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

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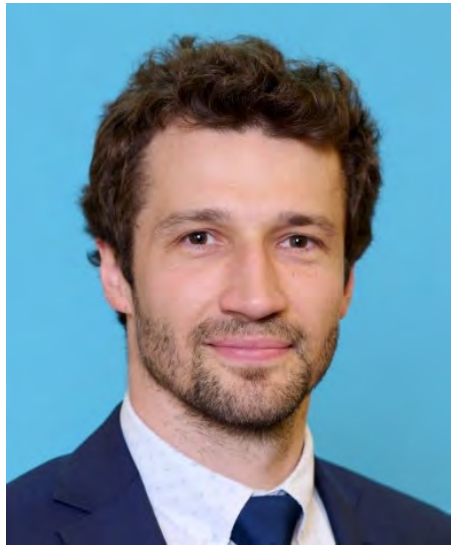

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Comparability of Alternative Analytical Procedures (5.27)

Mihaela Buda and Igor Bratoš

European Pharmacopoeia Department

17 January 2024

Outline of the Presentation

- **Ph. Eur. - setting the scene**
  - General principles
  - **Pharmacopoeial procedures**
- Ph. Eur. General notices
  - **Alternative procedures**
- Comparability of alternative procedures: ***new*** **general chapter 5.27**
  - Elaboration process, key aspects
  - **A walk through the text**: preliminary conditions, comparability study, data evaluation
- Take-home messages

The EDQM, a Directorate of the COUNCIL OF EUROPE

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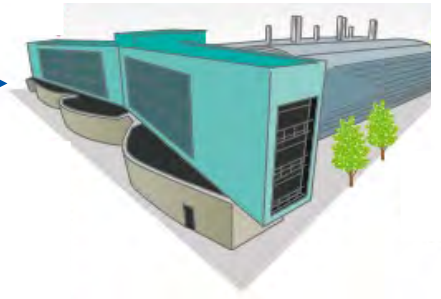
COMMITTEE OF MINISTERS | PARLIAMENTARY ASSEMBLY | CONGRESS OF LOCAL AND REGIONAL AUTHORITIES | EUROPEAN COURT OF HUMAN RIGHTS | COMMISSIONER OF HUMAN RIGHTS | CONFERENCE OF INGOS

- 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)



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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**

European Pharmacopoeia

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
- Analytical procedures verified & standardised

► **About 3000 reference standards shipped to 132 countries**

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

Biological Standardisation Steering Committee

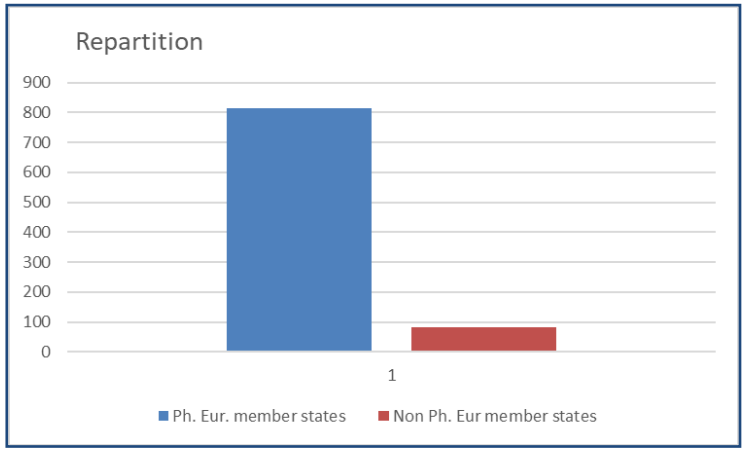
Laboratory, production, storage and distribution

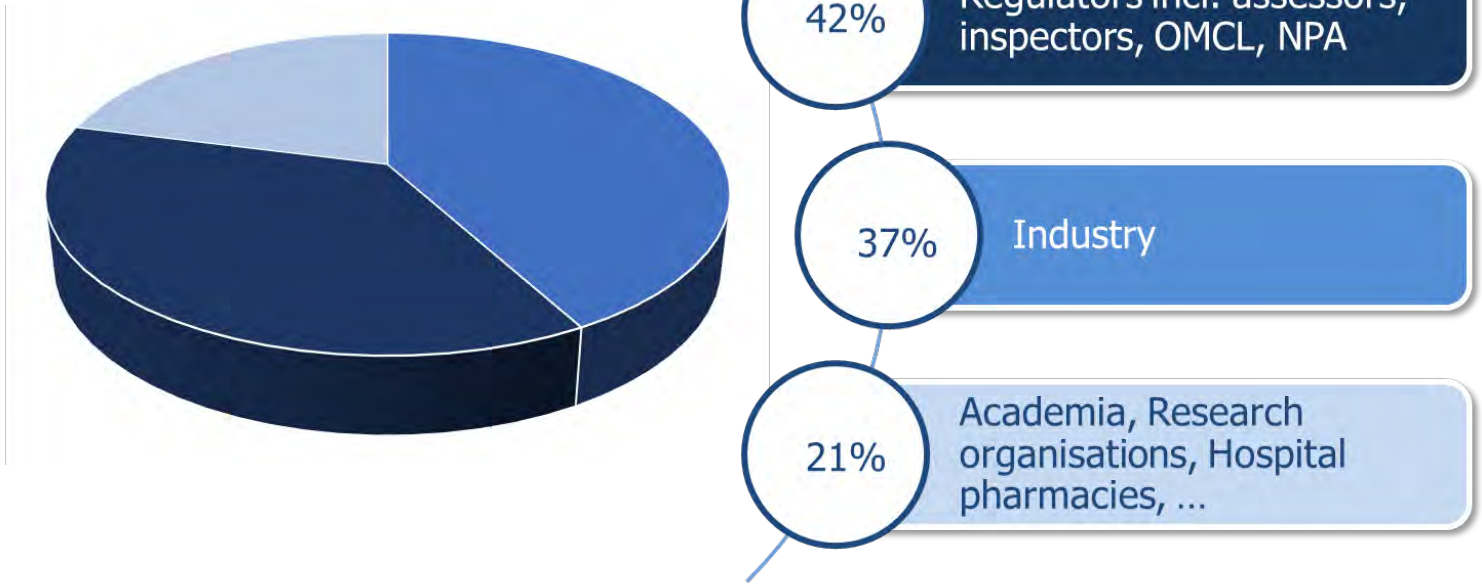
PUBLIC HEALTH IMPACT

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

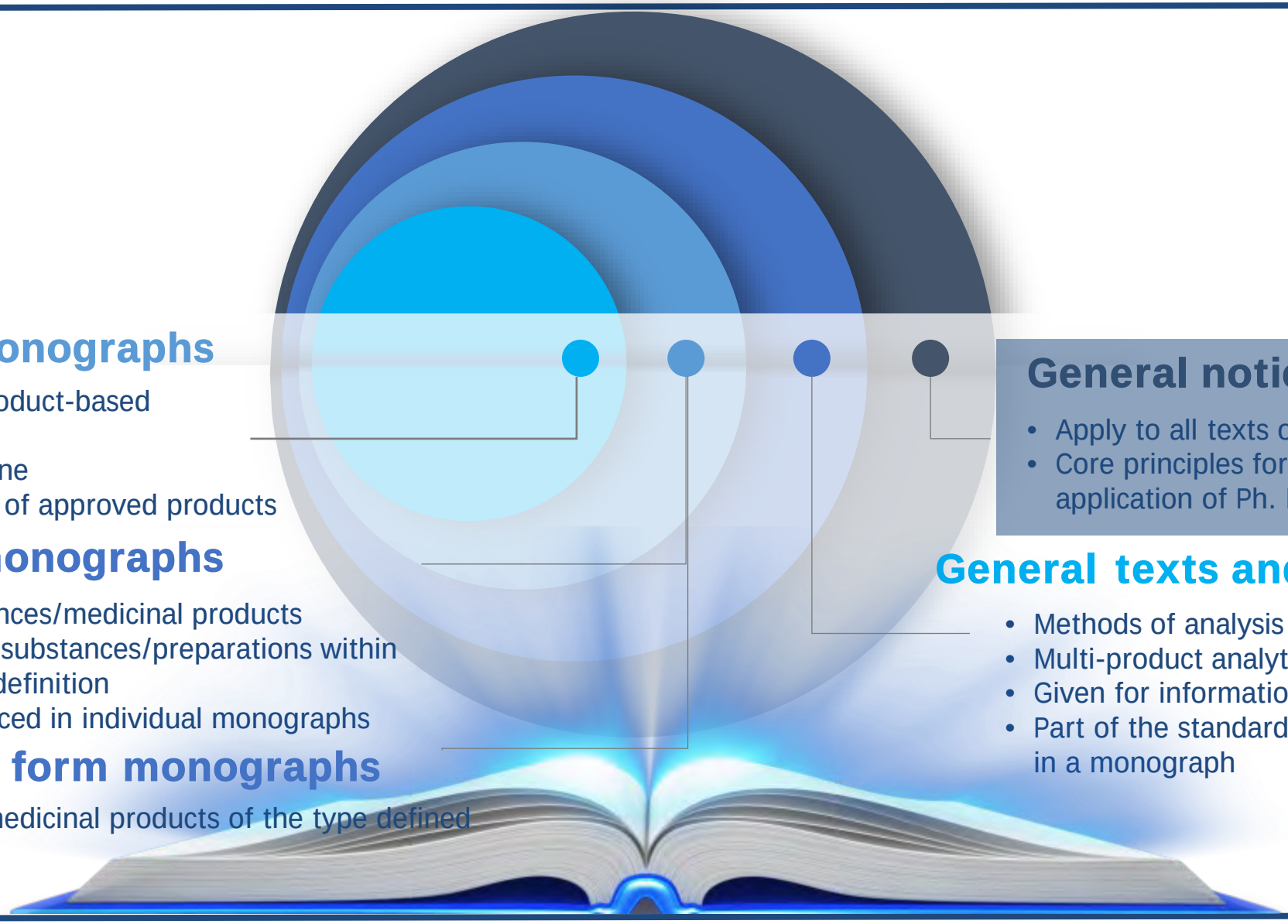
… relying on nearly 900 experts[1] working together …

[1] This number does not include:
- Chairs of Groups
- ad hoc specialists (around 100/year)
- Members of the Ph. Eur. Commission





Ph. Eur.: Content and Structure



Individual monographs

- Substance/product-based
- Specific
- Not stand-alone
- Take account of approved products

General monographs

- Classes of substances/medicinal products
- Mandatory for all substances/preparations within the scope of the definition
- Not cross-referenced in individual monographs

Dosage form monographs

- Apply to all medicinal products of the type defined

General notices

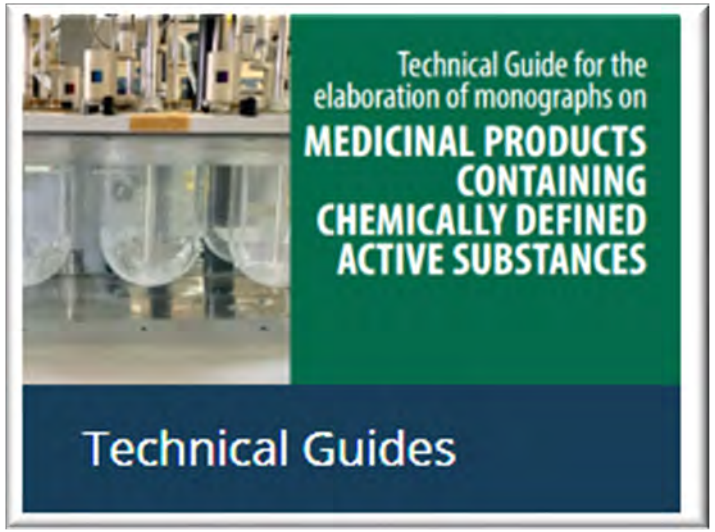
- Apply to all texts of the Ph. Eur.
- Core principles for interpretation and application of Ph. Eur. texts

General texts and chapters

- Methods of analysis & general texts
- Multi-product analytical procedures
- Given for information
- Part of the standard when referred to in a monograph

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)

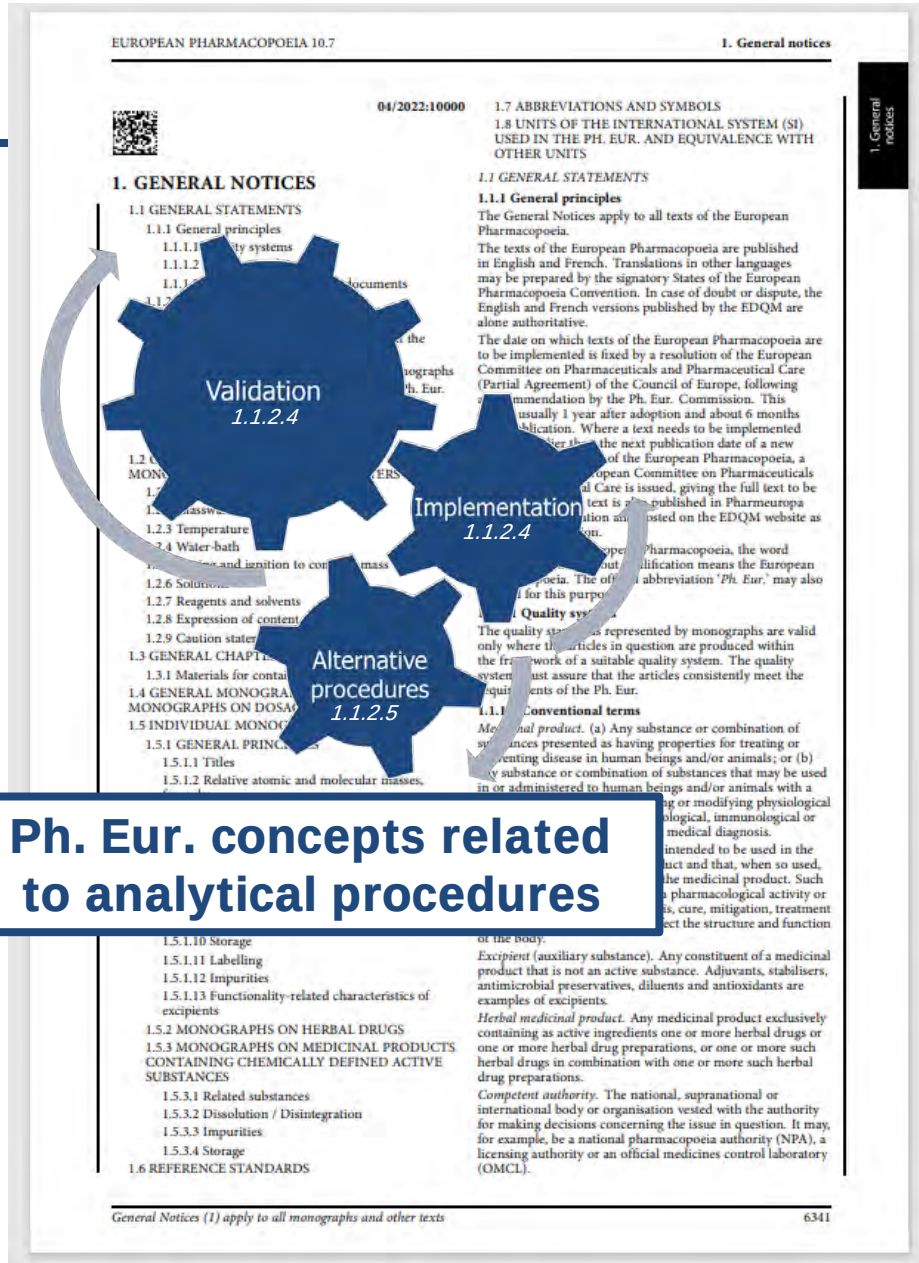


General Notices

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

Ph. Eur. Concepts Related to Analytical Procedures

- **Ph. Eur. Chapter 1 *General Notices*:**

1.1.2.4 Validation and implementation of Ph. Eur. analytical procedures

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.

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.

1.1.2.5 Alternative analytical procedures

*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**.*

Concept of „Alternative”

The TASK: cross the river

Ways of reaching the other side

Basic

Improved

Advanced

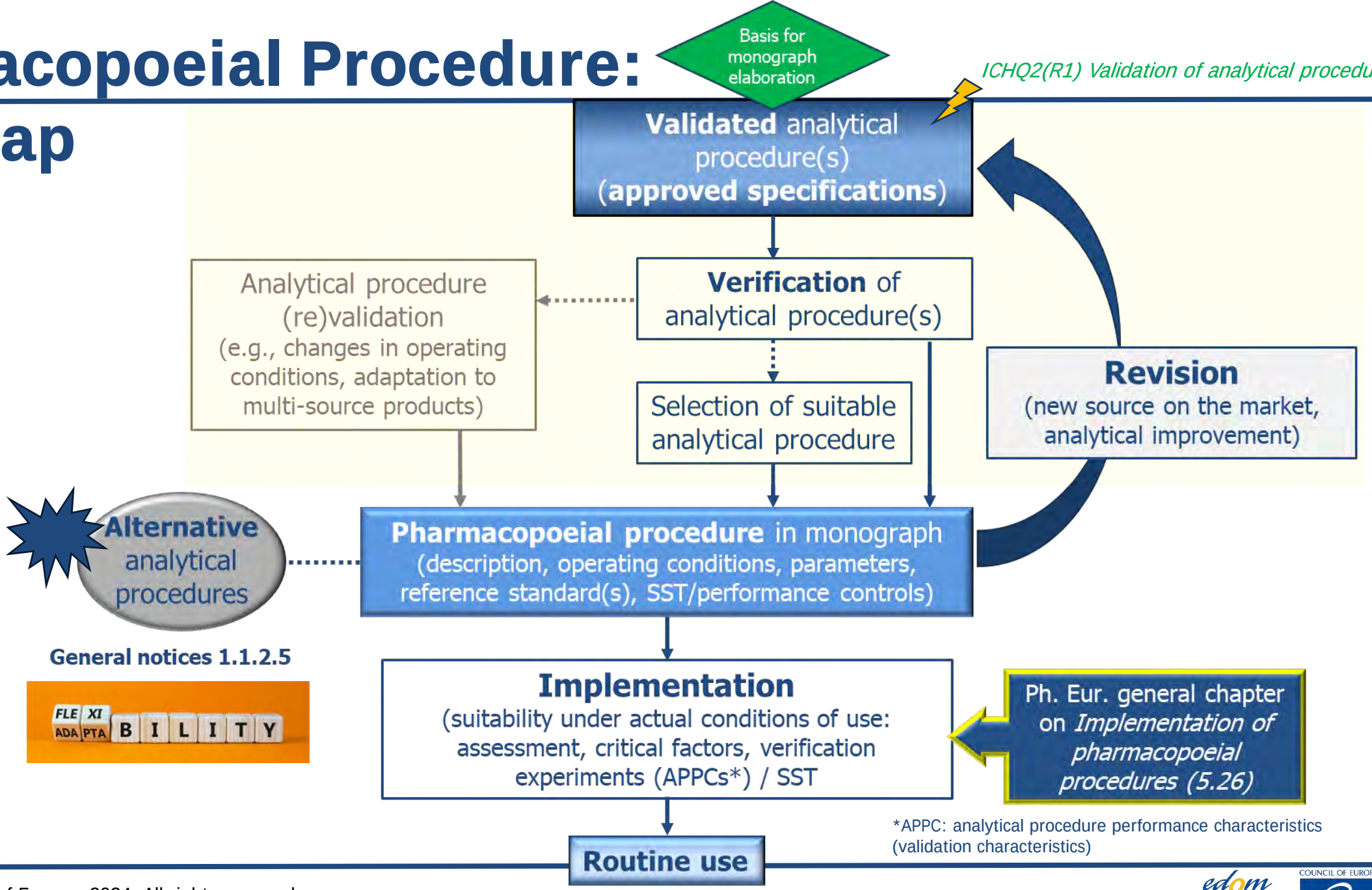
Pharmacopoeial procedure: legally binding, robust, established, widely accessible

Alternative analytical procedure:

- Different approach
- Comparability needs to be demonstrated

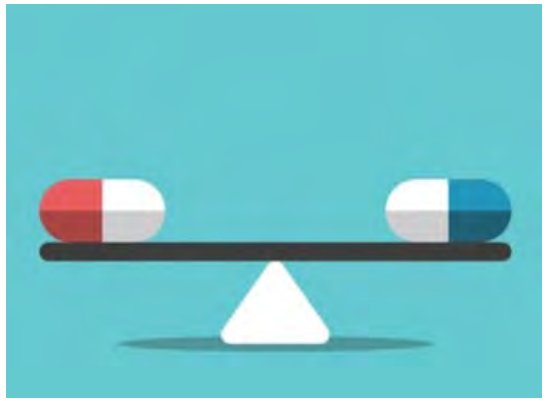
Alternative

Pharmacopoeial Procedure: Roadmap



Elaboration of New General Chapter 5.27: Rationale

- Need for guidance on how to demonstrate equivalency when the **official analytical procedure** (*i.e.,* the pharmacopoeial procedure) is replaced by an alternative analytical procedure for control purposes.



Elaboration of a new general chapter on **Comparability of alternative analytical procedures** with the aim to provide practical guidance for alignment with the statement in **General notices section 1.1.2.5.**

Elaboration of New General Chapter 5.27: Timeline

2017 — Addition to the Ph. Eur. work programme

- 159th session of Ph. Eur. Commission, November 2017

2018 — Drafting of the chapter by the MG WP

- **Brainstorming and discussions**
- Define general framework for demonstration of comparability
- Harmonisation of approaches
- Guidance/recommendations on assessment of comparability
- Key concepts, practical aspects

2022 — Public enquiry – **Pharmeuropa 34.2**

- Stakeholder feedback: about 140 comments
- Resulted in refinement of the text
- Aligned understanding/ interpretation of the *process*

2023 — Adoption by the Ph. Eur. Commission

- 176th session of Ph. Eur. Commission, June 2023

2024 — Publication in Ph. Eur.

- **Supplement 11.5**, January 2024

Implementation date: **1 July 2024**

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.

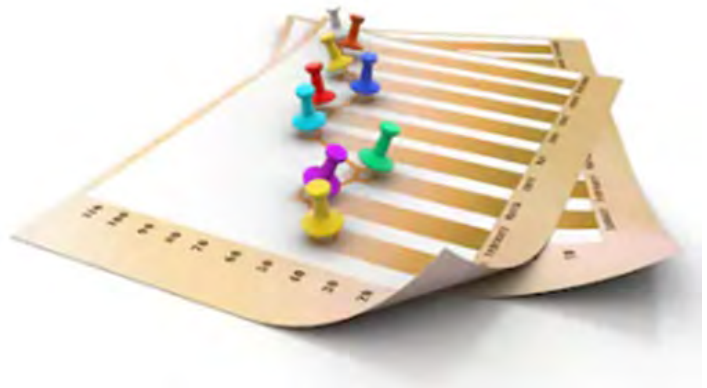
5.27. COMPARABILITY OF ALTERNATIVE ANALYTICAL PROCEDURES

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

General Chapter 5.27: Outline

- PREAMBLE
- INTRODUCTION
- PRELIMINARY CONDITIONS FOR THE COMPARABILITY STUDY
- COMPARABILITY STUDY
  - Study design
  - Acceptance criteria for comparability

    DATA EVALUATION: Statistical evaluation of results



General Chapter 5.27: Preamble

This general chapter is published for information. It describes how the comparability of an alternative analytical procedure to a pharmacopoeial analytical procedure may be demonstrated. Other approaches to demonstrating comparability may also be appropriate. The use of an alternative procedure is subject to authorisation by the competent authority. The final responsibility for the demonstration of comparability lies with the user and 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 analytical procedure.

General Chapter 5.27: Introduction

- **Tests and assays described in monographs 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 analytical procedures were used.
- The chapter aims to provide guidance on possible approaches to the assessment of the comparability of an alternative procedure that is used instead of a pharmacopoeial procedure.
- **In the event of doubt or dispute, the analytical procedures of the Ph. Eur. are alone authoritative.**

- Comparability of alternative microbiological methods is covered in general chapter ***5.1.6. Alternative methods for control of microbiological quality***.
- Specific guidance to facilitate the use of *in vitro* methods as substitutes for existing *in vivo* methods for testing vaccines is given in general chapter ***5.2.14. Substitution of in vivo method(s) by in vitro method(s) for the quality control of vaccines***

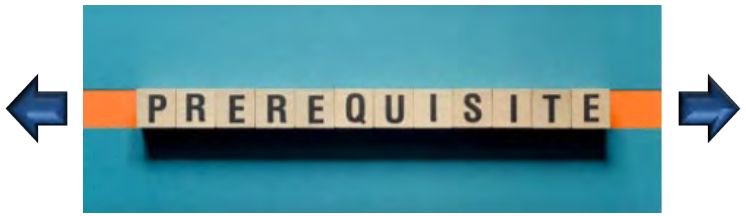
1.How do I apply a pharmacopoeial procedure in my lab?

2. I have another suitable (validated) analytical procedure that I consider superior to the pharmacopoeial procedure – can I replace the latter?

3. Is it sufficient to compare the performances of the alternative analytical procedure and pharmacopoeial procedure to demonstrate their comparability?

Preliminary Conditions

- **Alternative analytical procedure is validated** for its intended purpose in accordance with accepted scientific practice, current recommendations on analytical validation and guidelines that are relevant with regard to setting appropriate specification limits.



- **Pharmacopoeial procedure is implemented** as defined in general chapter *5.26. Implementation of pharmacopoeial procedures*, including verification experiments if appropriate.

Preliminary Conditions: Comparability Assessment

Alternative analytical procedure (validated)

Pharmacopoeial procedure (implemented)

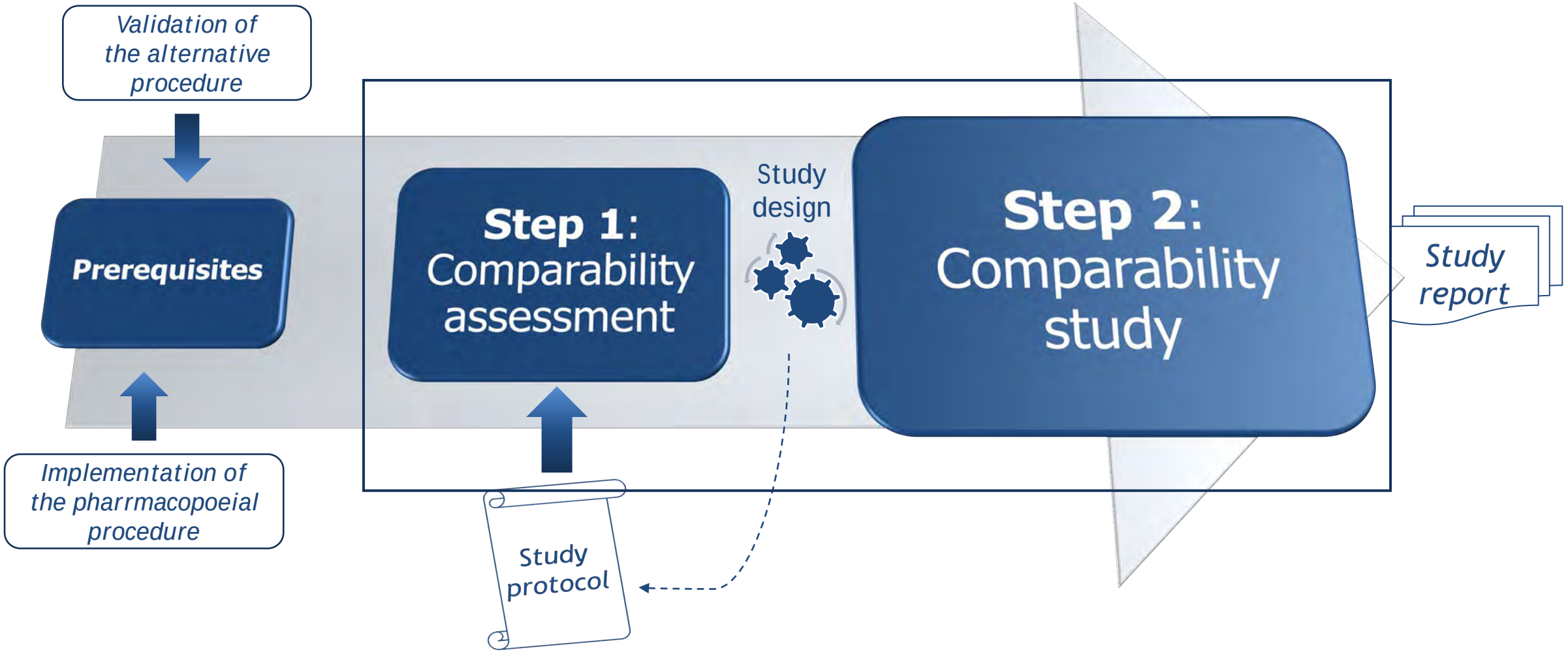
Comparison of analytical procedure performance

Demonstration that the alternative procedure meets its performance criteria during **validation** is not sufficient to imply comparability with pharmacopoeial procedure.

Comparability assessment of data generated during implementation of pharmacopoeial procedure and validation studies on alternative procedure:

- APPCs, such as **specificity / selectivity, sensitivity** (at the lower range limit), **linearity** and **range** should be assessed to ensure that the alternative procedure is at least as capable as the pharmacopoeial procedure
- Outcome of the comparability assessment may form the basis for the design of the *comparability study*

Process



Comparability process

Step 1: Comparability assessment

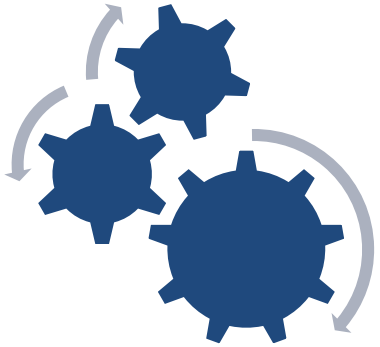
- Comparison of data obtained in the implementation of the pharmacopoeial procedure and validation data in terms of analytical procedure performance characteristics (APPCs)

Step 2: Comparability study

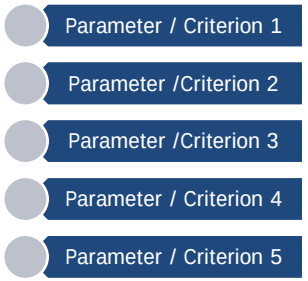
- Head-to-head testing, with the aim of reaching the same analytical decision
  → particularities: same experiments, same samples

Study design

- Based on the outcome of the comparability assessment
- Considers special cases where testing in a head-to-head format is not feasible



- **Study protocol**
  - Is established on the basis of the study design
  - 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** and their justification



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

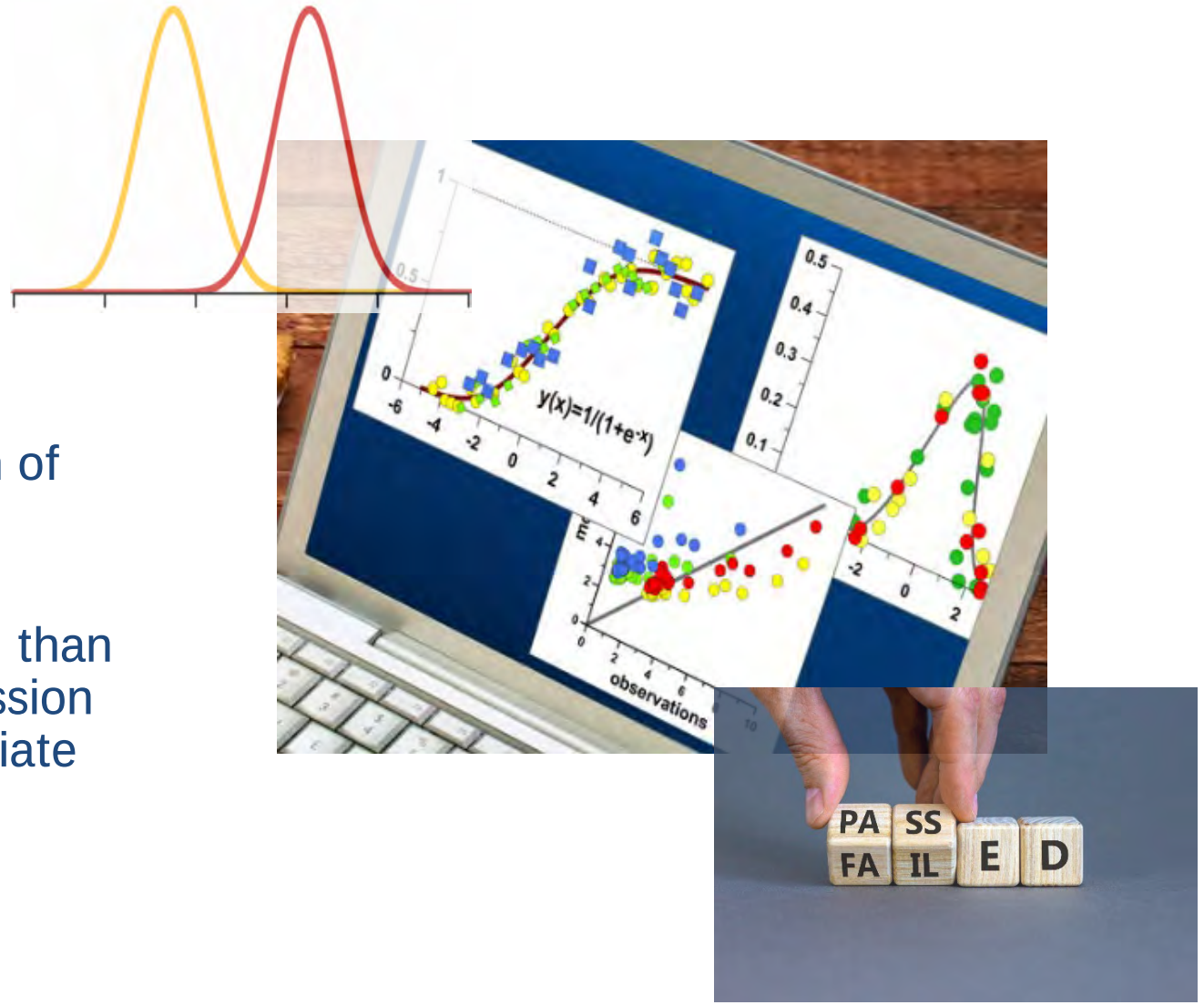
Acceptance criteria for comparability

- 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

Statistical evaluation of results

Statistical evaluation of results

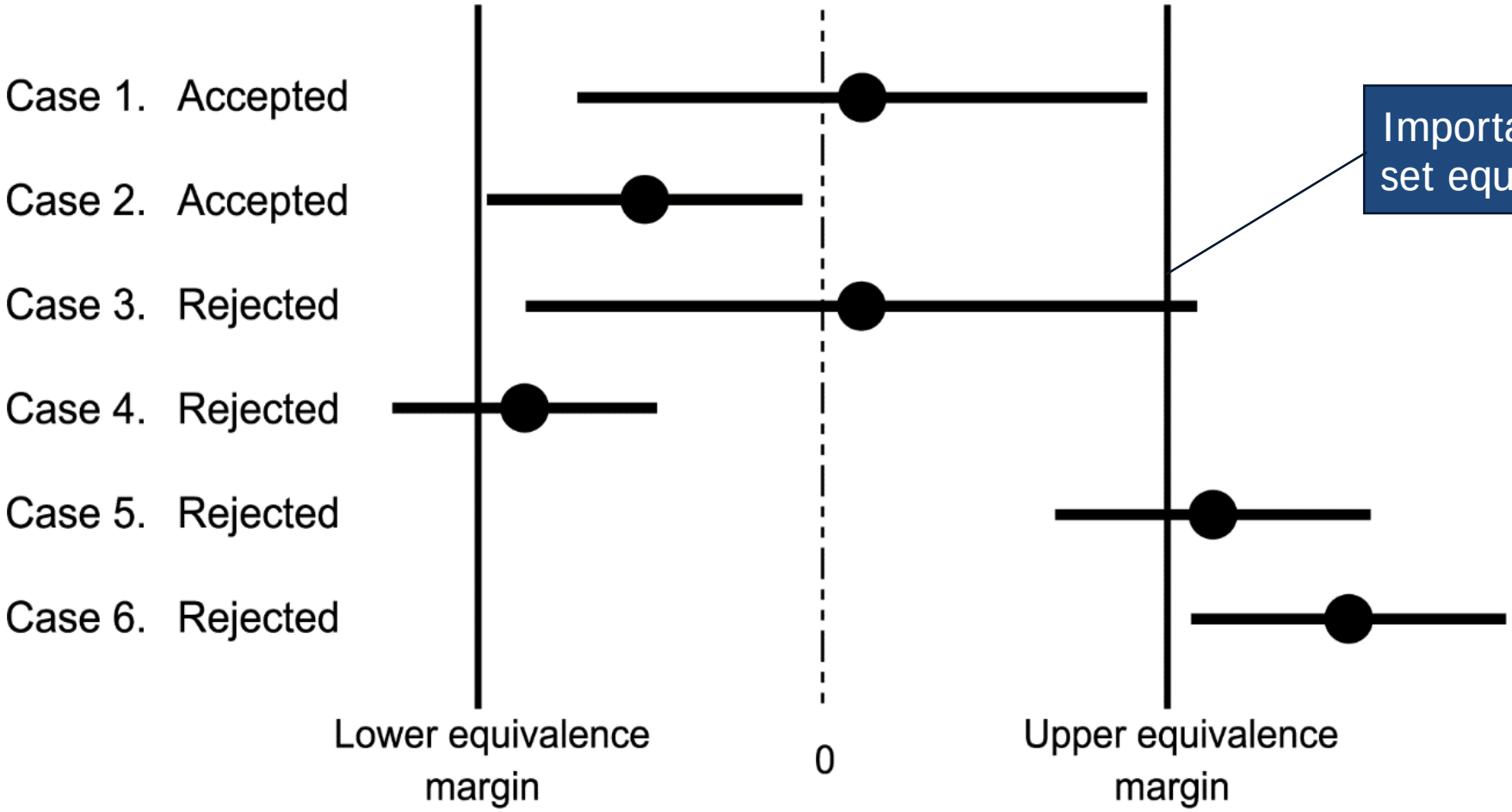
- *Step 1. Data description*
- *Step 2. Statistical assumptions*
- *Step 3. Equivalence testing*



- For quantitative results: example (most commonly used approach) - Comparison of two group means: <u>two one-sided t-tests (TOST) method</u>
- For results spreading over a wider range than those obtained at a single level, a regression approach (e.g. Deming regression, bivariate least squares regression)

- Other approaches may be appropriate
- **Pass/Fail criterion is key**

Typical outcomes of a comparability study



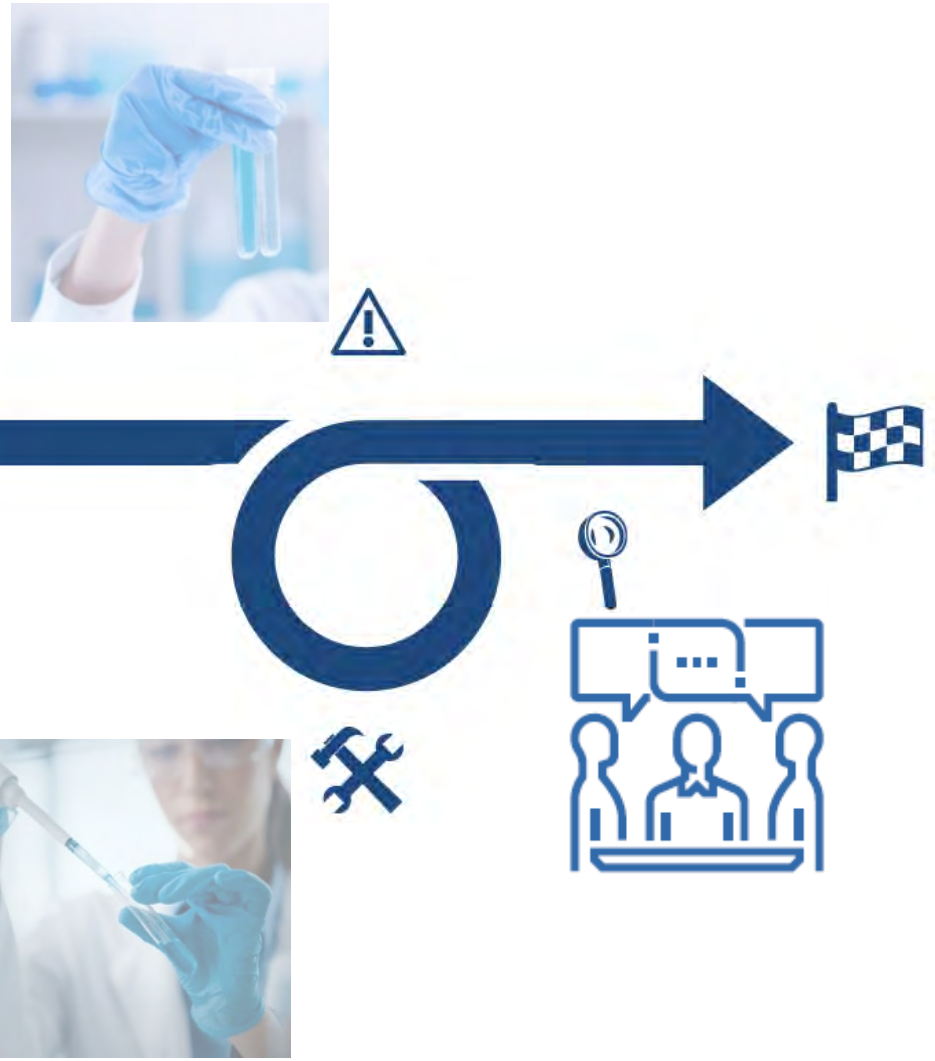
Importance of correctly set equivalence margin!

- When the equivalence as part of the comparability study is accepted, the alternative procedure may be considered statistically equivalent to the pharmacopoeial procedure.

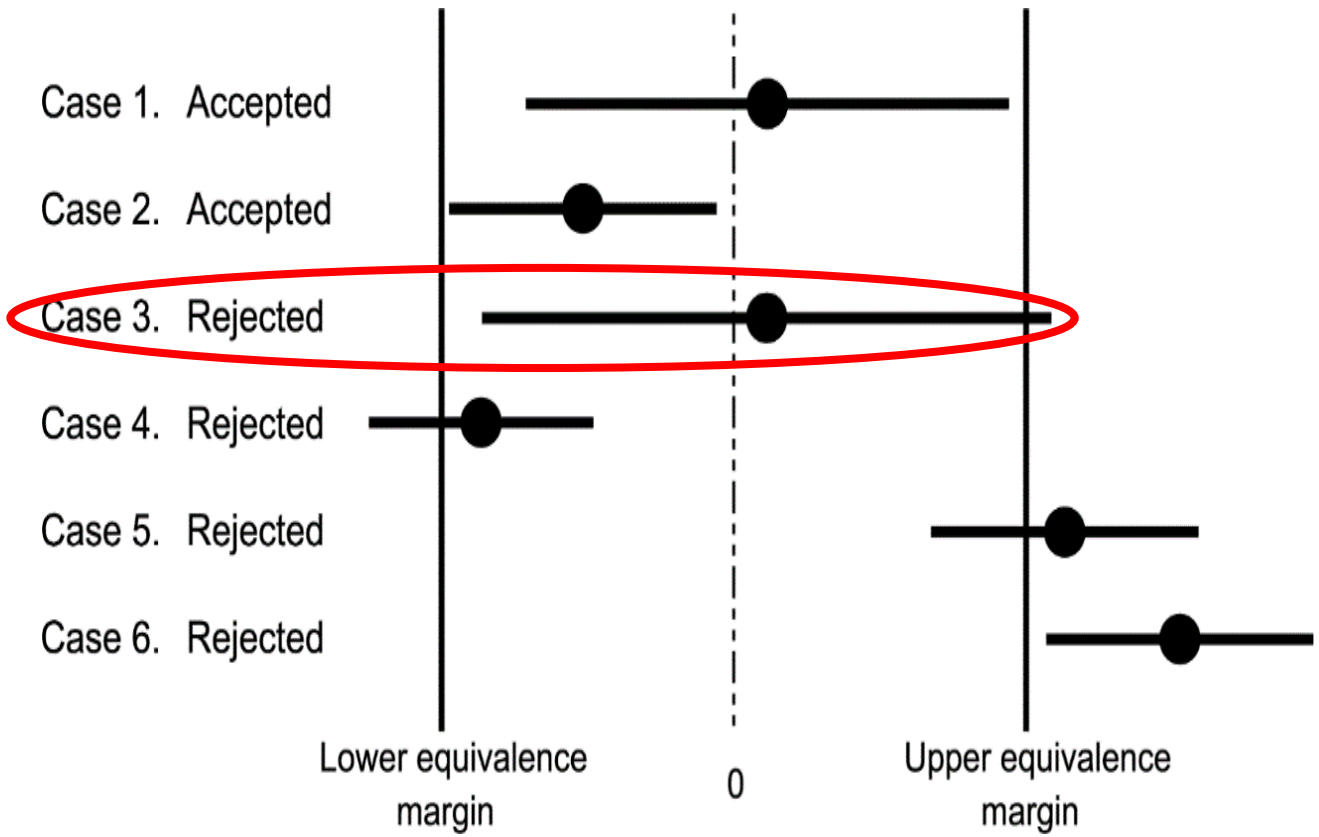
Unexpected outcome

In cases where the comparability cannot be accepted directly, certain flexibility is present:
- available data may be reviewed and if bias and/or variability is observed and steps taken to reduce it, the assessment may be relaunched, including e.g. performing additional experiments.

This possibility needs to be clearly defined in the study protocol.



Unexpected outcome (continued)



Case 3: Potential for acceptance

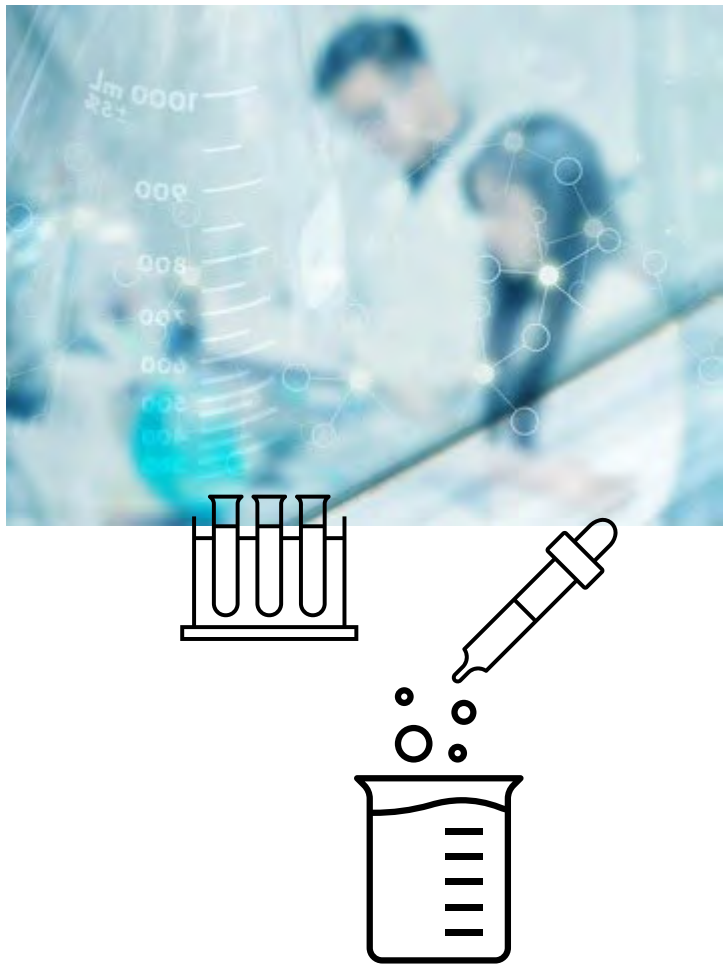
- Identify the root cause for the high variability of the results
- Can its influence be reduced or negated?
- Perform additional experiments after addressing the root cause
- E.g. better precision with more replicates → the outcome changes to accepted.

Practical aspects – Reference standards

- Establishment of reference standards for the alternative procedure in accordance with Ph. Eur. General chapter 5.12 is the responsibility of the user
- Ph. Eur. reference standards are established solely for the use with a pharmacopoeial procedure, therefore any use of Ph. Eur. RS for the alternative procedure must be supported by a full establishment procedure

N. B.! Use of Ph. Eur CRSs in an alternative procedure has no bearing on their official status

Practical aspects – Representative samples



- How to choose representative samples:

  - head-to-head testing of same homogeneous, authentic (i.e. non-spiked) samples preferred

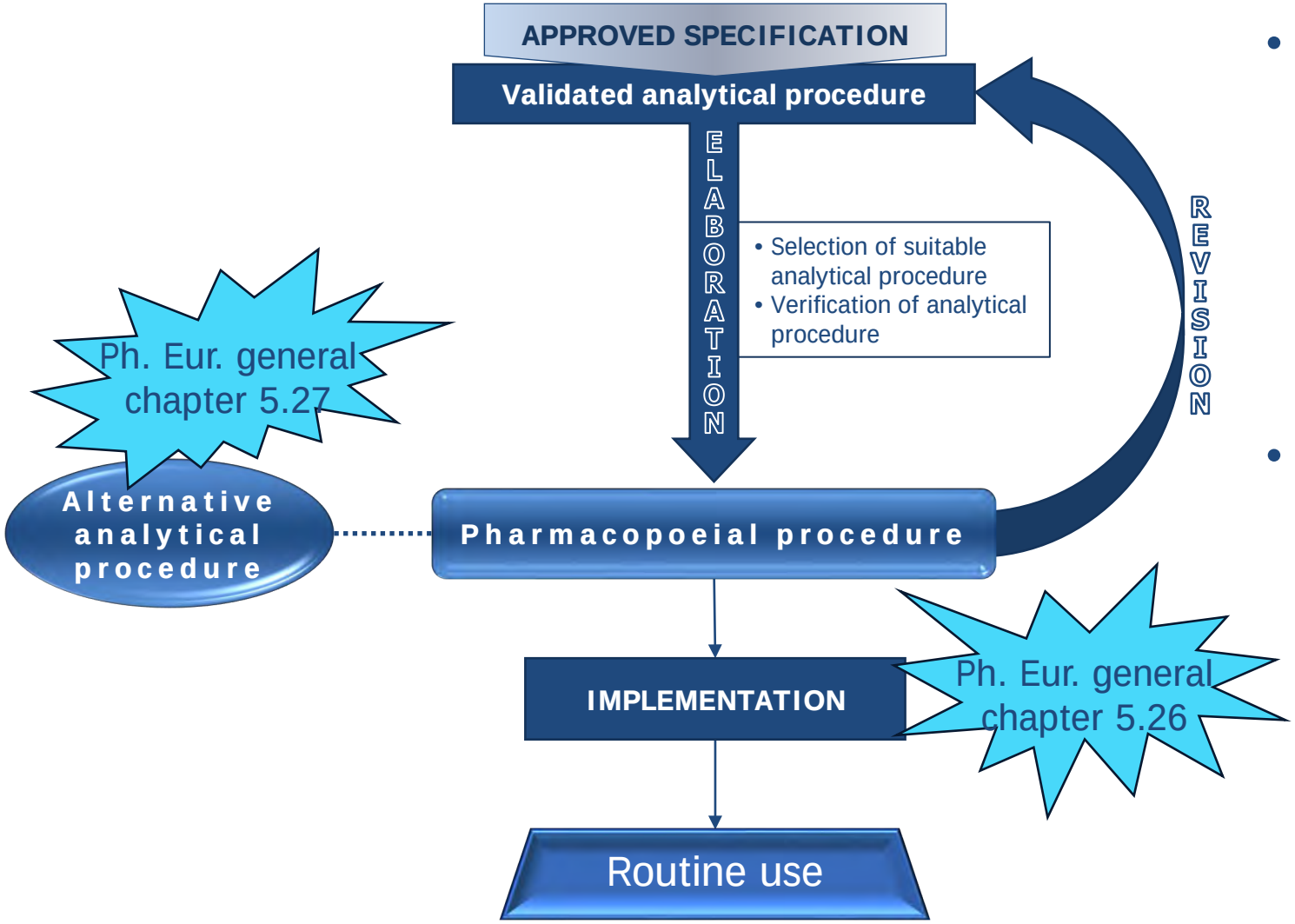
  - synthesised (spiked) samples or forced degradation are an option

  - variability of samples and sample matrices needs to be considered

  - it may be useful to include samples at or near the specification limit and/or reporting threshold

- Depending on the intended purpose of the procedures, useful comparability information for certain APPCs may be generated in the comparability study by analysing Ph. Eur. reference standards using the alternative procedure.

Lifecycle of the Pharmacopoeial Procedure



- If a user considers the alternative analytical procedure to bring significant improvement for the quality of the article, they are encouraged to contact EDQM and/or submit a **request for a revision** via the NPA
- In the event of an issue with a pharmacopoeial procedure (e.g. implementation difficulties), EDQM should be contacted via the Helpdesk and if confirmed, this may result in a revision
  → **In itself not a case for an alternative procedure**

Task completed!

- Or is it? Reminder:

Agreement of the competent authority needed!

- Comparability needs to be maintained over the lifecycle of both procedures

Thank you for your attention

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