ *2.2.24 IR spectrophotometry,* referred in many ID tests ⟹ Mandatory application

✓ *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 GMs

(Not exhaustive)


- N-Nitrosamines in active substances, 2.5.42
- Balances for analytical purposes, 2.1.7
- Contaminant pyrrolizidine alkaloids, 2.8.26
- Particulate contamination: s-v particles in non-injectable liquid preparations, 2.9.53
- Raman spectroscopy, 2.2.48
- ★ Chromatographic separation techniques, 2.2.46
- Cell-based assays for potency determination of TNF-alpha antagonists, 2.7.26
- Osmolality, 2.2.35

★ International harmonisation

# Balances for analytical purposes, 2.1.7

SUPPL. 10.6, 01/2022

- 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)

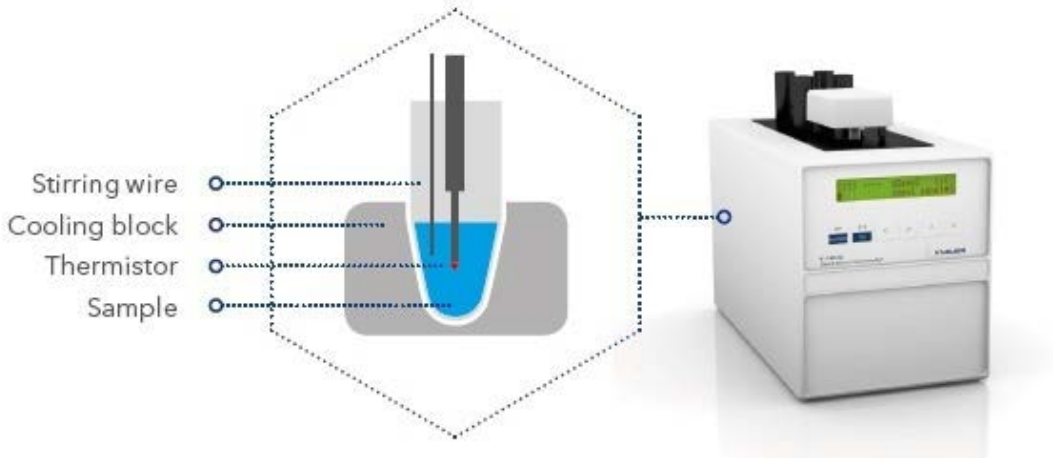
Further reading available: https://pbiosn.edqm.eu/app/pbiosn/content/default/2022-1_Weighing_according_to_the_European_Pharmacopoeia.pdf

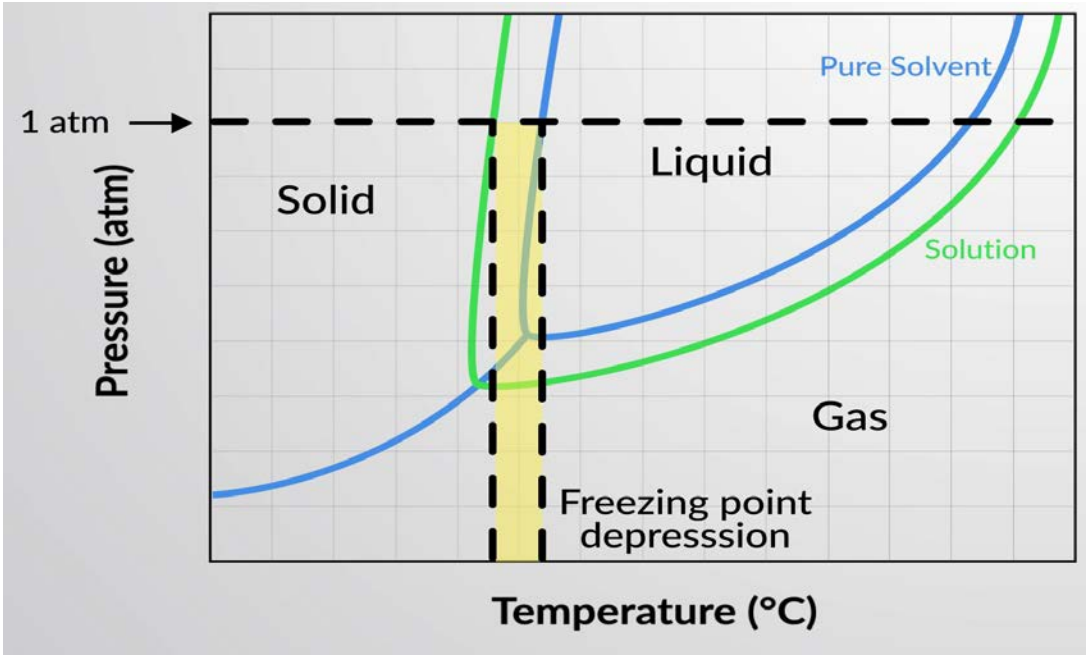
# Osmolality, 2.2.35

SUPPL. 11.3, 01/2024

Updates to the osmolality general chapter centered on the **calibration** and **accuracy check**:

- Zero point determination **not mandatory**
- Preparation of reference NaCl aqueous solutions in the extended range up to **4000 mosmol / kg**
- **Distinction** between the calibration and adjustment of the instrument made
- Allows for performing a measurement outside the adjusted range
- Clarified **requirements** for the accuracy check




Measurement principle remains unchanged:

- Osmolality is a measure of the **total number of chemical entities** per kilogram of solvent
- Determined by measuring the **freezing-point depression ($\Delta T_f$)** of a solution (deviation of the solution from ideal behaviour acc. to Raoult's law).

# Contaminant pyrrolizidine alkaloids (2.8.26)

*PAs*: naturally occurring in weeds contaminants of raw plant material. Acute toxicity, genotoxicity and carcinogenic potential.
Not possible to describe a unique procedure covering for all target *PAs* in all possible matrices.

## Intended purpose

Trace analysis of 28 target PAs in herbal drugs, preparations thereof and medicinal products

## Link to CQA

The analytical procedures should allow for the determination of the total sum of target PAs in the sample in a range not exceeding the max. daily intake agreed by the competent authority

- Allows for use of any procedure consisting of LC-MS/MS or high resolution MS that meets the validation requirements given in the chapter

## Definition of AP performance standard ("ATP-like")

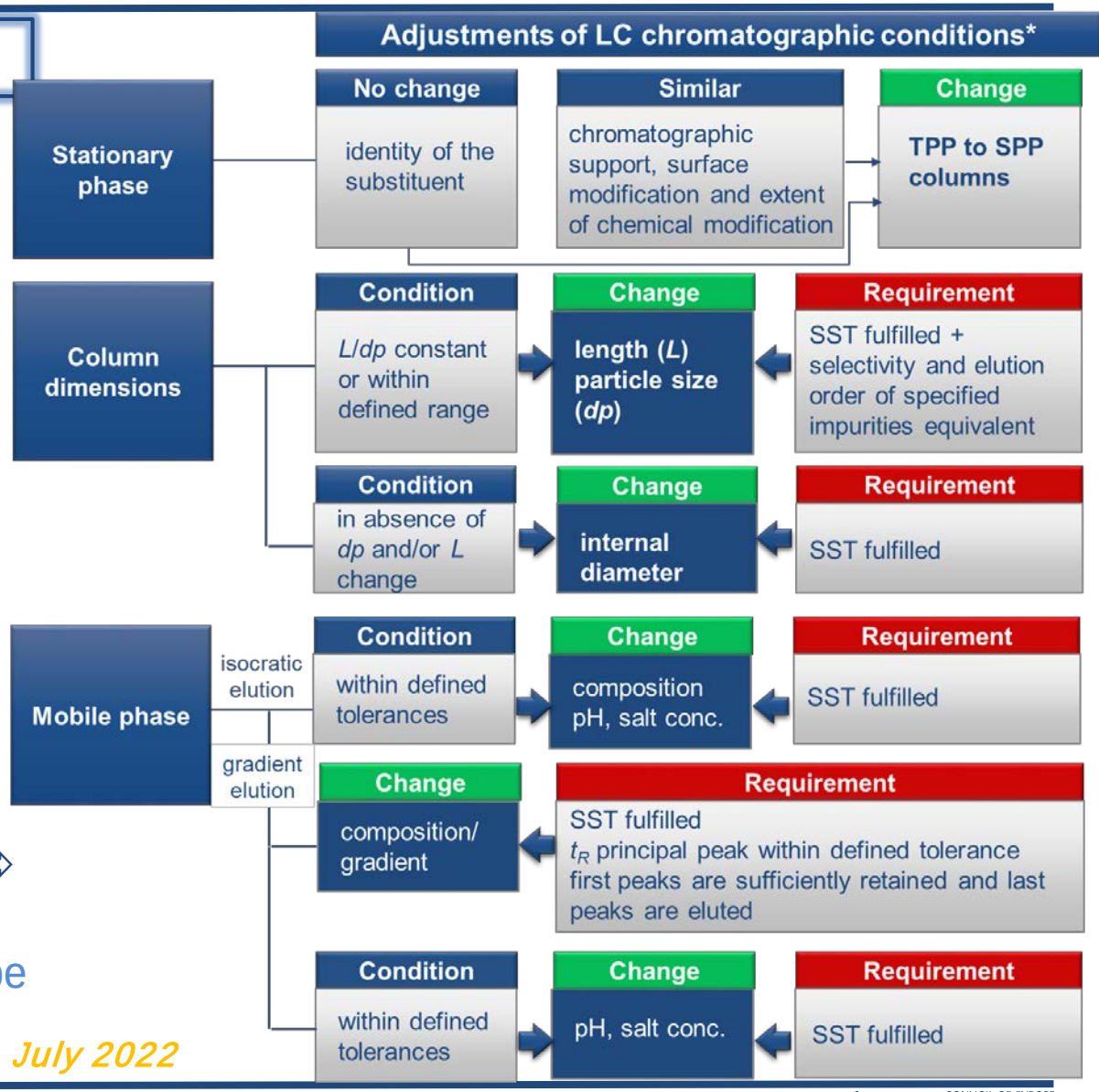
| Validation parameter (to be assessed for each target PA in the corresponding extracted ion chromatograms) | | | Requirement |
|---|---|---|---|
| *Identification* | *MS/MS* | Position of the peaks due to at least 2 product ions acquired in SRM or MRM mode and obtained with a spiked matrix sample[1] at least at the limit of quantitation (LOQ) | fully overlap |
| | | Difference in ion ratio[3] between a spiked matrix sample[1] and a reference solution, both at least at the LOQ | maximum ± 30 per cent |
| | *High-resolution MS* | Position of the peaks due to at least 2 ions[2] obtained with a spiked matrix sample[1] at least at the LOQ | fully overlap |
| | | Mass accuracy[1] of each of at least 2 ions[2] obtained with a spiked matrix sample[1] at least at the LOQ | maximum 5 ppm for ions with masses ≥ 200 Da |
| | | | maximum 1 mDa for ions with masses < 200 Da |
| | | Signal-to-noise ratio of each of at least 2 ions[2] obtained with a spiked matrix sample[1] at least at the LOQ | minimum 3[3] |
| *Matrix effect* | Difference in response between reference solutions and matrix-matched standard solutions within the working range[1], at one or more concentration points chosen by the analyst | | maximum ± 20 per cent |
| *Specificity* | Difference in retention time between spiked matrix samples[1] and reference solutions within the working range[1] (applicable if the identification criteria in this table are met), at one or more concentration points chosen by the analyst | | maximum ± 0.1 min |
| | Difference in response of each interfering peak between matrix blank solution and solvent blank[1] | | maximum 30 per cent of the LOQ |
| *Linearity* | Deviation of the concentration of the calibration standards (reference solutions or matrix-matched standard solutions) calculated by the calibration function, from the true concentration, for at least 5 concentrations covering the working range[1] | | maximum ± 20 per cent |
| *Accuracy* | Percentage recovery obtained with spiked matrix samples[1] for a minimum of 3 concentrations within the working range[1] (the lowest representing the LOQ) and with at least 3 determinations at each of these concentrations | | 70-120 per cent[4] |
| *Repeatability* | Relative standard deviation (RSD), obtained with spiked matrix samples[1], for a minimum of 3 concentrations within the working range[1] (the lowest representing the LOQ) and at least 3 determinations at each of these concentrations | | maximum 20 per cent |
| *Limit of quantitation (LOQ)*[5] | Signal-to-noise ratio, obtained with a spiked matrix sample[1] at the lowest concentration in the working range[1] (applicable if the accuracy and repeatability criteria in this table are met) | | minimum 10 |

# Chromatographic separation techniques (2.2.46)

## Elements of flexibility in Ph. Eur. text

- 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:**
  - pharmacopoeial procedure = basis for adjustments ⇨ no further adjustments without revalidation
  - fulfilling the SST no longer the only trigger for adjustments
  - SST = bottom-line requirements but additional verification may be required
  - multiple adjustments ⇨ potential cumulative effects ⇨ proper evaluation / risk assessment by user
  - non-pharmacopoeial analytical procedures not in scope




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

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

# Cell-based assay for potency determination of TNF-alpha antagonists (2.7.26)

## Some elements of AQbD

- **NEW type of general chapter** with experimentally verified specific procedures
- TNF-alpha neutralisation assays (procedures A, B, C and D):
  - ➔ different cell lines/readouts
  - ➔ validated for specific TNF-alpha antagonists
  - ➔ suitability (specificity and precision) demonstrated for each TNF-alpha antagonist substance, during verification experiments
  - ➔ procedure applied to substances outside the scope of the initial validation or not covered in an individual monograph for a TNF-alpha antagonist, require validation.
- Diversifies the choice of bioassays and facilitates migration to different assays

## Performance-based standards

- Cell preparation
- TNF-alpha working solutions preparation
- Test solution preparation
- Reference solution preparation (product-specific: BRP or IHRS)
- Assay execution
- Dose-response curve construction
- Calculation of reportable result

### Analytical procedure control strategy

- ✓ system suitability test: quality of RS and control curves, proper functioning of the system (max to min ratio between controls)
- ✓ sample suitability assessment: compare performance of the sample to the performance of the RS (similarity/parallelism)
- ✓ **procedure-independent performance controls and one-size-fits all criteria**

### Sources of variability identified and potential mitigation strategies described:

- ✓ adjustment of assay conditions to satisfy the system suitability criteria without fundamentally modifying the procedures

# 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).
- ✓Process analytical technology, 5.25 (Supp. 10.4)
  - general approach to the integration of analytical techniques in the process environment
- ✓Monographs on essential oils, 5.30 (Supp. 10.7)
  - underlying principles for the elaboration of monographs on essential oils (production methods, chromatographic profiles and potential contaminants)
  - conditions under which skip testing is justified and the various uses of rectification
- ✓Implementation of pharmacopoeial procedures, 5.26 (Ed. 11.0)
  - provides guidance on how users should assess and eventually verify that the pharmacopoeial procedure is performing suitably under the actual conditions of use
- ✓Chemometric methods applied to analytical data, 5.21 (Suppl. 11.1)

# 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**

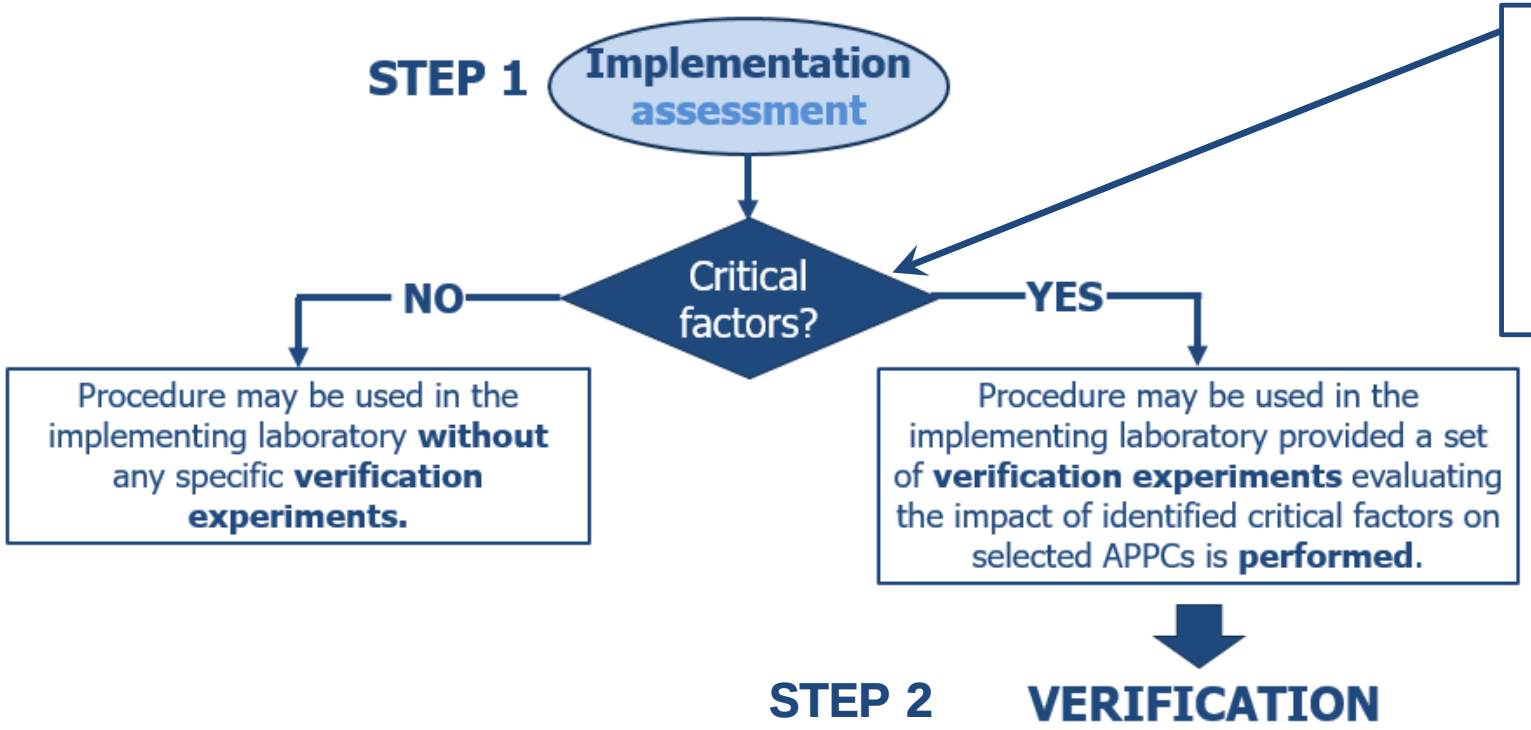
When implementing a Ph. Eur. analytical procedure, the **user must assess** whether and to what **extent** its **suitability under the actual conditions of use needs to be demonstrated** according to relevant monographs, general chapters and quality systems.

**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

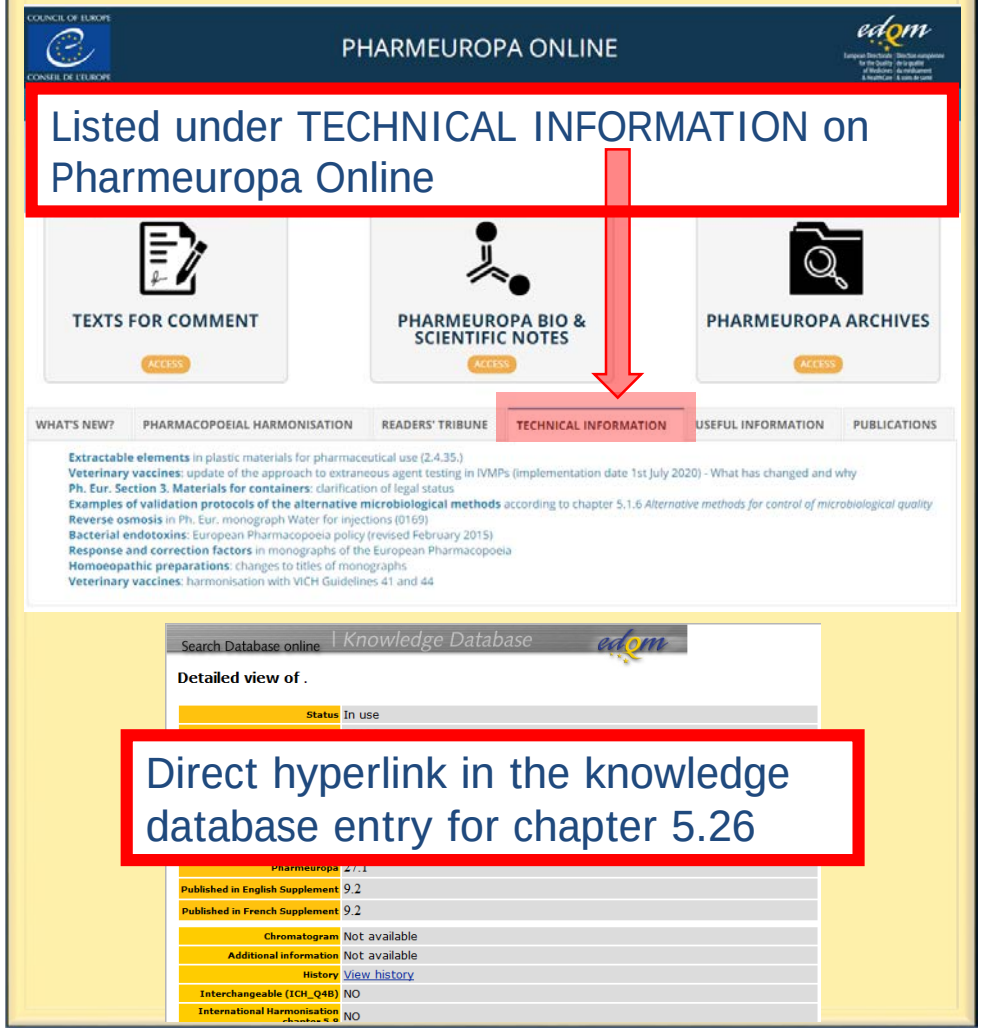
AVAILABLE ONLINE

## 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




# Some updates in the pipeline

★ International harmonisation

★ Determination of elemental impurities, 2.4.20 (after Pharmeuropa)

★ Particulate contamination: sub-visible particles, 2.9.19 (after Pharmeuropa)

- *N*-Nitrosamines in active substances, 2.5.42 (prepared for Pharmeuropa)

★ Capillary electrophoresis (prepared for Pharmeuropa)

- Design of experiments, 5.33 (after Pharmeuropa)

★ Disintegration of tablets and capsules, 2.9.1 (in Pharmeuropa 35.2)

- Comparability of alternative procedures, 5.27 (recently adopted)

# 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

✓Alternative analytical procedure = validated according to relevant scientific guidance

✓Comparison study with head-to-head testing format with same experiments – where feasible, using the same samples

✓method for data evaluation proposed by comparison of the means and standard deviations


Just recently adopted by the European Pharmacopoeia Commission

# 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


Just recently adopted by the European Pharmacopoeia Commission

**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.

# 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

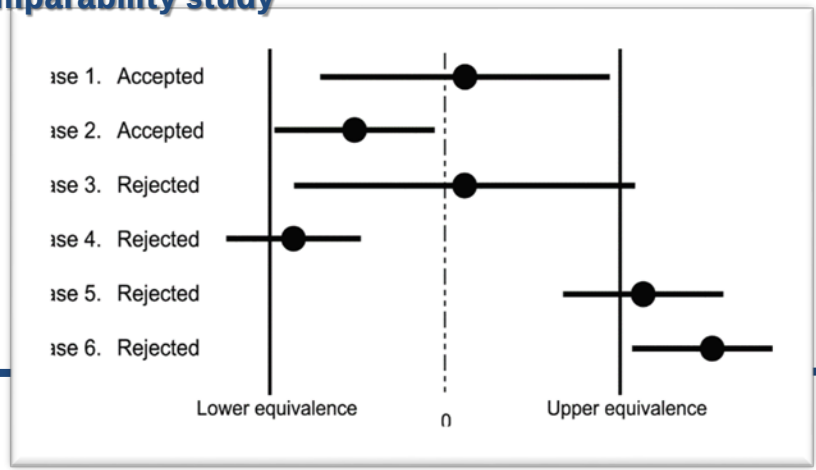
*Study report*

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**



# Recent major additions on the work program

NON EXHAUSTIVE

- General procedures for analysis of recombinant therapeutic mAbs, 2.5.43 & 2.5.44
  - *Development of general SEC and cIEF procedures for mAbs*
- High Throughput Sequencing for the detection of extraneous agents in biological products (2.6.41)
- Evaporative light scattering detection, 2.2.62
- Charged aerosol detection, 2.2.69
- Identification and control of residual solvents, 2.4.24
  - *Alignment with ICH Q3C(R8) and general revision*
- Cell-based preparations, 5.32
- Recombinant viral-vectored vaccines for human use, 5.37
- Quality aspects for data analysis, 5.38
  - Framework to ensure that the data used for analysis, decision making and subsequent actions is reliable

# Focus on 2 Ph. Eur. Texts in the Pipeline (SEC & cIEF)

- Explore **flexible concepts** and **new types of standardisation**:
  - Focus on key quality attributes and associated testing strategies
  - Establish suitable common expectations and general methodologies with broad applicability
  - Reflect robust and established practices applicable to wide range/classes of mAbs
  - Multi-laboratory collaborative studies

- SE-HPLC, SE-UPLC, ciEF and imaged cIEF procedures, widely applicable to mAbs, given as examples (*'platform methodologies'*)
- tools to control AP performance; common reference standard (ATP-connected, but technology-specific)
- guidance on aspects to consider for product-specific application (validation)

## Performance-based standards



**Size-exclusion chromatography** for recombinant therapeutic monoclonal antibodies (2.5.43)

**Capillary isoelectric focusing** for recombinant therapeutic monoclonal antibodies (2.5.44)

SE-HPLC
SE-UPLC

Maximum versatility

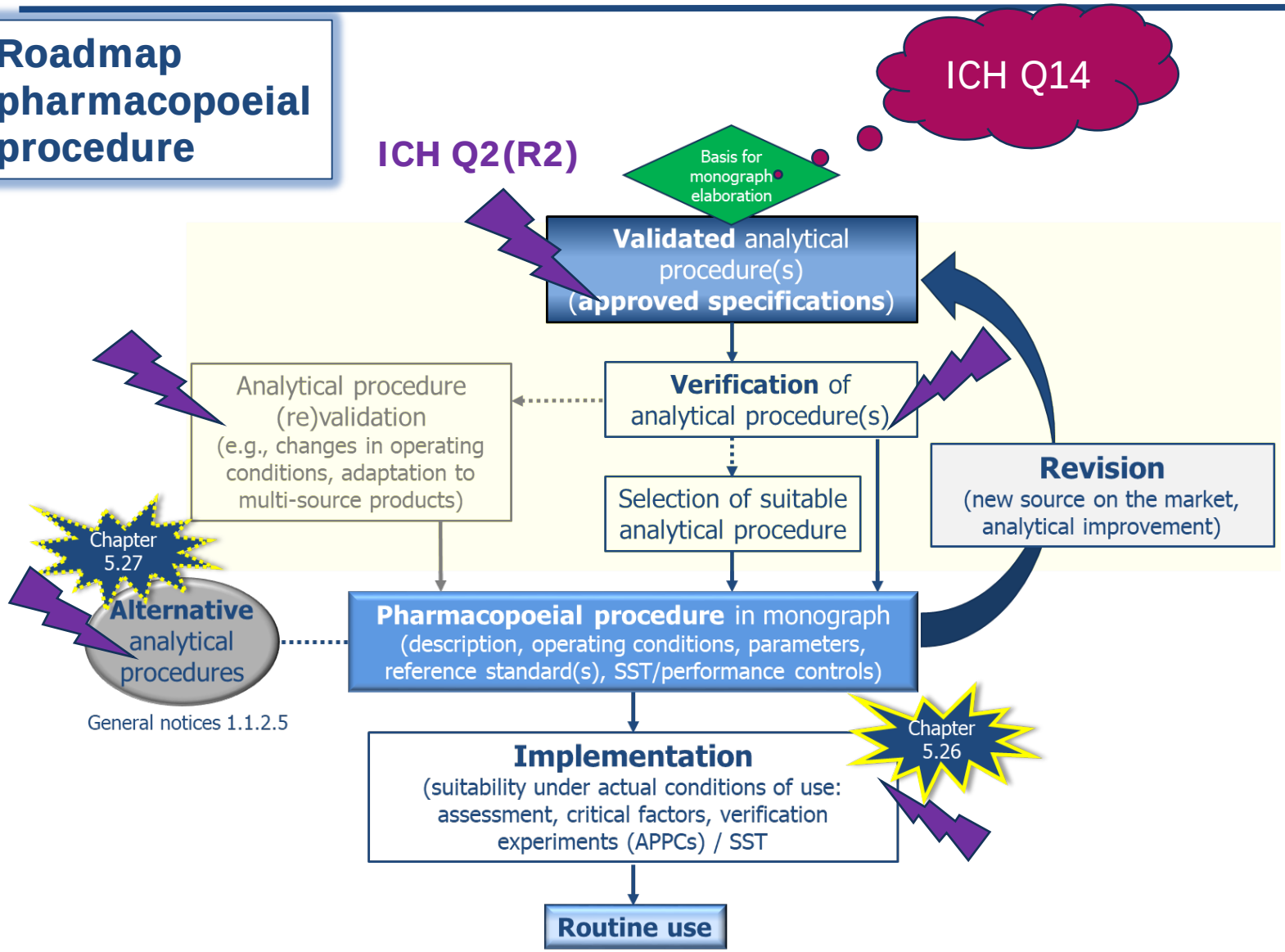
Applicability to any mAb

cIEF
imaged cIEF

# Update on strategy

# Analytical Quality by Design ('enhanced approach')

**Roadmap pharmacopoeial procedure**




## New AQbD Working Party

- Assess the feasibility and impact of incorporating analytical procedures developed using the concepts of AQbD in Ph. Eur. monographs
- Advise the Commission and expert groups on appropriate elaboration/revision strategies for incorporating such analytical procedures in monographs
- Identify verification and revision approaches for analytical procedures developed using AQbD

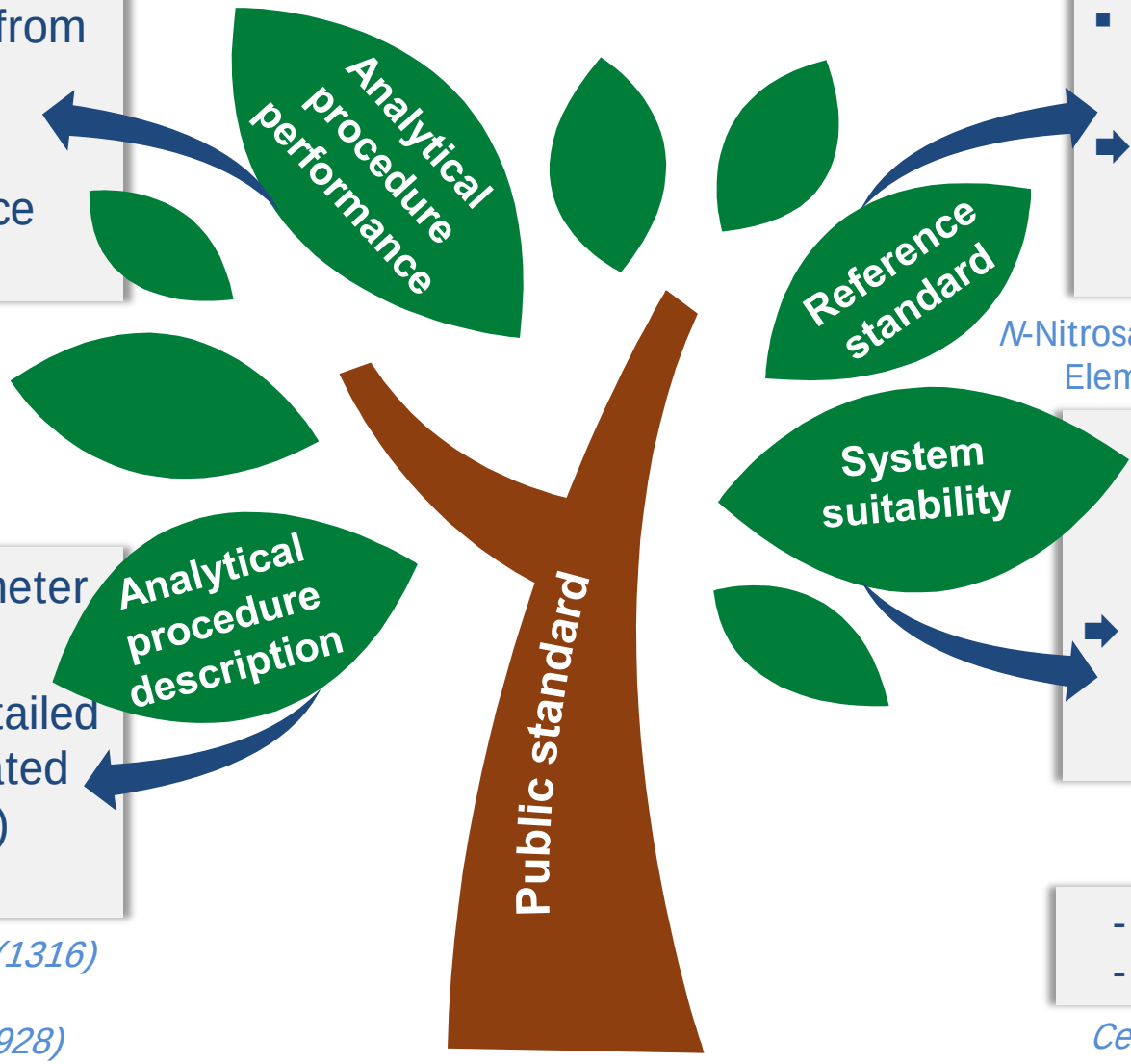
# AQbD-Oriented Elements in Ph. Eur. Texts

- partially derived indirectly from SST, specifications
- ➡ **enhanced approach**: definition of AP performance standard (ATP-like)

*Determination of elemental impurities (2.4.20)*
*Contaminant pyrrolizidine alkaloids (2.8.26)*

- detailed description, parameter setting, attributes, SST
- ➡ **enhanced approach**: detailed *example procedure*, facilitated use on in-house (validated) procedure

*Erythropoietin concentrated solution (1316)*
*Etanercept (2895)*
*Infliximab concentrated solution (2928)*




- reference standards connected to specific analytical procedure
- ➡ **enhanced approach**: reference standards connected to ATP

*N*-Nitrosamines CRSs *(2.5.42)* [MS-based techniques]
Elemental impurity solutions CRS *(2.4.20)*

analytical procedure-dependent with additional tests given in general chapters

- ➡ **enhanced approach**: *overarching*, risk-based SST as part of AP control strategy

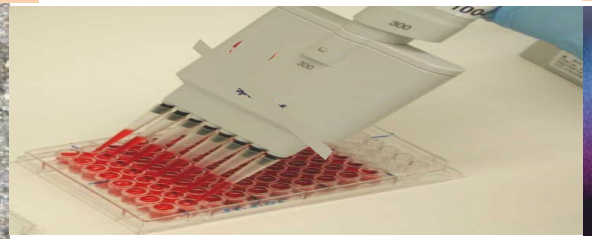
*Chromatographic separation techniques (2.2.46)*

- performance-based standards
- *platform* methodologies; "toolbox"

*Cell-based assay for potency determination of TNF-alpha antagonists (2.7.26)*

# New Pyrogenicity strategy

https://go.edqm.eu/NewPyrogenicityStrategy

| 1971 | 1987 | 2010 | 2020 |
|---|---|---|---|
|  |  |  |  |
| Pyrogens (2.6.8) | BET (2.6.14) | MAT (2.6.30) | BET using rFC (2.6.32) |

**The RPT continues to be widely performed**

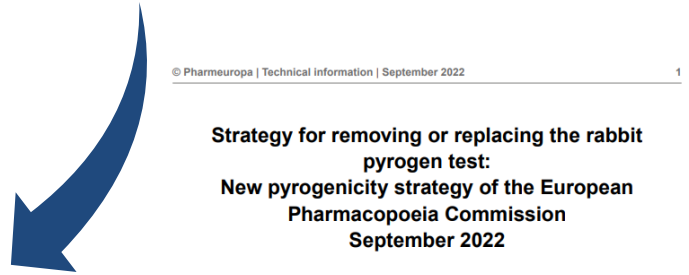
**Experts of the Ph. Eur.**

The European Partnership for Alternative Approaches to Animal Testing

# Proposal:

**Pharmeuropa 35.1**

**New chapter *5.13* Pyrogenicity**
**Deletion of the rabbit pyrogen test from 60 Ph. Eur. texts by 2025 and suppression of chapter *2.6.8* from the Ph. Eur. by 2026**



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**Strategy for removing or replacing the rabbit pyrogen test:
New pyrogenicity strategy of the European Pharmacopoeia Commission
September 2022**

# EPAA/EDQM International Public Conference

*To mark the first official milestone of the strategy, i.e. the publication of revised Ph. Eur. texts omitting the RPT in Pharmeuropa 35.1 (January 2023)*

Date: **14-16 February 2023**

Venue: European Commission premises, Brussels

Streaming available here: https://single-market-economy.ec.europa.eu/events/epaa-edqm-event-future-pyrogenicity-testing-2023-02-14_en

# Water monographs: BET using rFc

SUPPL. 11.4, 04/2024

## Purified Water (0008) and Water for Injections (0169)

- Test for bacterial endotoxins (BET)
  - ➢Current version: LAL, a reagent derived from the horseshoecrab
  - ➢Revised monographs: LAL or recombinant Factor C, a reagent produced by rDNA technology (chapter 2.6.32 of the Ph. Eur.)

**OR**

  - ➢Users will be to select the test described in *2.6.32* directly when testing pharmaceutical waters, i.e. without a side-by-side comparison against the tests described in general chapter *2.6.14 Bacterial endotoxins*

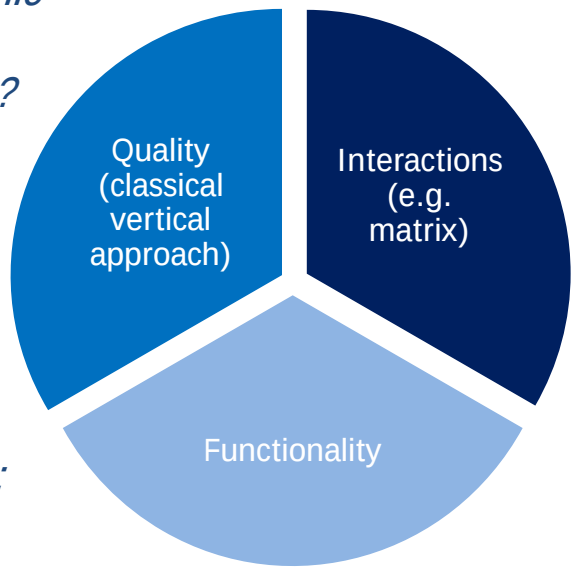
# Excipients strategy: new working party

# Excipients strategy: Preamble

- The Ph. Eur. general monograph on *Substances for pharmaceutical use* (*2034*) covers both active substances and excipients. However, several parts of this general monograph, apply only to active substances. In addition, certain aspects beyond quality – functionality and interactions, for example – are recognised as being specific to excipients. Therefore, in the spirit of continuous improvement, the EPC wishes to assess whether the current approach to these essential and widely used substances is optimal.

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

*Presence of mutagenic impurities, solvents, elemental impurities?*




*Role of excipients in formation of N-nitrosamines in medicinal products (e.g. residual nitrite)*

*Interdependencies: Different routes of administration*

# New '*Excipients strategy*' Working Party

- Identify and discuss best possible approach(es) to address the quality and the standard setting process of excipients for pharmaceutical use
- Review the typical structure and content of an individual monograph on such an excipient
- Evaluate the need for optional test(s) depending on the possible uses of the excipients (e.g. FRC section)
- Evaluate the need for (a) specific technical guide(s)
- Review existing general monographs (such as Substances for pharmaceutical use (2034)) to appropriately cover such excipients


Newsroom

European Pharmacopoeia Commission creates new Excipients Strategy Working Party

EDQM | STRASBOURG, FRANCE | 03/03/2023

https://www.edqm.eu/en/-/european-pharmacopoeia-commission-creates-new-excipients-strategy-working-party

# Emerging modalities of medicines

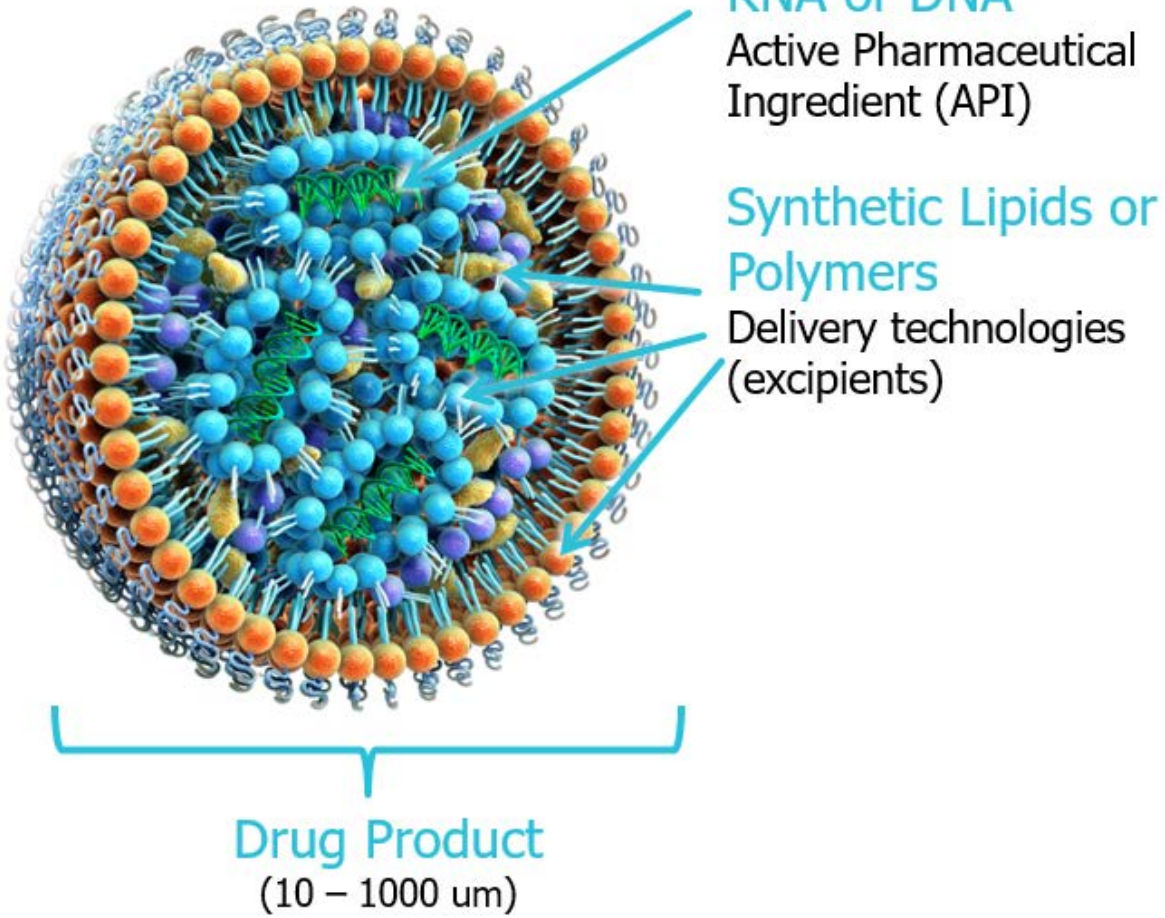
mRNA Vaccines

Nanomedicines

Phage therapies

# Quality of mRNA vaccines and their components

RNA & DNA are large molecules that require nanoparticle delivery technologies to get into tissues and cells.



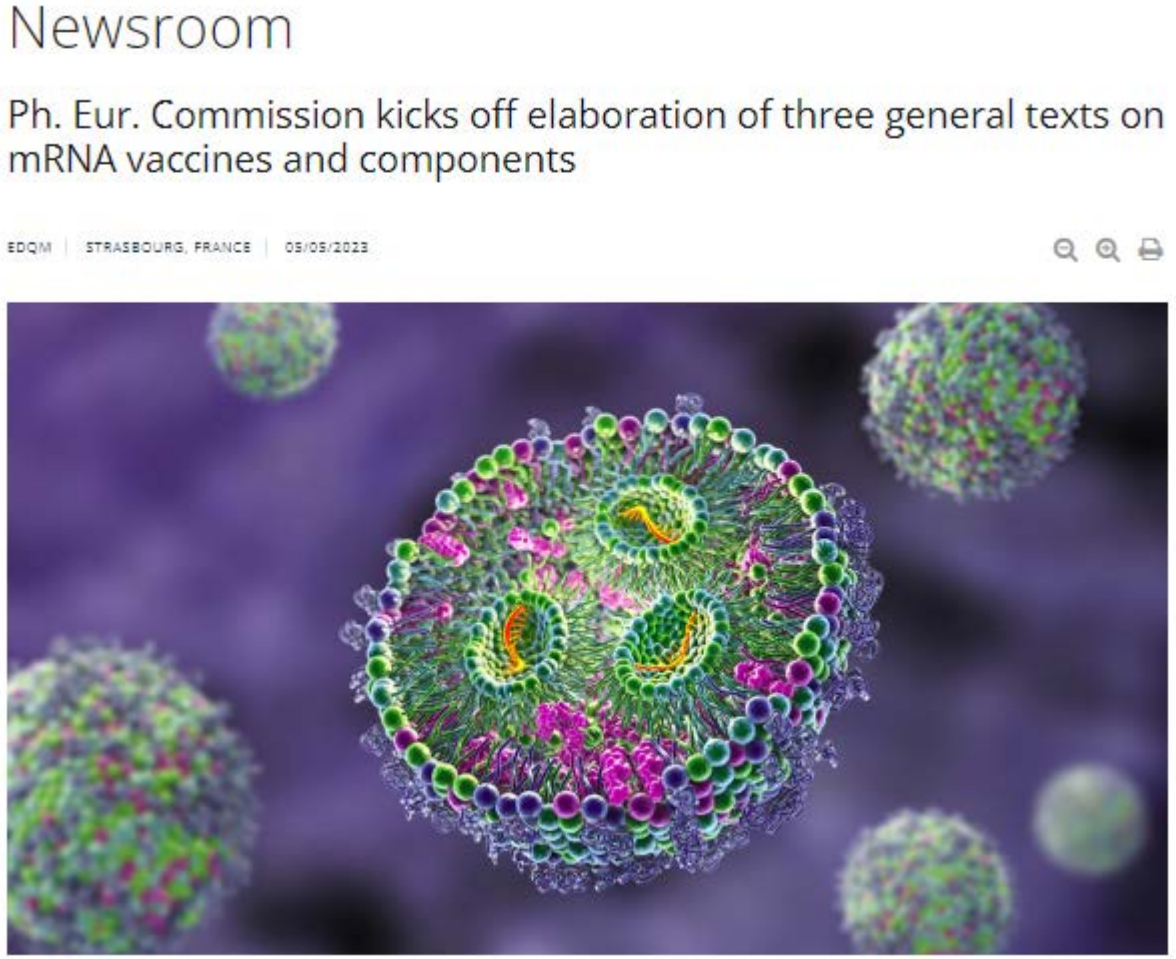

**New Working Party mRNAVAC**:

- Appointed by the Ph. Eur. Commission at its November 2022 session
- News item https://www.edqm.eu/en/-/ph.-eur.-commission-establishes-a-new-working-party-on-mrna-vaccines?p_l_back_url=%2Fen%2Fsearch-edqm%3Fq%3DmRNAVAC

# Quality of mRNA vaccines and their components

Recent addition to the Work Programme of **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.




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

# Nanomedicines

Specialists with expertise 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)

Newsroom

Call for Experts - NANO Working Party (Nanomedicines)

EDQM | STRASBOURG, FRANCE | 01/06/2023


EDQM news: https://www.edqm.eu/en/-/call-for-experts-nano-working-party-nanomedicines-

# Bacteriophages Working Party (BACT WP)

**Creation of BACT WP**

**Addition to the WP**

*Phage therapy active substances and medicinal products for human and veterinary use (5.31)*


**Public consultation**

*Public deadline: 30 June 2023*
*NPA deadline: 31 Aug 2023*

**167th Ph. Eur. Commission** — 06 2020

**170th Ph. Eur. Commission** — 06 2021

**Pharmeuropa 35.2** — 04 2023

# Phage therapy general chapter (5.31)

**Phage therapy active substances and medicinal products for human and veterinary use (5.31)**

1. **Definition**
2. **Production**
   - **2.1 General Provisions**
   - **2.2 Bacterial MCB and WCB**
   - **2.3 Phages used for production of PTMPs**
   - **2.4 Production and purification**
   - **2.5 Final lot**
   - **2.6 Adapted product**
3. **Labelling**

- Text for information
- Framework of requirements for phage therapy API and phage therapy medicinal products (PTMPs) production and control
- Alternative production and control approaches allowed (subject to approval by the competent authority)
- Applicable to preparations of naturally occurring or genetically modified, single phages or their mixtures administrated by various routes

# Join us in paving the way for the future...


Contribute to the protection of public health by:

- Making your comments count !!!

PHARMEUROPA ONLINE

TEXTS FOR COMMENT

ACCESS

- Becoming part of a dynamic scientific community !!!

# Thank you for your attention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